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Association of interleukin-6 polymorphisms with obesity: A systematic review and meta-analysis

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ABSTRACT

Obesity is a common metabolic disorder with increasing trend all around the world. Owing to the role of pro-inflammatory cytokines on obesity, we aimed to investigate the role of interleukin-6 (IL-6) polymorphisms on risk of obesity.

Electronic literatures were searched in Web of Science, PubMed, Embase, and Scopus. The references of relevant reviews and included studies were also manually checked. All types of observational studies from 1 January 1992 to 28 February 2018 were included. Odds ratio (OR) was estimated by fixed and random effect model. Subgroup analysis was carried out based on age statues.

Pooling analysis of eligible studies have been considered for rs2069845 and rs1800796, and no significant results were observed. Minor allele of IL-6 rs1800797polymorphism decreased the risk of obesity/overweight in allelic 0.74 (0.59–0.92), dominant 0.65 (0.49–0.85), and over-dominant 0.66 (0.51–0.87) models. Fourteen eligible studies were included for rs1800795. According to BMI, C allele showed increased risk of obesity in genetic models containing homozygote model 1.47 (1.02–2.12) for body mass index (BMI) ≥ 25 vs. BMI < 25, recessive model 1.32 (1.07–1.63) for BMI ≥ 30 vs. BMI < 25, and homozygote model 1.35 (1.10–1.66) for BMI ≥ 30 vs. BMI < 30. In overall definition of obesity more significant results were observed, including homozygote model in obese vs. normal 1.71 (1.14–2.56). Similarly, subgroups analysis revealed additional significant results.

Minor alleles of rs1800795 raised and rs1800797 reduced the risk of obesity, while rs1800796 and rs2069845 may not be associated. However, more observational studies are recommended to confirm these results.

1. Introduction

Obesity is a common disease and considered as a disproportionate increase in adipose tissue [1]. In recent decades, the prevalence of obesity has been doubled in many countries and is continuously increased in most parts at the rest of the world [2]. It is estimated that more than 50% of the world population could be obese or overweight by 2030 [3]. Obesity is strongly associated with a pro-inflammatory state, vascular dysfunction, multiple organ damage, thrombotic disorders, high blood cholesterol and imbalances in metabolic homeostasis. These physiological effects ultimately lead to the development of a range of morbidities, including cardiovascular disease, type 2 diabetes, osteoarthritis, gallbladder disease and cancers [4–6].

Obesity as a multifactorial disease is caused by different factors such as genetic and environmental. More than 40 percent of the body mass index (BMI) variations are related to genetic factors [7]. Recent studies provide significant evidence for risk loci of obesity and its related traits [8,9], which plays key role in understanding the pathophysiology of obesity. Many studies have revealed that polymorphisms in some protein-coding genes are involved in biological processes that influence body composition, body weight regulation, and obesity. For instance the first intron of the fat mass and obesity-associated (FTO) gene (rs9939609 and rs17817449 variants), iroquois homeobox3 (IRX3) gene (rs3751723), methylene tetrahydrofolate reductase (MTHFR) gene

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(C677T), adiponectin gene (ADIPOQ) gene (rs266729) and APOA2 (c.-492T > C) polymorphism are correlated with obesity [10–13].

Accumulation of the pro-inflammatory macrophages in adipose tissues is one of the hallmarks of obesity, as a chronic inflammatory disease, this condition prominently release cytokines [14]. IL-6 is a pleiotropic inflammatory cytokine linked to obesity and has been considered as a "metabolic hormone" which affects glucose, protein and lipids metabolism [15].

