Medicine®

OPEN

Association between -174G>C polymorphism in the IL-6 promoter region and the risk of obesity
A meta-analysis

Man Hu, MD[a], Zhaomin Yu, MD[a], Dan Luo, MD[a], Haiming Zhang, MD[b], Jinxiao Li, MD[a], Fengxia Liang, PhD[c], Rui Chen, PhD[d,*]

Abstract

Background: Many researchers have suggested that the -174G>C polymorphism in the interleukin-6 (IL-6) promoter region contributes to the risk of obesity; however, this hypothesis is still inconclusive. Therefore, we conducted a meta-analysis to combine the data from several studies to arrive at a conclusion regarding the association between -174G>C polymorphism and the risk of obesity.

Methods: The PubMed and Embase databases were searched up to February 20, 2018. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using a random-effects model. Subgroup analysis and sensitivity were also performed.

Results: Ten eligible studies involving 7210 cases were performed to identify the association strength. The association strength was measured by the ORs and 95% CIs. By pooling the eligible studies, we found a significant association between the -174G>C polymorphism and obesity risk (C vs G: OR = 1.37; 95% CI, 1.08–1.74; $P_{heterogeneity} < .01$). Overall, individuals with the variant CC (OR = 1.58; 95% CI, 1.09–2.28; $P_{heterogeneity} < 0.01$) and GC/CC (OR = 1.61; 95% CI, 1.13–2.29; $P_{heterogeneity} < .01$) were associated with a significantly increased risk of obesity.

Conclusion: The meta-analysis results suggested that the polymorphism -174G>C in the IL-6 promoter region was associated with a significantly increased risk of obesity.

Abbreviations: BMI = body mass index, HWE = Hardy–Weinberg equilibrium, IL-6 = interleukin 6, SNP = single nucleotide polymorphism.

Keywords: -174G>C polymorphism, IL-6, obesity

1. Introduction

Obesity-related disorders have become a major public health problem worldwide and can lead to metabolic disorders. Obesity is caused by several genetic, metabolic, social, and environmental factors. Among these internal and external factors, the

contribution of genetic factors has been recognized widely, but the genes involved have not been fully elucidated.[1]

Interleukin (IL)-6 is a cytokine that has dual roles, namely, it exhibits both inflammatory and anti-inflammatory effects.[2] IL-6 is critical in the inflammatory signaling pathway and is involved in the development of obesity and insulin resistance.[3] High circulating IL-6 concentration has been associated with obesity and the visceral adipose tissue.[4]

Genetic variants, especially functional polymorphisms in the promoter region of genes, may alter the function and expression of genes associated with energy intake and energy expenditure. Several indications of the linkage between single nucleotide polymorphisms (SNPs) and obesity phenotypes have been found.[5,6]

The functional IL-6–174G/C promoter polymorphism has been shown to affect IL-6 transcription.[7,8] The IL-6–174C mutation change is expressed at a lower level in cellular constructs relative to the 174G construct.[9] The human *IL-6* gene is located on chromosome 7p21, and the -174G/C polymorphism consists of a single nucleotide change from G to C at position -174 in the promoter region.

In recent years, the association of the IL-6–174G/C polymorphism with obesity risk has been evaluated in several genetic studies. Some studies have suggested that IL-6–174G/C increased the obesity risk,[10,11] while some found no association between IL-6–174G/C and obesity.[12] The relation between IL-6–174G/C and risk of obesity is not conclusive. In this study, we investigated

whether the IL-6–174G>C polymorphism is associated with the risk of obesity.

2. Methods

2.1. Literature search

Study data were extracted by an electronic search from online databases (PubMed and Embase) and a manual search of references of relative articles using the search terms "IL-6," "polymorphism(s)," and "obesity." The search had no limitations, and the last search was conducted on February 20, 2018.

2.2. Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: case–control studies or cohort studies; studies investigating the associations between IL-6 polymorphisms and obesity susceptibility; studies providing detailed genotype distribution data, or data for calculating genotype; the standard of obesity was defined according to body mass index (BMI) > 25 or waist-hip ratio (WHR) > 0.85; and participants in studies were not limited by age. The exclusion criteria were as follows: articles that did not present detailed genotype frequencies; review articles; articles that did not address obesity susceptibility; and articles that were not in Hardy–Weinberg equilibrium (HWE) according to an exact test.

2.3. Data extraction

Two reviewers (Yu and Luo) extracted eligible studies independently according to the inclusion criteria. Disagreements between the 2 reviewers were discussed with another reviewer (Zhang) until a consensus was reached. We extracted the following data from the original publications: name of first author; year of publication; country of the study; ethnicity; obesity definition; the age group of the population; and genotype frequency in cases and controls.

