

The Association between IL6-174 G/C Gene Polymorphism and Obesity: A Systematic Review and Meta-analysis

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Abstract

Background: The interaction between genetic and environmental factors has resulted in growing prevalence of obesity around the world. IL6-174 G/C gene polymorphism is widely studied as the involved factor in developing obesity.

Objectives: The aim of the present study is to evaluate the relationship between Interleukin 6-174 G/C promoter gene polymorphism and obesity in a systematic review and meta-analysis study.

Methods: In the present study Science Direct, Medline, Embase, Google Scholar, PubMed and SID search engines have been searched until March 2016. Articles were evaluated using the key words IL6 plus polymorphism or mutation or variant and adiposity, BMI and obesity. Data was analyzed using STATA software (12th version). OR ratio was calculated with 95% confidence interval to evaluate the strength in link between IL6 gene and obesity. *Heterogeneity* was calculated using I² test. Articles bias was evaluated using funnel plot versus standard error (SE). The asymmetry degree of the funnel plot was tested using linear regression tests of Egger's and Begg's.

Results: Generally, 12 articles entered systematic review and 6 articles entered final meta-analysis. After data was extracted, the total case group consisted of 5343 people and control group consisted of 3449 people. The odds ratio was estimated for additive model CC vs GC (OR= 1; CI: 95%: 0/9-1/12), recessive model CC + GC vs GG (OR= 1/04; CI: 95%: 0/95- 1/15) and for dominant model (OR= 1/10; CI: 95%: 1-1/21). Also the results showed that there is a statistically significant relationship between IL-61-74 G/C gene polymorphism and obesity (P<0/05).

Conclusion: Generally, the results of the present study show that the IL-6 -174 G/C gene polymorphism is related to the obesity.

Keywords: IL6 gene, Meta-analysis, Obesity

1. Background

Obesity is worryingly growing all over the world and is related to the prevalence of many diseases like diabetes, cardiovascular disease and cancer (1). It is well proved that genetic factors can determine how susceptible someone is to obesity in relation with environmental factors (2). With growing development in genetic science and the diversity of human genome, many involved genes in obesity have been identified (3). Generally, obesity can be considered as an inflammatory status (4) which is simultaneous with immune system chronic activation (5). In obesity, markers of inflammation are disturbed and one of the best ways to determine fat tissue regulatory mechanism is the discovery of genetic relationship between inflammatory cytokines and obesity (6). Among different cytokines, IL6 is a pre-inflammatory cytokine expressed in different tissues like: fat tissue, muscles, immune cells and hypothalamus and it is related to regulating energy balance of the body (7). To prove this, it has been said that recycling and high level of IL6 in Adipose tissue are related to obesity and Caul fat (8). Also many *single-nucleotide* polymorphisms have been identified for IL6. Among them, G174C polymorphism has been identified in 174 G/C promoter gene which affects transcription regulation (6). Genetic studies among different populations showed that IL-61-74 G/C

promoter gene polymorphism affects transcription and cytokine level in plasma. The relationship between normal changes in IL6 gene and obesity has been evaluated in many studies focused on 174 G/C (rs 1800795). Generally, the results of these studies in evaluating a relationship between IL-61-74 G/C promoter gene polymorphism and obesity are contradictory. Some studies point to a significant relationship between 174 G/C IL6 gene and obesity (5,9,10). Some others could not prove this (11-13). Thus our aim is to evaluate the relationship between 174 G/C IL6 and obesity in human with a systematic and meta-analysis review from published results to prove this relationship in a larger population.

2. Objectives

The object of present study was to evaluate the relationship between 174 G/C IL6 and obesity in human by systematic review and meta-analysis approach.

3. Methods

3.1. Research Method

In order to find English and non-English articles Medline, Cochran database, ISI web of knowledge, PubMed, Embase, ScienceDirect, Google Scholar and

(Scientific Information Database-SID) databases were evaluated until March 2016. To make sure the references of the articles were also searched. The key words using (MeSH) Medical Subject Heading database included: IL6 plus polymorphism or mutation or variant and Obesity, BMI and obesity. Also a search with no language limitation was conducted. We also included "grey literature" such as abstracts, letters, and articles presented at relevant conferences and meetings. The literature retrieval was performed independently by three investigators (Ali Khazani, Reza Kazemi, and Zohreh Mazaheri) and discrepancies were resolved by reaching a consensus among the investigators. If a consensus could not be established, a fourth reviewer (Mostafa Bahrami) was consulted to resolve the discrepancy.