The positive and negative associations between obesity and IL-6 polymorphisms have been demonstrated in previous studies. For instance; some studies indicate the association between IL-6 polymorphisms in multiple locus rs2069845 [16], rs1800796 [17], and rs1800795 [18] with obesity/obesity related traits while the others found no association for rs2069845 [19], rs1800796 [20], rs1800797 [17], and rs1800795 [16]. Association between IL-6 polymorphisms and obesity has been investigated in two previous review studies. A systematic review on association between adipokines genes and obesity has also been previously reported in 2012 [21] that included limited studies. In addition, the control group was not healthy subjects (for instance in Bouhaha et al), and also defined obesity as BMI ≥ 25. Another is a meta-analysis about rs1800795, in 2018 [22], which cannot be considered as a reliable meta-analysis, based on multiple critical reasons. It contains several critical mistakes in study inclusion, data extraction, searching relevant studies, obesity definition, and also some limitations in data analysis. In this case, Suazo et al [23] only studied the obese subjects but which was not eligible for inclusion. Obese children with and without metabolic syndrome have been compared in this study. The most important mistake have been taken place about Hamid et al [20], authors of the meta-analysis that changed case and control genotypes, related numbers of the cases in both the control and original article and vice versa. Furthermore, original genotype of the control group was not in Hardy–Weinberg equilibrium (HWE) [20]. Bouhaha et al [24] also included T2DM patients in healthy control group. In addition, there were several other problems in their meta-analysis, for example, people with BMI more than 25 (overweight) were considered as obese.

Till now, the relation between IL-6 polymorphisms and the risk of obesity has not been clearly defined. Owing to the significance of IL-6 in obesity and inflammation, and lack of a comprehensive study, this study seeks the following questions; what are the relationships between IL-6 polymorphisms, and the risk of obesity/obesity related traits? Which polymorphisms show more relevant association with susceptibility to obesity/obesity related traits? Consequently, we aim to systematically search and investigate the relation between obesity and polymorphisms in the IL-6 gene in order to perform a comprehensive meta-analysis based on obesity and its traits.

2. Material and methods

2.1. Flow diagram

The methods of this systematic review was developed according to the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist [25]. The PRISMA 2009 flow diagram [26] was used to depict the flow of process and numbers of articles being reviewed through the different phases of our systematic review (Fig. 1).

2.2. Registration

The protocol of this systematic review was registered in International Prospective Register for Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/), with registration number ID = CRD42018098907.

2.3. Inclusion and exclusion criteria

Any observational studies (case-control, cross-sectional, and cohort) describing the association between IL-6 related polymorphisms and obesity/obesity related factors, were eligible for inclusion in this systematic review. All other studies such as interventional, diagnostic value, review articles, opinions, animal studies, commentaries, duplicate publications (the most recent and complete version will be used), anonymous reports were not included. Primary documents were screened according to this review objective and PECO criteria (Participants, Exposure, Comparisons, and Outcomes). Studies with deviation from adjusted HWE and with lack of primary data or insufficient data for estimating odds ratios and 95%CI were excluded. The studies which possess only obese people were excluded. Studies along with limitation in grouping (normal and overweight/obese) were excluded, for instance the studies investigating difference in mean of BMI without any classifications, or considering association of IL-6 polymorphisms with weight gain or fat mass were excluded. Obesity related traits, BMI, waist-to-hip ratio (WHR), Waist circumference (WC), were included. Subjects included as control group should be clearly divided in mentioned studies (according to the above traits) based on normal weight, and obesity/overweight. Controls were also not restricted to healthy people.

This study imposed a restriction on publication date from 1 January 1992 to 28 February 2018. This restriction was based on the reason that most recent publications were relevant studies.

There was no restriction on the language of relevant documents. Other languages except English were translated by free language translation services or by a translator. Participants are in both genders (female or male), with no limitation for age and ethnicity. All genotyping methods were included.

2.4. Electronic searches

In order to identify the relevant papers on IL-6 miRNA polymorphisms and obesity, online systematic search of literature was performed on PubMed, Web of Science, Scopus, and Embase. A total of 7251 documents were identified, which 2928 of them were duplicate publications and were excluded. Search syntax was performed by combine medical subject headings (MeSH, from PubMed), Emtree terms (from Embase), and using free text words. Key search terms were "obesity", "Interleukin-6", "Polymorphism, Single Nucleotide" and their equivalents. Boolean operators "OR" and "AND" were used for combining search terms. Detailed PubMed search syntax is presented in supplementary Table 1. Also, quality assessment has been applied by Newcastle-Ottawa Scale (NOS) method [27].