2.4. Statistical analysis

The association strength between the IL-6–174G>C polymorphism and obesity risk was measured by the odds ratio (OR) with a 95% confidence interval (95% CI). The estimates of the pooled ORs were achieved by calculating the weighted average of the OR from each study. A 95% CI was used for the statistical significance test and a 95% CI without 1 for the OR, indicating a significant increased or decreased cancer risk. The pooled ORs were calculated for an allelic comparison (C vs G), homozygote comparison (CC vs GG), heterozygote comparison (GC vs GG), dominant model (CC/GC vs GG), and recessive model (CC vs GG/GC). C was the variant allele. G was the wild-type allele. The heterogeneity assumption was validated using Chi-squared based on the Q and I^2 test. An I^2 value of > 50% signified a "substantial heterogeneity." A random-effects model was used to account for possible heterogeneities between studies. Funnel plots and the Egger linear regression test were used to diagnose potential publication bias ($P < .05$) as indicated statistically (significant publication bias). The statistical analysis was calculated using the STATA 12.0 (StataCorp, College Station, Texas). All P values were 2-sided.

2.5. Ethical approval

All analyses of this meta-analysis were based on previous published studies, and this meta-analysis did not have original
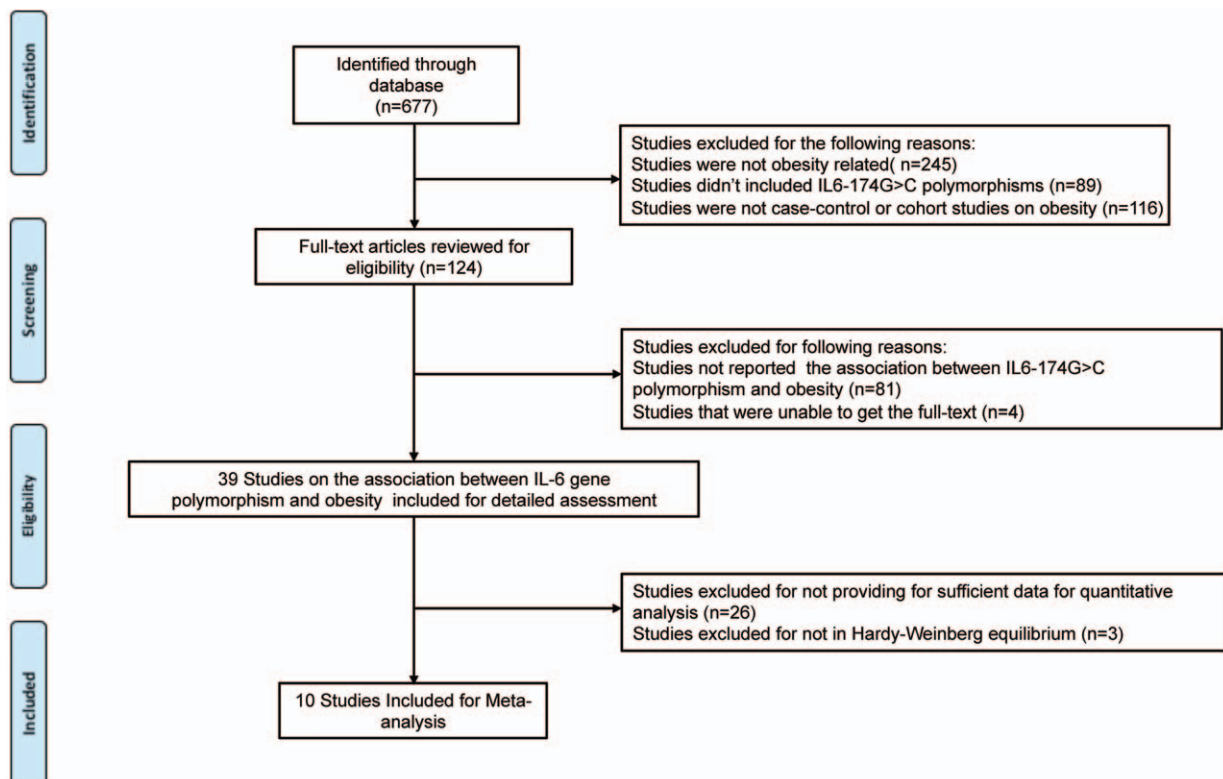

Figure 1. Prism flow chart for the meta-analysis.

Table 1

Characteristics of eligible studies.

Ref.	Year	Country	Ethnicity	Obesity definition	Population	Control source	HWE	Case–control	Case (genotype) GG/GC/CC			Control (genotype) GG/GC/CC		
Ibrahim et al[14]	2017	Egypt	Caucasian	BMI z score ≥2	Juveniles‡	CB	0.85	85/64	24	61	0	61	3	0
Joffe et al[15]	2014	South African	Caucasian	BMI* ≥30	Adults	CB	0.56	120/146	82	26	12	91	47	8
Suazo et al[16]	2014	Chile	Caucasian	BMI (children)	Juveniles	HB	0.98	68/191	42	22	4	107	76	8
Gupta et al[17]	2011	North Indian	Caucasian	WHR ≥0.85	Adults§	CB	0.13	192/178	45	97	50	71	75	32
Bouhaha et al[18]	2010	Tunis	Caucasian	BMI ≥25	Not mention	HB	0.63	242/208	175	60	7	160	44	4
Popko et al[19]	2009	Poland	Caucasian	BMI >25	Adults	HB	0.62	102/77	20	50	32	24	36	17
Pyrzak et al[20]	2009	Poland	Caucasian	BMI z score†	Juveniles	Not mention	0.60	124/56	38	65	21	30	23	3
Poitou et al[21]	2005	France	Caucasian	BMI ≥ 40	Adults	Not mention	0.33	445/214	192	192	61	86	94	34
Hamid et al[13]	2005	Denmark	Caucasian	BMI ≥ 30	Adults	HB	0.61	2566/1661	474	771	416	717	1275	574
Wernstedt et al[22]	2004	Sweden	Caucasian	BMI ≥ 25	Adults	HB	0.13	347/124	92	165	90	50	51	23