3.2. Criteria's for Choosing Articles

We evaluated the articles with the following criteria:

1- The relationship between 174 G/CIL6 and obesity was evaluated. 2- The number of control and case group members was stated. 3- Genotype distribution was available in case and control groups and to determine the odds ratio (OR), confidence interval (CI) of 95% was considered. 4- Original researches 5- The sample was taken from adult population. 6- Studies were designed as clinical trials and randomization and controlled. 7- Articles considering 174 G/CIL6 gene polymorphism were used as the independent variable.

3.3. Exclusion Criteria

The studies with the following features were excluded: 1- reviews and letters to editors 2- review reports 3- repeated or overlapping studies 4- studies lacking enough information for extracting data 5- Studies with samples of healthy obese individuals.

3.4. Data Extraction

Two authors extracted data from all eligible articles using PRISMA checklist for systematic and meta-analysis reviews in 2009. Disagreements were settled after talking of authors and taking advice from a third party. Standard data form was used for gathering data which included: author's name, publish year, the original country of the subject ethnic, type of genotype evaluation, total members in case and control groups, genotype distribution in case and control groups and dominant gene frequency in case and control groups (Figure 1 and Table 1).

3.5. Quality assessment

Methodological quality of the included studies was independently assessed by two authors using the Newcastle-Ottawa Quality Assessment Scale (NOS) criteria (14). Using this method, each study was judged on standard criteria by two authors (Rahmati M and Mirnasouri R) and subsequently categorized

based on three factors: (1) subject selection: 0-4 points; (2) comparability of subject: 0-2 points; (3) clinical outcome: 0-3 points. Studies that were awarded 5 stars or more could be considered as of medium to high quality (15). Moreover, the P value of Hardy-Weinberg equilibrium (HWE) was assessed with the χ^2 test among the control genotypes.

3.6. Evaluating Statistical Relationship

The odds ratio (OR) with 95% confidence interval (CI) was used to evaluate the strength in 174 G/CIL6 gene and obesity relationship. In this review the correlation between 174 G/CIL6 gene polymorphism was evaluated using additive model (CC vs GG), dominant model (CC+ GC vs GG) and recessive model (CCvsGC+ GG). Heterogeneity was calculated using I^2 test. I^2 index from 25%, 50% and 75% showed low, medium and high level of heterogeneity (16,17). Articles using funnel plot were evaluated versus Standard error (SE). The asymmetry degree of the funnel plot was tested using linear regression tests of Egger's and Begg's (18). If articles were TEP heterogeneous ($I^2 > 50\%$), random effect model was used, otherwise fixed effect model was used. Hardy-Weinberg equilibrium (HWE) is an application of the binomial theorem to population genetics and stating that the genetic variation in a population will remain constant from one generation to the next in the absence of disturbing factors. The assessment of departure from HWE is performed by chi-square test in the controls because a deviation from HWE in the cases might indicate a genetic association, and the difference of HWE between the cases and the controls can be used to test for association. STATA software 12th edition was used for analyzing all data and P-value was considered as the significance level.

4. Results

4.1. Evaluating the Quality of Studies

In this study, the obesity index was BMI ≥ 25 (19,20). The case group included a total number of 5343 people and the control group included a total number of 3449 people. All the six studies were assessed in terms of quality according to the Newcastle-Ottawa Scale and most studies scored 5 stars or more, suggesting a moderate to good quality (Table 2). There was no significant relationship between 174 G/C polymorphism in additive model and recessive model but the relationship was significant in dominant model (P: 0/933, 0/391 and 0/04 respectively). For additive model OR=1 CC Vc GC (Confidence interval 95%, 0/9-1/12), for recessive model OR=1/04 CC Vc GG (Figure 2) (Confidence interval 95%, 0/95-1/15), and for dominant model OR= 1/10 CC Vc GG (Confidence interval 95%, 1-1/21) were reported. Generally, the results show that there is a significant relationship between CC genotype in IL-6 174 G/C gene polymorphism and