2.5. Searching other sources

To identify any additional relevant studies, we also manually checked the references of included primary studies (hand searching), references of the relevant review.

2.6. Screening/Eligibility/Included studies

Screening and eligibility were performed in three following steps. First, All 4323 identified documents were imported into Excel database and were numbered. Second, two reviewers independently scrutinized relevant documents by checking the title and/or abstract (M.G and S.S.). They categorized each document in one of the included, excluded and borderline groups. Included documents by both of the reviewers were selected for full-text eligibility assessments. Excluded documents were eliminated from the study. Inclusion or exclusion of other documents was resolved by consensus strategy and/or third person strategy. Accordingly, 72 documents were included based on eligibility assessment. Finally, full texts eligibility for remained documents

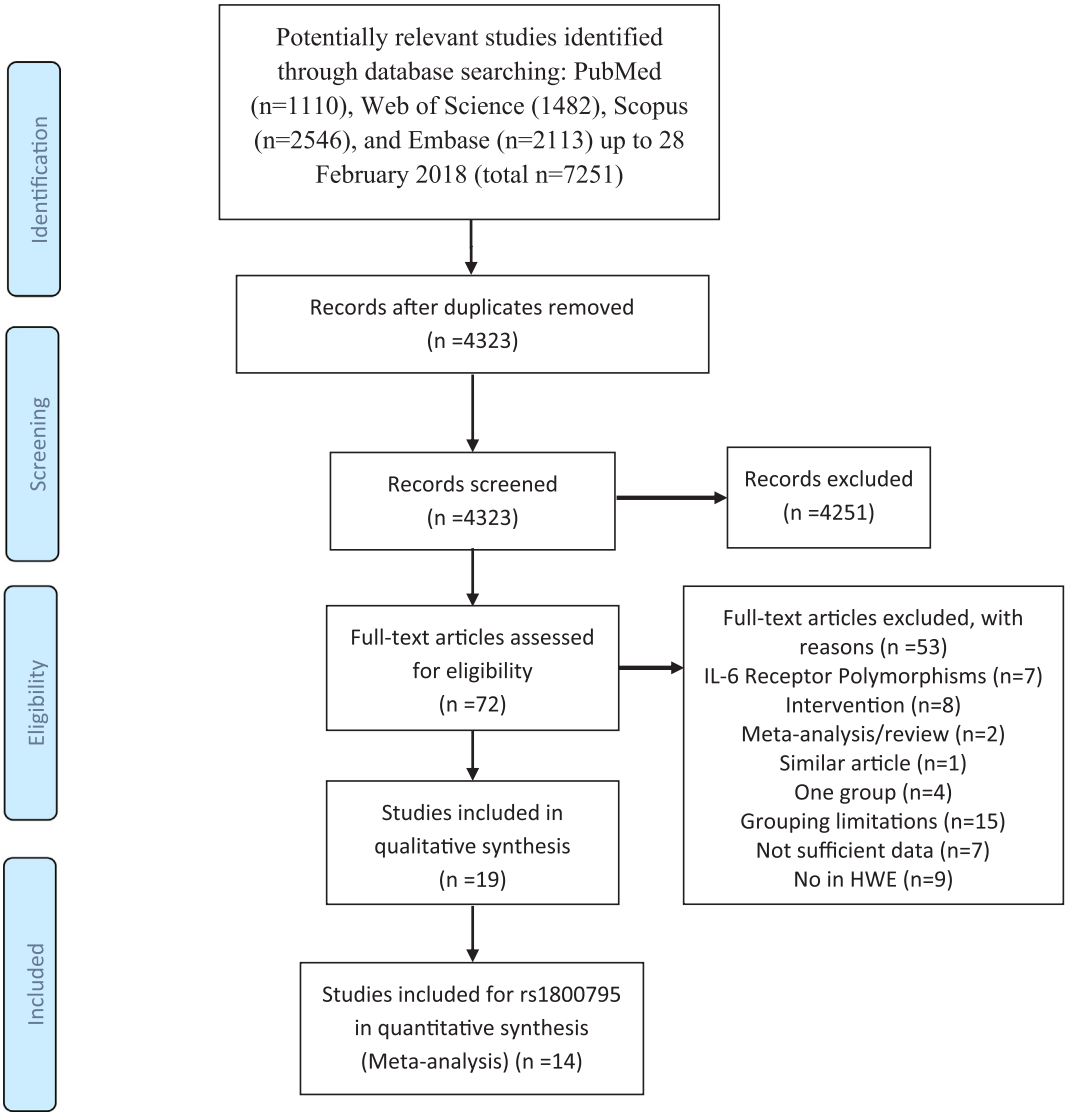


Fig. 1. The flow diagram of the screening possess.

independently were scrutinized by two reviewers. Eligibility checking was made according to the inclusion criteria described in the type of study and type of participant (see above). Agreement and disagreement strategies described in screening were also carried out for eligibility. Eligibility assessment was carried out using data extraction forms and methods of dealing with missing data that are described in the following sections. However, a total 19 studies were qualified for being included in this systematic review and adequate data were included in final meta-analysis for quantitative synthesis. Other studies were excluded based on described reasons in Fig. 1. Fourteen included studies were related to rs1800795.

2.7. Data extraction and management

First, the data extraction was performed by two reviewers (M.G. and S.S.) for included documents using the forms desinged to obtain the following data: (1) Study data: the name of first author, country of the study implementation, year of publication, study design, (2) Other data: age status, ethnicity, type of polymorphism, genotyping methods, obesity trait, genotyping data, minor allele frequency (MAF), sample size, source of controls (CP; clinical base or PB; population base), odds ratio (OR),95% CIs and other related raw data.