BMI = body mass index, CB = community-based population, HB = hospital-based population, WHR = waist-hip ratio.
* BMI: weight/height^2.
† BMI z score: BMI (kg/m^2) adjusted for age and sex calculated using normative data.
‡ Juveniles: ages between 3 and 20 years.
§ Adults: ages over 20 years.

data. Thus, no ethical approval and patient consent were required.

3. Results

3.1. Characteristics of eligible studies

In our study, 124 articles were identified after the first screening according to the inclusion and exclusion criteria. The detailed screening process is shown in Fig. 1. Here, 39 articles were retained after the full-text articles were reviewed. Among these articles, 26 studies were excluded because the genotype frequencies in the case and control groups were not provided. Three studies that were not in the HWE were also excluded. Seven of the studies consisted of Caucasian populations. Three studies were of children or adolescent. The obesity cases were diagnosed by the BMI or WHR in all studies. The polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay was used for genotyping in nine studies, and a chip-based matrix-assisted laser-desorption/ionization time-of-flight (MALDI-TOF) genotyping assay was performed in 1 study.[13] Blood samples were used for genotyping in all studies. The HWE of genotype distribution in the controls was tested in all the studies and was 10, consistent with the HWE. Further, 3 additional studies that were not consistent with the HWE were excluded. Overall, 10 studies satisfied the meta-analysis criteria.[13–22] The details of the studies are summarized in Table 1.

3.2. Quantitative synthesis

The pooled results from the assessment of the association between the IL-6–174G/C polymorphism and obesity susceptibility in 4 genotypes (dominant model: GC/CC vs GG; recessive model: CC vs GC/GG; homozygote: CC vs GG; and heterozygote model: GC/GG) are summarized in Table 2. We observed a significantly increased risk of obesity susceptibility, which was inconsistent with the study by Grallert et al.[23] This occurred in the dominant model (GC/CC vs GG: OR = 1.58, 95% CI: 1.09–2.28, $P_{heterogeneity} < .01$, Fig. 2) and homozygote comparison (CC vs GG: OR = 1.61, 95% CI: 1.13–2.29, $P_{heterogeneity} < .01$, Fig. 3) when all eligible studies were pooled. Moreover, we conducted the subgroup studies using the confounded factors. We found increased risks between the IL6–174G/C polymorphism and the control source under the heterozygote model (CC vs GG). The result is shown in Fig. 4.

3.3. Sensitivity analysis and publication bias

We performed a sensitivity analysis to assess the stability of the results by sequentially removing each eligible study. Because no substantial change was found, the sensitivity analysis showed that no individual study affected the pooled results. The potential publication bias was assessed by Begg funnel plot (Fig. 5) and Egger test. The funnel plots did not indicate evidence of obvious asymmetry. In addition, the Egger test did not demonstrate

Table 2

Pooled results and the subgroup analysis results in all genotypes.

Subgroup	N (study)	Case–control	Dominant (GC+CC vs GG) OR	95% CI		Recessive (CC vs GC+GG) OR	95% CI		Homozygote (CC vs GG) OR	95% CI		Heterozygote (GC vs GG) OR	95% CI	
Total	10	4291/2919	1.58	1.09	2.08	1.28	1.07	1.55	1.61	1.13	2.29	1.48	1.01	2.17
Source of control														
CB	3	397/388	3.38	0.79	19.93	1.67	1.08	2.60	2.21	1.35	3.65	3.61	0.59	22.03
HB	5	3325/2261	1.23	0.90	1.70	1.20	1.05	1.38	1.50	1.01	2.22	1.15	0.84	1.58
Not mention	2	569/270	1.46	0.51	4.22	1.54	0.37	6.38	1.91	0.29	12.77	1.36	0.57	3.25
Population														
Adults	6	3327/2400	1.26	0.91	1.74	1.25	1.03	2.57	1.60	0.46	5.57	1.17	0.84	1.62
Juveniles	3	277/311	4.35	0.64	29.71	2.25	0.90	5.65	2.62	0.61	11.21	4.06	0.56	29.46
Not mention	1	242/208	1.28	0.83	1.96	1.52	0.44	5.26	1.50	1.03	2.19	1.25	0.80	1.94