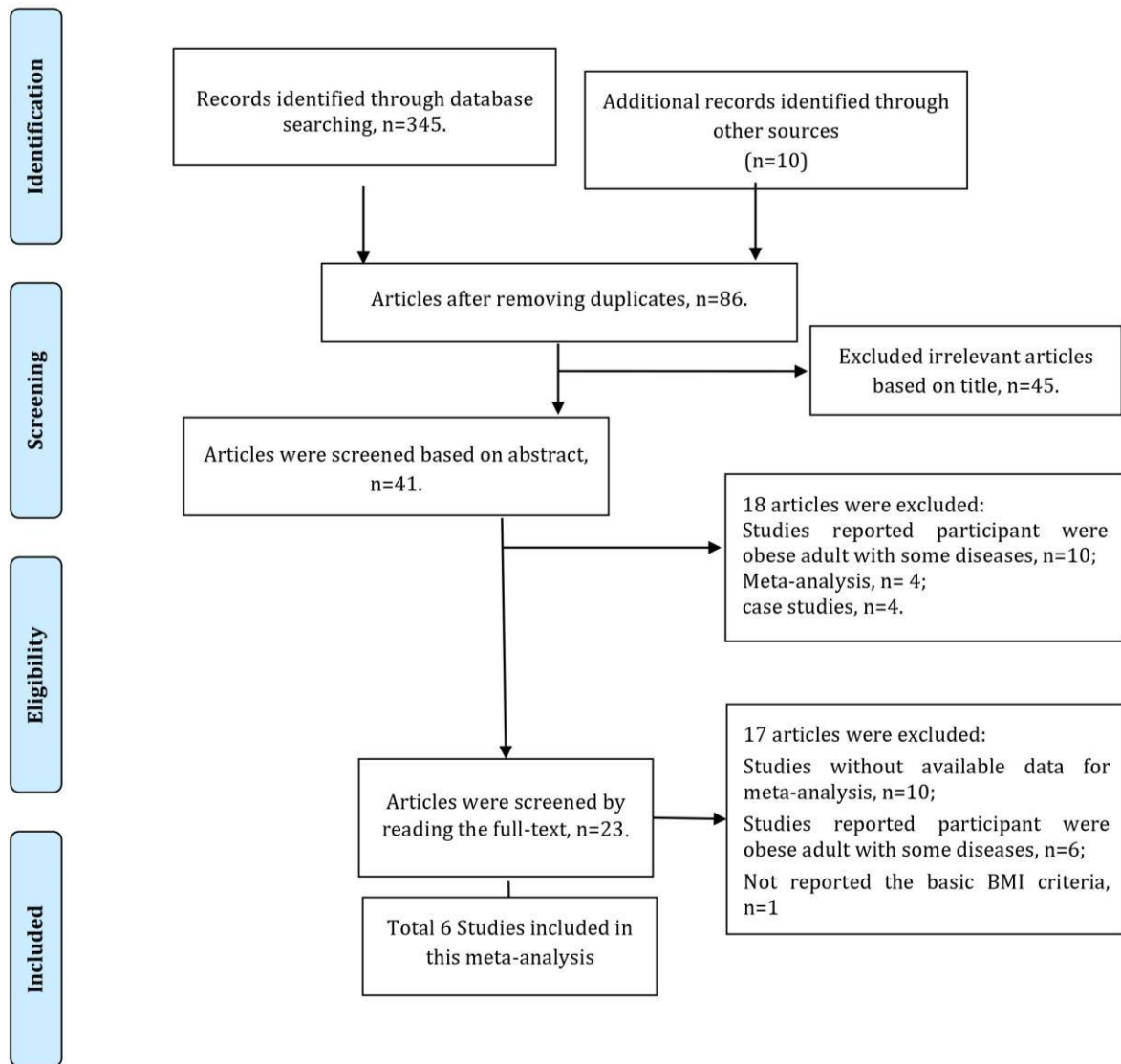


Figure 1. Literature search and study selection

Table 1. Features of used articles for genotype to evaluate the relationship of IL6-174 G/C gene polymorphism.