Second, data extraction forms and full texts of eligible documents were evaluated by two reviewers (M.G. and S.S.). They independently extracted the original data based on designed formats. Disagreements between reviewers were resolved by two strategies described in screening. Plot digitizer (http://arohatgi.info/WebPlotDigitizer/app/) used to assess the exact data presented in the charts.

2.8. Dealing with missing data

The missing, incompletion or unclearness was resolved by contacting the corresponding author(s). Three emails were sent. If we did not receive any response, the document was excluded from the meta-analysis.

2.9. Analysis

2.9.1. Meta-analysis

Meta-analysis was performed when sufficient studies were included. Meta-analysis was done by using R program (3.5.2) and STATA software V.13 (StataCorp LP, College Station, Texas, USA). Odds ratio (effect size) and 95% CI were assessed to investigate the associations between each polymorphism in IL-6 gene and obesity. The meta-analysis was done by using five following genetic models: dominant model, recessive model, homozygous model, heterozygote model, and allelic

model. Level of heterogeneity between primary studies was obtained by the Cochran's Q test ($p < 0.05$ is statistically significant), random effect model was performed for significant Cochran's Q and other non-significant results were interpreted with a fixed effect model. Subgroup analysis was applied based on age status.

2.9.2. Sensitivity analysis

Sensitivity analyses were performed with leave-one-out method by excluding studies one by one to investigate the effect of each primary study on the final meta-analysis results.

2.9.3. Assessment of reporting biases

The potential publication bias in primary studies was assessed by Begg's and Egger's tests.

3. Results

3.1. Characteristics of eligible studies

A total of 7251 articles were retrieved based on our systematic search. The flow diagram of the screening process is presented in Fig. 1. Finally, 27 observational studies were included. These studies were related to six IL-6 polymorphisms (rs1800795, rs1800796, rs1800797, rs2069845, IL-6 190 C/T, and rs1554606).