95% CI = 95% confidence interval, CB = community-based population, HB = hospital-based population, OR = odds ratio.
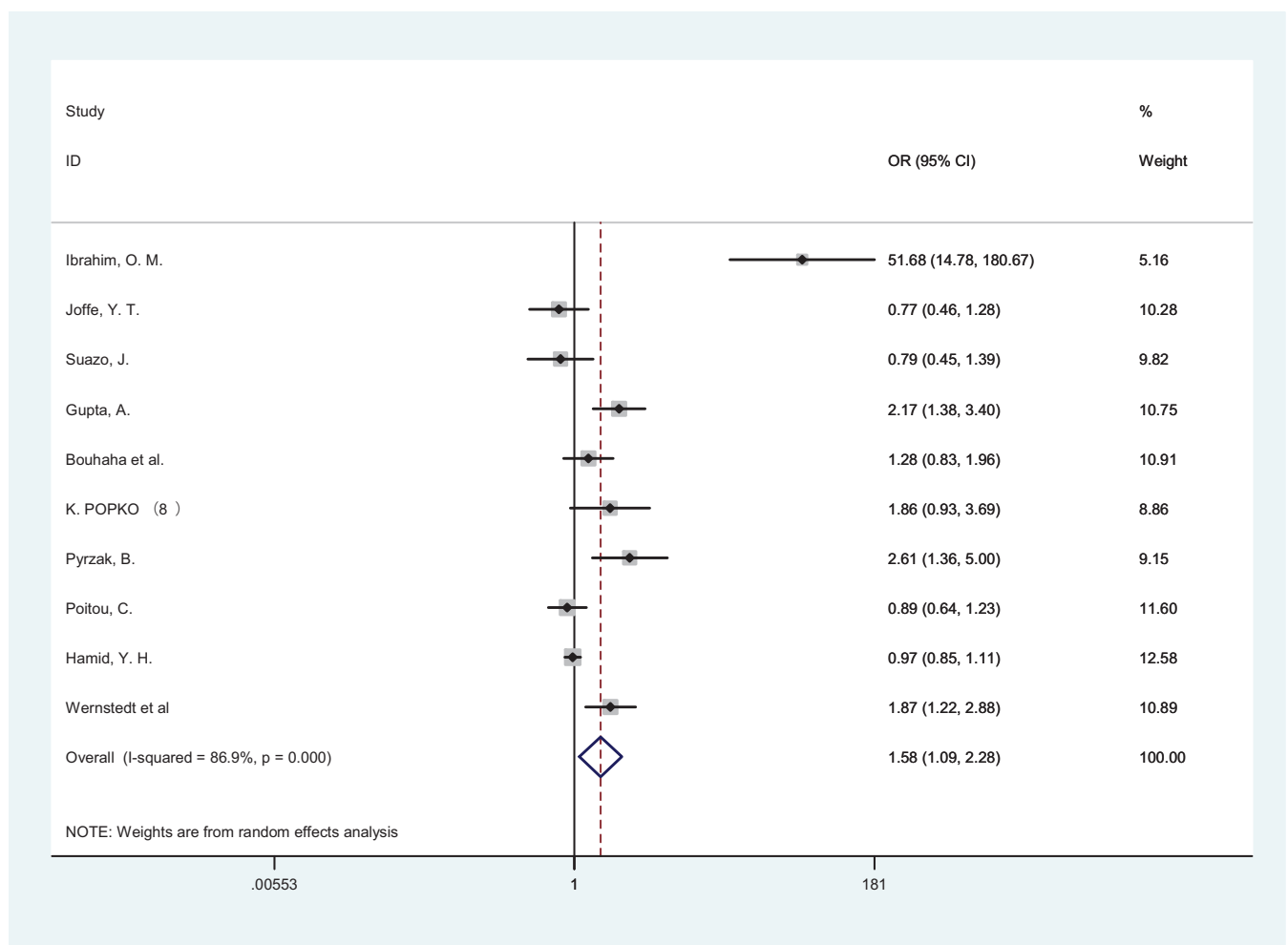
Figure 2. Forest plot of obesity risk with the IL-6–174G>C polymorphism in the dominant model (GC/CC vs GG).

significant publication bias (C vs G: $P = .442$; CC vs GG: $P = .782$; CG vs GG: $P = .148$; CG+CC vs GG: $P = .180$; CC vs GC+GG: $P = .483$).

4. Discussion

Obesity has become a worldwide health problem because it is associated with a number of diseases, including heart disease, insulin resistance, hypertension, and atherosclerosis, which reduce life expectancy and contribute to higher medical expenses. The unbalanced production of inflammatory factors can contribute to the pathogenesis of obesity-linked diseases.[9] IL-6 inhibits the action of Treg cells and is involved in metabolic processes.[24] The adipose tissue is a major source of circulating IL-6, and the excessive secretion of IL-6 appears to be directly related to obesity.[24] In addition, IL-6 can affect metabolism directly or indirectly by its action on skeletal muscle cells.[25] Recently, numerous studies suggested that SNPs in the promoter region of the *IL-6* gene might be risk factors for the development of diabetes.[26] A number of studies indicated that the IL-6–174G/C polymorphism was highly associated with obesity, fatty liver, insulin resistance, and the metabolic syndrome.[27,28] Meanwhile, many studies found that the IL-6–174G/C polymorphism was

significantly associated with susceptibility to obesity.[13,20] However, some studies have reported no significant associations between adiposity and the IL-6–174G/C genotypes.[12,29]