Author	Publich year	Country	Case group members	Control group members	Genotype frequency Case group CC/GC/GG	Genotype frequency Control group CC/GC/GG	P _{HWE}
Yael T. Joffe	2014	South African	120	146	12/26/82	8/47/91	0.781
DanutCimponeriu	2013	Romania	150	150	11/61/78	3/58/89	0.814
Klipstein	2006	Canada	344	344	65/177/92	42/180/112	0.708
Y. H. Hamid	2005	Caucasian Danes	2566	1661	574/1275/717	416/771/474	0.509
Christine Poitou	2005	France	445	214	61/192/192	34/94/86	0.947
Jeffrey W.Stephens	2004	United Kingdom	1718	934	328/868/522	158/452/324	0.605

Abbreviations: P_{HWE}, the P value of Hardy-Weinberg equilibrium.

Table 2. Quality assessment conducted according to the Newcastle-Ottawa criteria for all the included studies in this meta-analysis.

First author	year	Quality indicators		
		Selection	Comparability	Outcome
Yael T. Joffe	2014	****	**	**
DanutCimponeriu	2013	****	**	**
Klipstein	2006	****	*	***
Y. H. Hamid	2005	**	*	**
Christine Poitou	2005	****	*	**
Jeffrey W.Stephens	2004	****	**	**

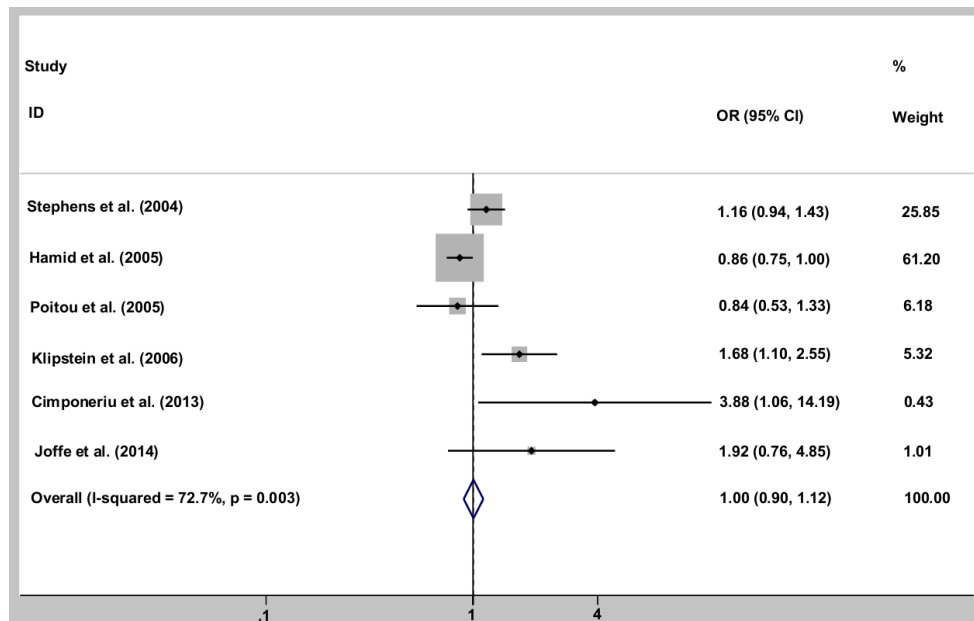


Figure 2. Meta-analysis Stock diagram for the relationship between CC additive models versus CC genotype in IL-6 174 G/C gene polymorphism with obesity.