3.2. Quantitative data synthesis

3.2.1. IL-6 rs2069845 polymorphism and risk of obesity

Four studies were related to rs2069845. Two of them did not have sufficient data. Meta-analysis for two other studies does no show significant results (results not shown).

3.2.2. IL-6 rs1800796 polymorphism and risk of obesity

Seven studies for rs1800796 were included. Two of them did not have sufficient data. Two others were not in HWE. In three other studies, two were classified in obese/overweight vs. normal subjects. They were analyzed but did not show any significant results (results not shown).

3.2.3. IL-6 rs1800797 polymorphism and risk of obesity

Six studies were found for rs1800797. Two of them did not have sufficient data. Data for four other studies had two different classifications for obesity, two studies were comparing obese/overweight vs. normal and two others compared obese vs. normal/overweight. There were significant results in meta-analysis of obese/overweight vs. normal group. Minor allele of IL-6 rs1800797 polymorphism decreased the risk of obesity/overweight in allelic model 0.74 (0.59–0.92), dominant model 0.65 (0.49–0.85), and over-dominant model 0.66 (0.51–0.87).

3.2.4. IL-6 rs1800795 polymorphism and risk of obesity

3.2.4.1. Basic characteristics and classifications. For IL-6 rs1800795 (174G/C) firstly twenty-one observational studies with genotyping data were included. Seven studies were not in HWE. Fourteen articles with control groups that their allele and genotype frequencies were in HWE were included in the meta-analysis. All the control groups were healthy individuals. The basic characteristics of the studies included in the systematic review are shown in Table 1. Total samplesize according to the different classification for cases and controls are shown in supplementary Tables 2 and 3.

3.2.4.2. Meta-analysis. The meta-analysis was carried out for rs1800795 polymorphism according to BMI and overall definitions of obesity and fourteen articles based on five genetic models were included. According to BMI ≥ 25 vs. BMI < 25 (overweight/obese vs. normal) C allele showed increased risk of obesity in dominant model 1.21 (1.08–1.36), allelic model 1.17 (1.08–1.27), recessive model 1.27 (1.08–1.49), heterozygote model CG vs. GG 1.16 (1.02–1.31), CC vs. CG 1.19 (1.01–1.41), and homozygote model CC vs. GG 1.55 (1.11–2.16). Also, two borderline increases in heterozygote model CC vs. GC 1.18 (0.99–1.39), recessive model CC vs. GC + GG 1.33 (0.98–1.81) were observed. In BMI ≥ 30 vs. BMI < 25 groups, the C allele increased the risk of obesity in dominant model 1.16 (1.00–1.36), allelic model 1.16 (1.04–1.30), heterozygote model CC vs. CG 1.27 (1.02–1.59), and a borderline increase in homozygote model 1.53 (0.99–2.35). In BMI ≥ 30 vs. BMI < 30 (obese vs. normal/overweight), the risk allele was associated with obesity in dominant model 1.15 (1.00–1.33), allelic model 1.14 (1.03–1.25), recessive model 1.23 (1.03–1.48), homozygote model CC vs. GG 1.35 (1.10–1.66) and a borderline increase in heterozygote model GC vs. GG 1.19 (0.99–1.44) was detected. All significant results are illustrated in Fig. 2. Funnel plots for publication bias are presented in supplementary Fig. 1. Results related to *P*-value for different genetic models are presented in supplementary Table 4. Results for sensitivity analysis are not shown.