Circulating IL-6 is derived from different cells in tissues, such as the adipose tissue, muscles, and hypothalamus, all of which contribute to controlling the energy balance.[30] Further, IL-6 gene expression is tightly regulated by hormones, cytokines, and their transcription factors. Therefore, the differences in study findings may relate to environmental factors, such as dietary intake. Indeed, several studies have reported the relationship between IL-6–174G>C and diet. Corpeleijn et al[31] reported that the ability to increase fat oxidation after a high-fat load was increased in obese European Caucasians with the IL-174C allele. Further, diet can affect an individual's genes and can, in turn, affect the response to supplementation.[32] Meanwhile, a study reported that the IL-6–174G>C polymorphism has been associated with exercise-related phenotypes.[33] With the combination of the reported studies, we hypothesized that environmental factors and lifestyle could affect the IL-6 polymorphism, and the IL-6–174G>C polymorphism, in turn, could affect the balance of energy intake and energy expenditure. However, whether the IL-6–174G>C polymorphism is related to obesity susceptibility remains controversial. To resolve this
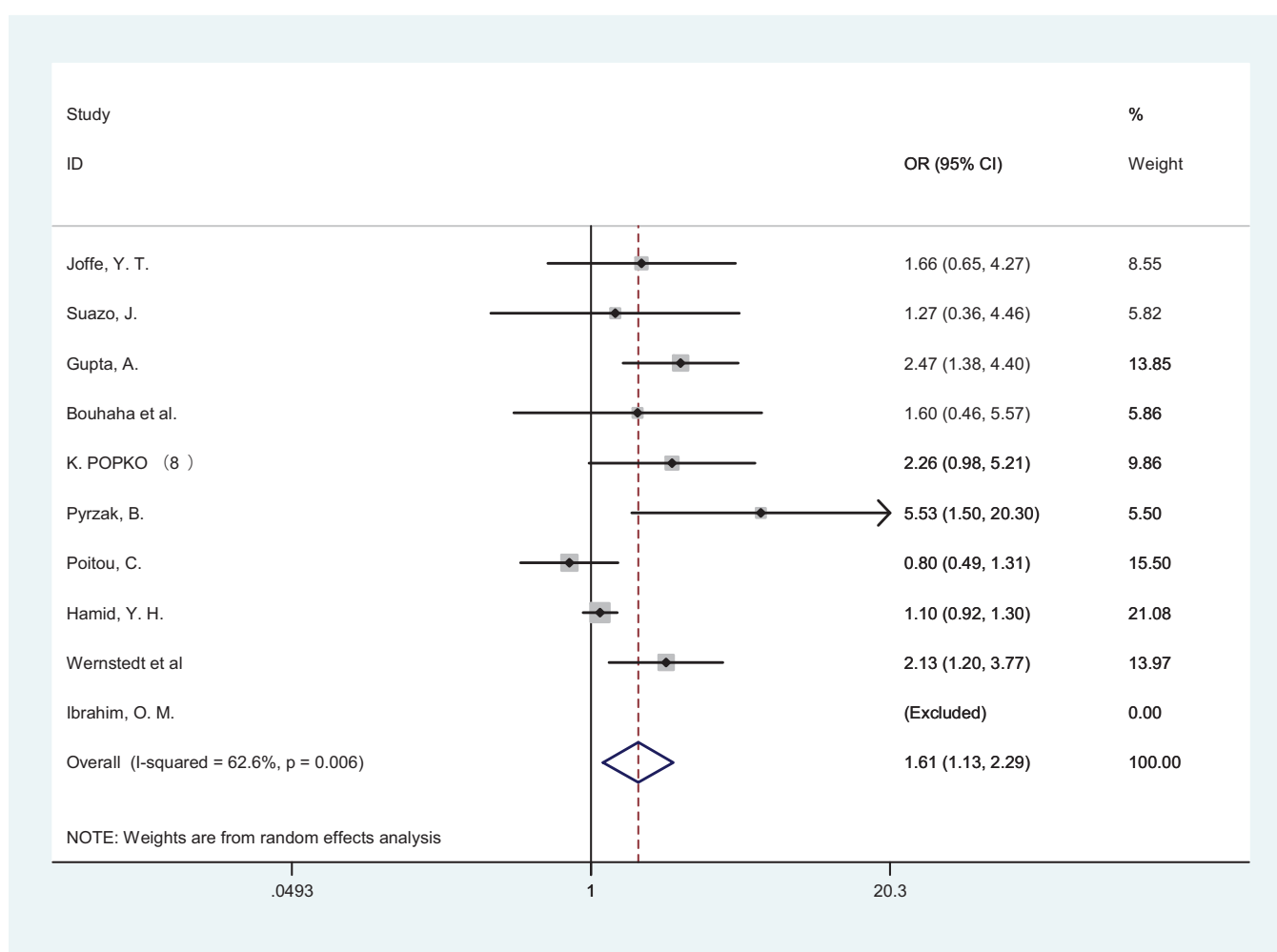
Figure 3. Forest plot of obesity risk with the IL-6–174G>C polymorphism in the homozygote model (CC vs GG).

conflicting theory, we conducted a meta-analysis that included 10 studies.

Overall, we observed that the IL6–174G>C polymorphism was associated with a statistically increased risk of obesity in all genetic models. The results are consistent with the study by Yu et al[34] who performed an analysis of 3 studies, whereas 1 of the studies was not consistent with the HWE due to confounding factors, such as race, age, and the control source. Therefore, we conducted subgroup studies by these factors. We found an increased risk between the IL-6–174G/C polymorphisms and the control source in the genotype of the homozygote model (CC vs GG), and the association between -174G/C and obesity susceptibility was increased in the community-based control.