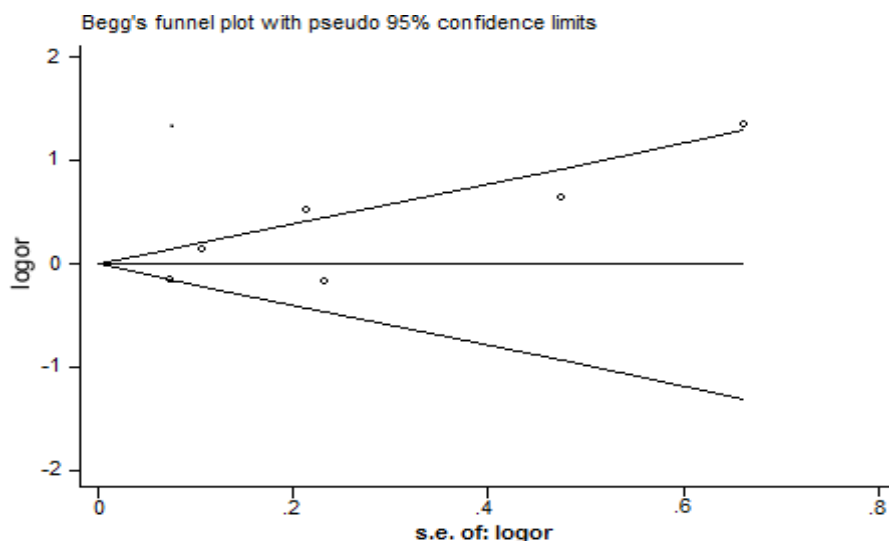


Figure 3. Publish bias for CC additive model versus GG

obesity. In the following pages, the related diagrams to each model are presented.

Regarding I^2 index, we can conclude that the studies are heterogeneous ($I^2=72/2\%$) and to combine ORs in studies, random effect model is used, so OR=1 was estimated (Confidence interval 95%, 0/9-1/12). Also, because confidence interval crosses line 1 (shown in rhombus shape), there is no significant relationship between additive mode IL-6 174 G/C gene polymorphism and obesity ($P=0/933$).

The results of [figure 3](#) show that in such studies,

bias had no effect and this has been presented in symmetry in funnel plot. The size of circles represents the size of the studies (the bigger the circle is, the larger the sample would be). Also, the reported P from Begg's test equals 0/154 and the Egger's test result equals 0/098 showing that the bias in the published articles was not statistically significant.

Regarding I^2 index, we can conclude that the studies are heterogeneous ($I^2=61/0\%$) and to combine ORs in studies, random effect model is used, so OR=1/04 was estimated (Confidence interval 95%,

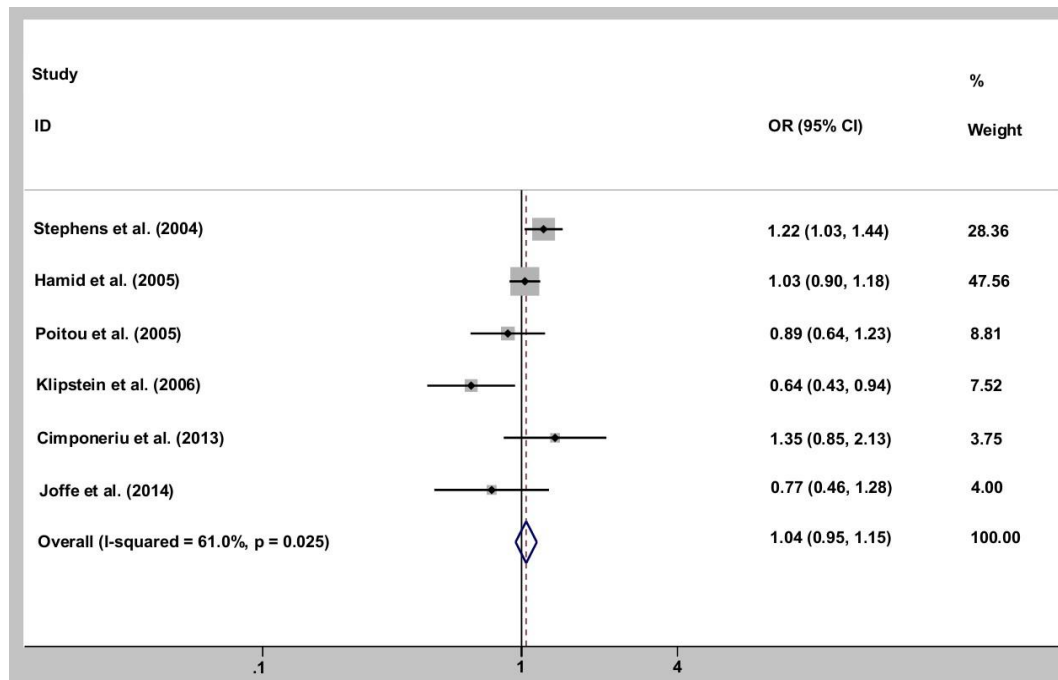


Figure 4. Meta-analysis Stock diagram for the relationship between CC recessive model versus GC+GG in IL-6 174 G/C gene polymorphism with obesity.