Overall it has been observed that based on classification of obesity, C allele increased obesity risk. In Obese vs. Normal groups, risk of obesity was significantly increased in recessive model 1.37 (1.12–1.67), allelic model 1.24 (1.03–1.48), heterozygote model CC vs. CG 1.30 (1.05–1.61) and homozygote model CC vs. GG 1.71 (1.14–2.56). In Obese vs. Normal/Overweight groups, risk allele increased the risk of obesity in homozygote model CC vs. GG 1.46 (1.17–1.82), allelic model C vs. G 1.16 (1.04–1.29), dominant model CC + CG 1.20 (1.02–1.42) and recessive model 1.26 (1.04–1.52). Finally in Overweight/Obese vs. Normal the association was observed in dominant model 1.46 (1.08–1.98), allelic model 1.31 (1.06–1.63), heterozygote model CG vs. GG 1.38 (1.02–1.89), homozygote model CC vs. GG 1.53 (1.08–2.17), and recessive model 1.35 (1.01–1.79). Also, subgroup analysis revealed additional significant results. All significant results are illustrated in Fig. 3. Funnel plots for publication bias is presented in supplementary Fig. 2. Results for sensitivity analysis are not shown. Results related to *P*-value for different genetic models are presented in supplementary Table 4.

4. Discussion

Pro-inflammatory adipokines are increased in enlarged adipose tissue based on the chronic inflammatory response. The relation between obesity, inflammation, and cancer are described in previous reviews [43–45]. It is clear that pro-inflammatory cytokines like IL-6 plays significant role in association between obesity and obesity related multifactorial diseases. IL-6 increases during obesity, diabetes, and insulin resistance [46]. Other obesity related cytokines including leptin, resistin, and visfatin can also increase production of IL-6. IL-6 blocks cells apoptosis and keep them alive during inflammation [47]. Furthermore, many observational studies focus on the relation between IL-6 polymorphisms and obesity, inflammation, metabolic syndrome [48] and obesity related cancers [49–51]. Based on aforementioned relations, we aimed to systematically investigate the role of IL-6 gene polymorphisms in obesity and its related traits. Eventually, nineteen eligible documents were finally included in our study, which were related to five polymorphisms in IL-6 gene (rs1800795, rs1800796, rs1800797, rs2069845, 190 C/T). Since the obesity definition was not similar in all included studies, we carried out different analysis based on BMI and overall definition of obesity (BMI/WC/WHR). We did not find any significant association between rs1800796 or rs2069845 variants and the risk of obesity. It may be related to the small number of eligible studies for these polymorphisms. The age status was different in included studies for rs2069845 variant. For rs1800796 variant in addition to the difference in age, definition of obesity and ethnicity were also variable in included studies. Thus, based on these factors were not able to conclusively rule out relation between rs1800796 and rs2069845 with obesity. More observational studies along with larger

Table 1
Basic characteristics of included studies in the systematic review (in HWE).