In this meta-analysis, 10 eligible studies, including 4291 cases and 2919 controls, were identified and analyzed to provide sufficient statistical power and strengthen the reliability of our results. In addition, the limitation of language did not exist when searching, thus the chance of selection bias was low. Compared with the previous meta-analysis,[3,34] our study included more studies, and all of the studies were consistent with the HWE, which increased the statistical power and provided stable results. However, some limitations of our meta-analysis still exist. First, because the selected studies were limited to inclusion and

exclusion criteria, heterogeneity in the studies was difficult to avoid due to cofounding factors in these criteria. Meanwhile, the selection bias was increased because of limited inclusion and exclusion criteria. Second, we only screened articles published electronically in 2 large-scale databases (PubMed and Embase), which contributed to selection bias. Third, because the meta-analysis was based on published literature, we had no access to the individual data and could not adjust and evaluate the effect of confounding factors, such as smoking, age, and family history, which could affect the final results. Fourth, we have no access to relevant data to assess the potential of gene–gene and gene–environment interactions. Thus, all data of this meta-analysis were interpreted cautiously. As such, we performed Egger test and Begg funnel plot to detect publication bias, used Q test and I^2 statistics to evaluate the heterogeneity in studies, and conducted subgroup analysis carefully in order to reduce the effect of confounding factors.

In summary, in this meta-analysis, we found that the IL-6–174G>C polymorphism was associated with the risk of obesity. Considering the variety of interference factors, larger studies related to the gene–environment interactions should be performed in the future to clarify the association between the IL-6–174G/C polymorphism and obesity susceptibility.
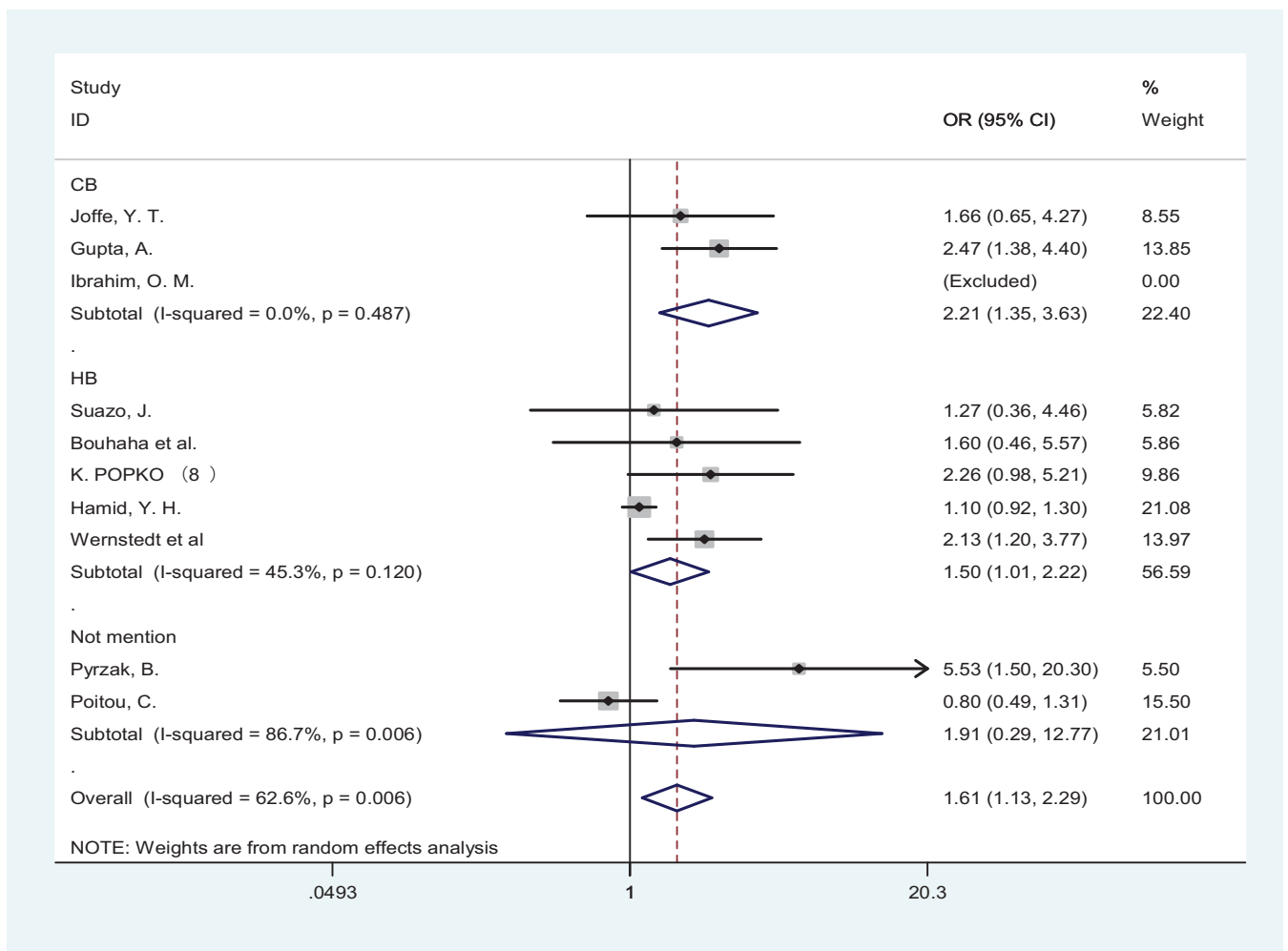
Figure 4. Subgroup results distinguished by control source in homozygote genotype (CC vs GG).
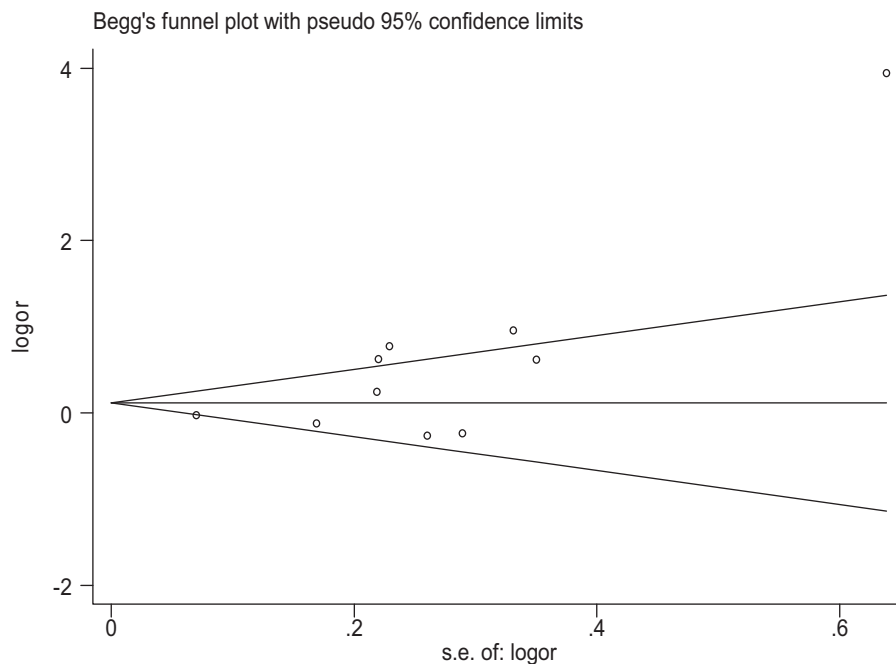