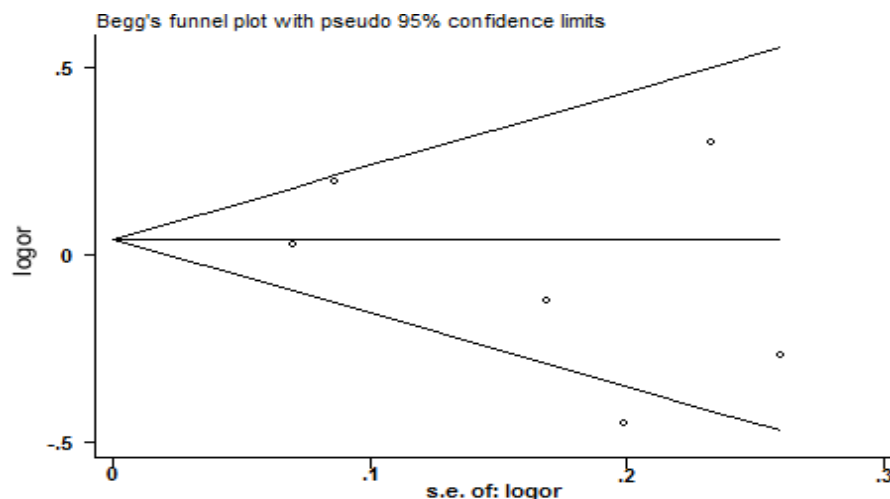


Figure 5. Publish bias for CC recessive model versus GC+GG

0/95-1/15). Also, because confidence interval crosses line 1 (shown in rhombus shape), There is no significant relationship between recessive mode CC versus GC+GG in IL-6 174 G/C gene polymorphism and obesity ($P=0/391$).

The results of figure 4 and 5 show that in such studies, bias had no effect and this has been presented in symmetry in funnel plot. The size of circles represents the size of the studies. Also, the reported P from Begg's test equals 0/298 and the Egger's test result equals 0/350 showing that the bias in published articles was not statistically significant.

Regarding I^2 index, we can conclude that the studies are heterogeneous ($I^2=42/7\%$) and to combine ORs in studies, random effect model is used, so $OR=1/10$ was estimated (Confidence interval 95%, 1-1/21). Also, because confidence interval doesn't crossed line 1 (shown in rhombus shape), There is a significant relationship between dominant mode CC versus GC+GG in IL-6 174 G/C gene polymorphism and obesity ($P=0/046$).

The results of figure 6 and 7 show that in such studies bias had no effect and this has been presented in symmetry in funnel plot. The size of circles