Author	Country	Publication year	Study design	Ethnicity	Source of controls	Age status	Gender	Genotyping	Trait	Quality score	Ref
IL-6 190 C/T											
Oana	Romania	2014	Case/Control	Caucasian	HB	Adolescent/Children	F/M	PCR-RFLP	BMI	4	[28]
rs1554606											
Joffe	South Africa	2014	Case/Control	African/Caucasian	PB	Adult	F	PCR-RFLP	BMI	8	[29]
rs2069845											
Joffe	South Africa	2014	Case/Control	African/Caucasian	PB	Adult	F	PCR-RFLP	BMI	8	[29]
Todendi	Brasil	2015	Cross-sectional	Caucasian	PB	Adolescent/Children	F/M	TaqMan	BMI	7	[16]
rs1800797											
Boeta-Lopez	USA	2018	Cohort	American	PB	Adolescent/Adult	F/M	TaqMan	BMI, WC	6	[17]
Vasku	Czech Republic	2003	Case/Control	Caucasian	PB	Adult	F/M	PCR-RFLP	BMI	5	[30]
Bienertova-Vasku	Czech Republic	2010	Case/Control	Caucasian	PB	Adult	F/M	PCR-RFLP	BMI	8	[31]
Tekcan	Turkey	2013	Case/Control	Caucasian	PB	Adult	F/M	PCR-RFLP	BMI	4	[32]
rs1800796											
Boeta-Lopez	USA	2018	Cohort	American	PB	Adolescent/Adult	F/M	TaqMan	BMI, WC	6	[17]
Hong	China	2011	Case/Control	Chinese	PB	Children	F/M	PCR-RFLP	BMI	7	[33]
Ramirez-Lopez	Mexico	2013	Cross-sectional	American	PB	Adolescent	F/M	PCR-RFLP	BMI, WC	6	[34]
rs1800795											
Adler	Poland	2016	Case/Control	Caucasian	PB	Adult	F/M	PCR-RFLP	BMI	4	[35]
Bienertova-Vasku	Czech Republic	2010	Case/Control	Caucasian	PB	Adult	F/M	PCR-RFLP	BMI	8	[31]
Bouhaha	Tunisia	2010	Case/Control	Caucasian	PB	Adult	F/M	PCR	BMI	5	[24]
Cimponeriu	Romania	2013	Case/Control	Caucasian	CB	Adult	F/M	PCR	BMI	6	[36]
Gupta	North India	2011	Case/Control	South Asian	PB	Adult	F	PCR-RFLP	WHR	5	[37]
Joffe	South Africa	2014	Case/Control	African/Caucasian	PB	Adult	F	PCR-RFLP	BMI	8	[29]
Poitou	France	2005	Case/Control	Caucasian	PB	Adult	F/M	HP[a]	BMI	5	[38]
Pyrzak	Poland	2009	Case/Control	Caucasian	CB	Adolescent	F/M	PCR-RFLP	BMI	4	[39]
Ramirez-Lopez	Mexico	2013	Cross-sectional	American	PB	Adolescent	F/M	PCR-RFLP	BMI, WC	6	[34]
Stephens	UK	2004	Case/Control	Caucasian	PB	Adult	F/M	MADGE[b]	BMI	7	[40]
Todendi	Brasil	2015	Cross-sectional	Caucasian	PB	Adolescent/Children	F/M	TaqMan	BMI	7	[16]
Wernstedt	Sweden	2004	Case/Control	Caucasian	PB	Adult	F/M	DASH[c], PCR-RFLP	BMI	5	[41]
Ibrahim	Egypt	2017	Cross-sectional	Caucasian	PB	Adolescent/Children	F/M	PCR–RFLP	BMI	7	[18]
Klipstein-Grobusch	South Africa	2006	cross-sectional	Caucasian	PB	Adult	F/M	SNuPE[d]	BMI	7	[42]

[a] Hybridizationprobes(LightCycler apparatus).
[b] MADGE: microtitre array diagonal gel electrophoresis.
[c] DASH: dynamic allele specific hybridization.
[d] SNuPE:single-nucleotide primer extension; F: Female; M: Male.