Figure 5. Begg funnel plot of the association between the IL-6–174G>C polymorphism and obesity risk under the dominant model (GC/CC vs GG).

Author contributions

Conceptualization: Man Hu, Rui Chen.
Data curation: Zhaomin Yu, Dan Luo, Haiming Zhang, Jinxiao Li.
Formal analysis: Man Hu, Haiming Zhang.
Investigation: Dan Luo.
Software: Man Hu, Fengxia Liang.
Visualization: Man Hu.
Writing – original draft: Man Hu.
Writing – review & editing: Rui Chen.

References

[1] Pigeyre M, Saqlain M, Turcotte M, et al. Obesity genetics: insights from the Pakistani population. Obes Rev 2018;19:364–80.

[2] Mauer J, Chaurasia B, Goldau J, et al. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol 2014;15:423–30.

[3] Underwood PC, Chamarthi B, Williams JS, et al. Replication and meta-analysis of the gene-environment interaction between body mass index and the interleukin-6 promoter polymorphism with higher insulin resistance. Metabolism 2012;61:667–71.

[4] Tabassum R, Mahendran Y, Dwivedi OP, et al. Common variants of IL6, LEPR, and PBEF1 are associated with obesity in Indian children. Diabetes 2012;61:626–31.

[5] Speakman JR. Functional analysis of seven genes linked to body mass index and adiposity by genome-wide association studies: a review. Hum Hered 2013;75:57–79.

[6] Valladares M, Obregon AM, Chaput JP. Association between genetic variants of the clock gene and obesity and sleep duration. J Physiol Biochem 2015;71:855–60.

[7] Joffe YT, Collins M, Goedecke JH. The relationship between dietary fatty acids and inflammatory genes on the obese phenotype and serum lipids. Nutrients 2013;5:1672–705.

[8] Popko K, Gorska E, Demkow U. Influence of interleukin-6 and G174C polymorphism in IL-6 gene on obesity and energy balance. Eur J Med Res 2010;15(suppl 2):123–7.

[9] Ouchi N, Parker JL, Lugus JJ, et al. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.

[10] De Filippo G, Rendina D, Moccia F, et al. Interleukin-6, soluble interleukin-6 receptor/interleukin-6 complex and insulin resistance in obese children and adolescents. J Endocrinol Invest 2015;38:339–43.

[11] Larder R, Lim CT, Coll AP. Genetic aspects of human obesity. Handb Clin Neurol 2014;124:93–106.

[12] Bienertova-Vasku J, Bienert P, Tomandl J, et al. No association of defined variability in leptin, leptin receptor, adiponectin, proopiomelanocortin and ghrelin gene with food preferences in the Czech population. Nutr Neurosci 2008;11:2–8.