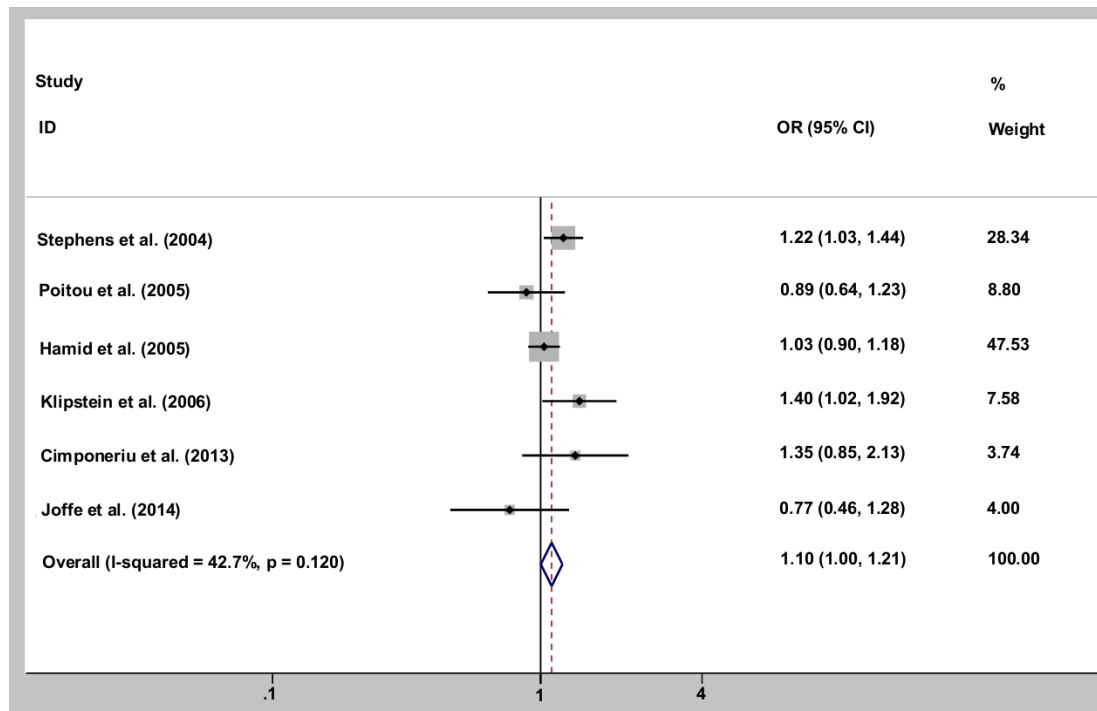


Figure 6. Meta-analysis Stock diagram for the relationship between CC+GC dominant model versus GG in IL-6 174 G/C gene polymorphism with obesity.

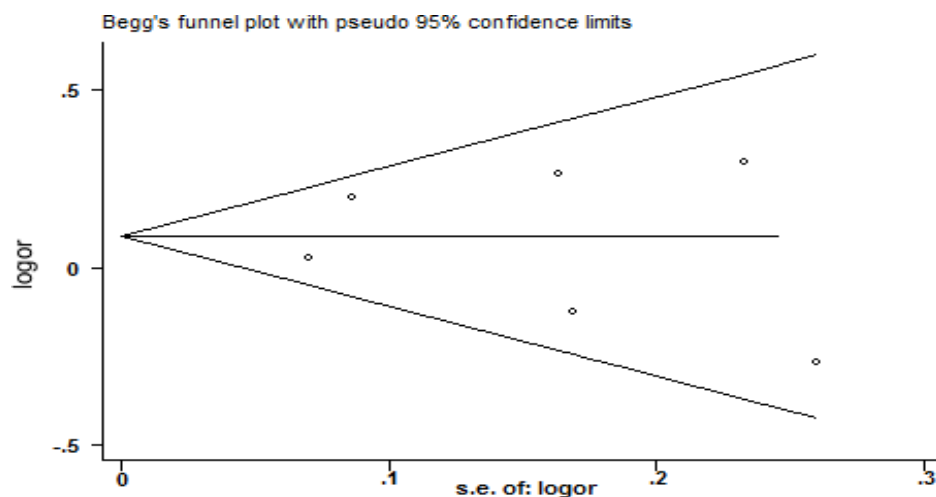


Figure 7. Publish bias for CC+GC dominant model versus GG

represents the size of the studies. Also, the reported P from Begg's test equals 0/543 and the Egger's test result equals 0/956 showing that the bias in published articles was not statistically significant.

5. Discussion

The most important factors for controlling weight and body composition are well identified in cooperation with environmental factors (5). Thus, the interaction between functional gene polymorphism

and environmental factors plays an important role in obesity. Presence of many obesity genes and environmental factors like high carbohydrates and less activity is related to higher risk of obesity in a population carrying polymorphism (21). IL6 gene is located in the short arm of chromosome 7 (7P21). Functional G/C polymorphism is described in -174 [rs1800795] locations on 5' side (11). Presence of G gene is related to increasing transcription responses in vitro (11) and in vivo (22). As a pre-inflammatory cytokine, IL6 gene is expressed in different tissues