[13] Hamid YH, Rose CS, Urhammer SA, et al. Variations of the interleukin-6 promoter are associated with features of the metabolic syndrome in Caucasian Danes. Diabetologia 2005;48:251–60.

[14] Ibrahim OM, Gabre AA, Sallam SF, et al. Influence of interleukin-6 (174G/C) gene polymorphism on obesity in Egyptian children. Open Access Maced J Med Sci 2017;5:831–5.

[15] Joffe YT, van der Merwe L, Evans J, et al. Interleukin-6 gene polymorphisms, dietary fat intake, obesity and serum lipid concentrations in black and white South African women. Nutrients 2014;6:2436–65.

[16] Suazo J, Smalley SV, Hodgson MI, et al. [Association between genetic polymorphisms of interleukin 6 (IL6), IL6R and IL18 with metabolic syndrome in obese Chilean children]. Rev Med Chil 2014;142:290–8.

[17] Gupta A, Gupta V, Singh AK, et al. Interleukin-6 G-174C gene polymorphism and serum resistin levels in North Indian women: potential risk of metabolic syndrome. Hum Exp Toxicol 2011;30:1445–53.

[18] Bouhaha R, Baroudi T, Ennafaa H, et al. Study of TNFalpha -308G/A and IL6 -174G/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population. Clin Biochem 2010;43:549–52.

[19] Popko K, Górska E, Pyrzak B, et al. Influence of proinflammatory cytokine gene polymorphism on childhood obesity. Eur J Med Res 2009;14(suppl 4):59–62.

[20] Pyrzak B, Wisniewska A, Majcher A, et al. Association between metabolic disturbances and G-174C polymorphism of interleukin-6 gene in obese children. Eur J Med Res 2009;14(suppl 4):196–200.

[21] Poitou C, Lacorte JM, Coupaye M, et al. Relationship between single nucleotide polymorphisms in leptin, IL6 and adiponectin genes and their circulating product in morbidly obese subjects before and after gastric banding surgery. Obes Surg 2005;15:11–23.

[22] Wernstedt I, Eriksson AL, Berndtsson A, et al. A common polymorphism in the interleukin-6 gene promoter is associated with overweight. Int J Obes Relat Metab Disord 2004;28:1272–9.

[23] Grallert H, Huth C, Kolz M, et al. IL-6 promoter polymorphisms and quantitative traits related to the metabolic syndrome in KORA S4. Exp Gerontol 2006;41:737–45.

[24] Illan-Gomez F, Gonzalvez-Ortega M, Orea-Soler I, et al. Obesity and inflammation: change in adiponectin, C-reactive protein, tumour necrosis factor-alpha and interleukin-6 after bariatric surgery. Obes Surg 2012;22:950–5.

[25] Kristiansen OP, Mandrup-Poulsen T. Interleukin-6 and diabetes: the good, the bad, or the indifferent? Diabetes 2005;54(suppl 2):S114–24.

[26] Saxena M, Srivastava N, Banerjee M. Association of IL-6, TNF-alpha and IL-10 gene polymorphisms with type 2 diabetes mellitus. Mol Biol Rep 2013;40:6271–9.

[27] Nelson JE, Handa P, Aouizerat B, et al. Increased parenchymal damage and steatohepatitis in Caucasian non-alcoholic fatty liver disease patients with common IL1B and IL6 polymorphisms. Aliment Pharmacol Ther 2016;44:1253–64.

[28] de Oliveira R, Moraes TI, Cerda A, et al. ADIPOQ and IL6 variants are associated with a pro-inflammatory status in obese with cardiometabolic dysfunction. Diabetol Metab Syndr 2015;7:34.

[29] Panoulasa VF, Stavropoulos-Kalinoglou A, Metsios GS, et al. Association of interleukin-6 (IL-6)-174G/C gene polymorphism with cardiovascular disease in patients with rheumatoid arthritis: the role of obesity and smoking. Atherosclerosis 2009;204:178–83.

[30] Sopasakis VR, Sandqvist M, Gustafson B, et al. High local concentrations and effects on differentiation implicate interleukin-6 as a paracrine regulator. Obes Res 2004;12:454–60.

[31] Corpeleijn E, Petersen L, Holst C, et al. Obesity-related polymorphisms and their associations with the ability to regulate fat oxidation in obese Europeans: the NUGENOB study. Obesity (Silver Spring) 2010;18:1369–77.

[32] Miranda-Vilela AL, Lordelo GS, Akimoto AK, et al. Genetic polymorphisms influence runners' responses to the dietary ingestion of antioxidant supplementation based on pequi oil (Caryocar brasiliense Camb.): a before-after study. Genes Nutr 2011;6:369–95.

[33] Eynon N, Ruiz JR, Meckel Y, et al. Is the -174 C/G polymorphism of the IL6 gene associated with elite power performance? A replication study with two different Caucasian cohorts. Exp Physiol 2011;96:156–62.

[34] Yu Z, Han S, Cao X, et al. Genetic polymorphisms in adipokine genes and the risk of obesity: a systematic review and meta-analysis. Obesity (Silver Spring) 2012;20:396–406.