like fat tissue, muscles, immune cells and hypothalamus and is related to energy regulation in human body (7). G174C polymorphism is identified in IL6 gene promoter which affects transcription regulation (6). It is also involved in Glucose and lipid metabolism (23) and it can increase the serum level of triglyceride and sugar. It also triggers anterior hypothalamus-pituitary axis which could be important for related activities to obesity side effects (24,25). To prove this, it has been said that recycling and high level of IL6 in Adipose tissue are related to obesity and Caul fat (8). Meanwhile, there are contradictory results in the literature, which could be a result of small sample size or the ethnic of subjects. But the results are controversial. Thus, our aim is to evaluate the relationship between 174 G/CIL6 and obesity in human with a systematic and meta-analysis review. In the present study, a significant relationship was found between IL6-174 G/C gene polymorphism and obesity but such a relationship was not found in additive and recessive models. Cimponeriu et al. (2013) showed that 174 CC genotype was more frequent in obese patients and CC and TTV genotype can be related to obesity among women (26). Berthier et al. (2003) conducted a study on IL6-174G/C gene polymorphism and its relationship with obesity indices and found that in men, 174G/C polymorphism is related to some body composition indices and glucose homeostasis and insulin (19). Our results were in consistent with theirs and were different from the results by Hamid et al. (2005) who showed that single-nucleotide polymorphisms and genotype composition or haplotype promoter IL6 can be linked with some metabolic syndrome features in the population (27). Poitou et al. (2005) showed that lose weight happened with increasing IL6 concentration in carrying 174CC genotype. While CG, GG genotypes happened with IL6 decrease (28). In a study conducted by Rostami et al., (2010) on the Iranian subjects, the results showed that IL6-174G/C gene polymorphism is linked with BMI and WHR and it is not a risk factor for obesity in Iran (5). Stephan et al. (2004) conducted a research on two diabetic and non-diabetic groups and showed that gene 174 C was in individuals with higher BMI among type-2 diabetes but among healthy individuals with average BMI (26.1 kg) no difference was observed in genotype (20).

To date, four studies have been conducted in the form of systematic and meta-analysis to evaluate the relationship between 174 G/CIL6 gene and obesity. Qi et al. (2007) studied 26944 people in the form of systematic and meta-analysis review and showed that there is no relationship between 174 G/CIL6 polymorphism and BMI as indices adiposity (6). Although in this study no border for obesity has been considered, average BMI was evaluated 24/4+3/5 among people showing the relationship

between 174 G/CIL6 polymorphism and BMI was not fully done among obese individuals. Huth et al. (2009) conducted a systematic and meta-analysis research and found that there is no evidence of relationship between 174 G/CIL6 and BMI. The point in this study is that all 17 reviews in this meta-analysis were chosen among the studies that were conducted on type-2 diabetes patients (29). Yu et al. (2012) conducted a meta-analysis study to evaluate the relationship between adipokines 7-polymorphism and obesity risk and stated that there is a significant relationship between 174 G/CIL6 polymorphism and obesity (30). But in this meta-analysis, only 3 studies were evaluated (7,31,32). Among them, one sample was taken from type-2 diabetes patients (32) and samples of another study were taken from hypertension patients (7). Also Underwood et al. (2012) showed that there was a significant relationship between 174 G/CIL6 and insulin resistance among Caucasian individuals with hypertension. Also meta-analysis results of this study showed that there was a statistically significant relationship between 174 G/CIL6 and BMI and insulin resistance among hypertension patients (33). One of the most important limitations of this study was the almost small sample size (n=10280 and focuses on hypertension individuals).

In this review, 6 studies entered the meta-analysis with 5343 individuals in case group and 3449 individuals in control group. Heterogeneity among studies existed in two additive and recessive models. The general resource of this heterogeneity could be diversity of ethnics, sample size, genotype errors and design errors. We assume that all potential resources must be considered. The strength of this meta-analysis is as follows: 1- Out sample consisted of healthy individuals; 2- there was no evidence of publish bias in any of the 4 models showing observed results sustainability. Meanwhile, some limitations were inevitable: 1- This meta-analysis only included published studies and non-published or ongoing studies were not included; 2- Chinese and Japanese studies were not available; 3- This meta-analysis only studied the relationship between 174 G/CIL6 gene and obesity and we couldn't study the role of environmental factors and their interaction with the body; 4- We only studied the relationship between 174 G/CIL6 gene and obesity and we couldn't study other genes polymorphism related to obesity and 5- This meta-analysis only studied interleukin 6-174 G/C promoter gene polymorphism and its relationship with obesity.

6. Conclusion

The present study shows that there is a relationship between CC genotype IL6-174 G/C gene polymorphism and obesity. Because obesity is a complex feature and there are many factors involved,

we must be cautious in presenting the results. Considering the limitations of the study, we suggest other studies with larger sample size, and more studies including more populations have to be conducted in the future.

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The results described in this paper were part of student thesis.

Conflicts of interest

The authors declare that there was no conflict of interest.

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