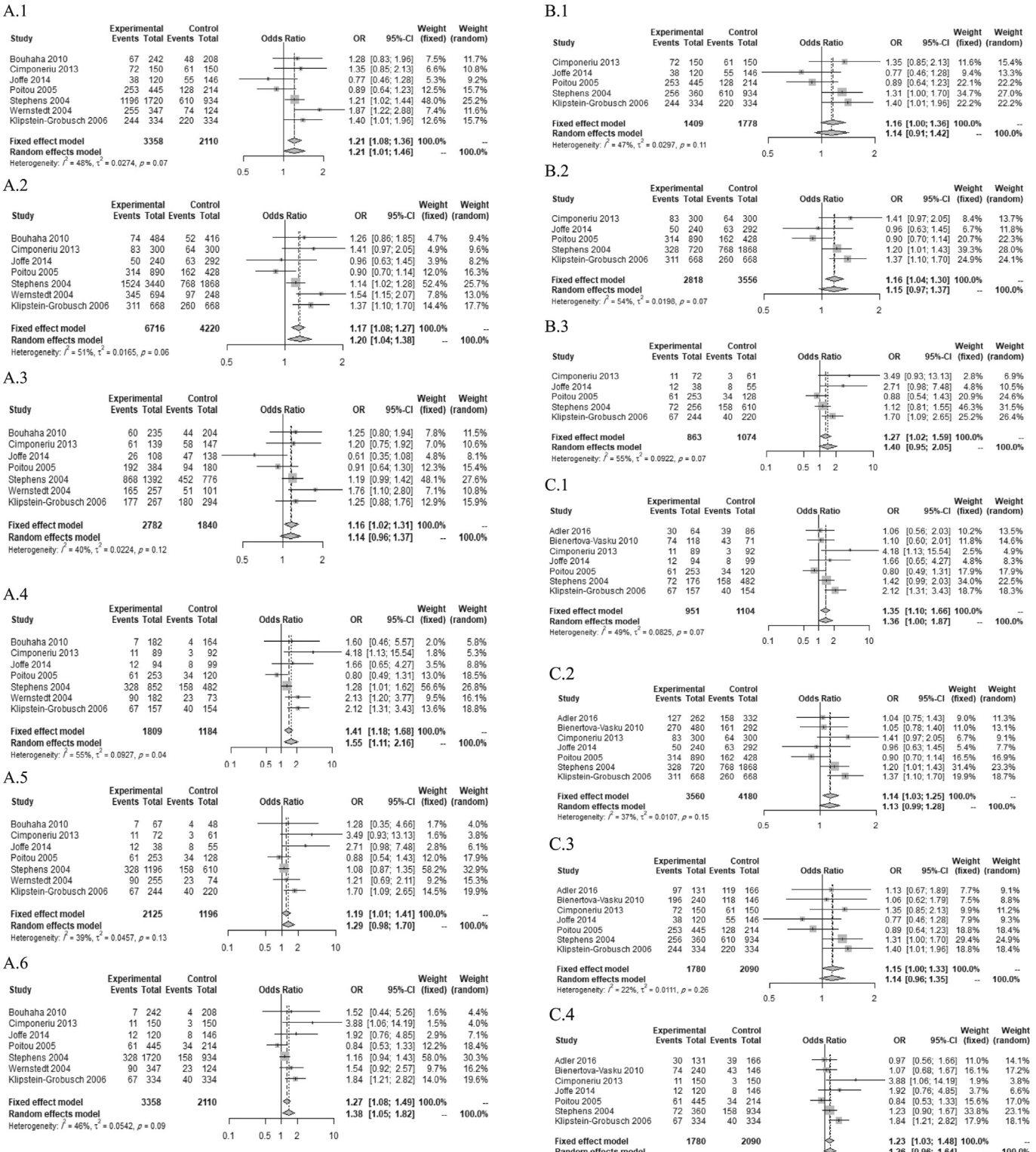


Fig. 2. Forest plots of ORs for the association of rs1800795 polymorphism with risk of obesity (according to BMI). Figure (A) shows BMI ≥ 25 vs. BMI < 25; A.1 (CC + CG vs. GG), A.2(C vs. G), A.3(CG vs. GG), A.4(CC vs. GG), A.5(CC vs. CG), A.6 (CC vs. CG + GG). Figure (B) shows BMI ≥ 30 vs. BMI < 25; B.1(CC + CG vs. GG), B.2(C vs. G), B.3(CC vs. CG). Figure (C) shows BMI ≥ 30 vs. BMI < 30; C.1(CC vs. GG), C.2(C vs. G), C.3(CC + CG vs. GG), C.4 (CC vs. CG + GG).

sample size are needed to proceed to a meta-analysis with definitive results.

The results for rs1800797 were significant. It seemed that this variant had a protective effect on overweight/obesity. While the number of included studies was small, but previous evidence assumed protective role of this variant on the risk of type 2 diabetes (T2D) [52]. The observation of these results might be due to the similar pro-inflammatory role of IL-6 on both obesity and T2D. But in overall, based on the low numbers of included studies for these variants the results were not conclusive. More observational studies are required to confirm

Fig. 2. (*continued*)

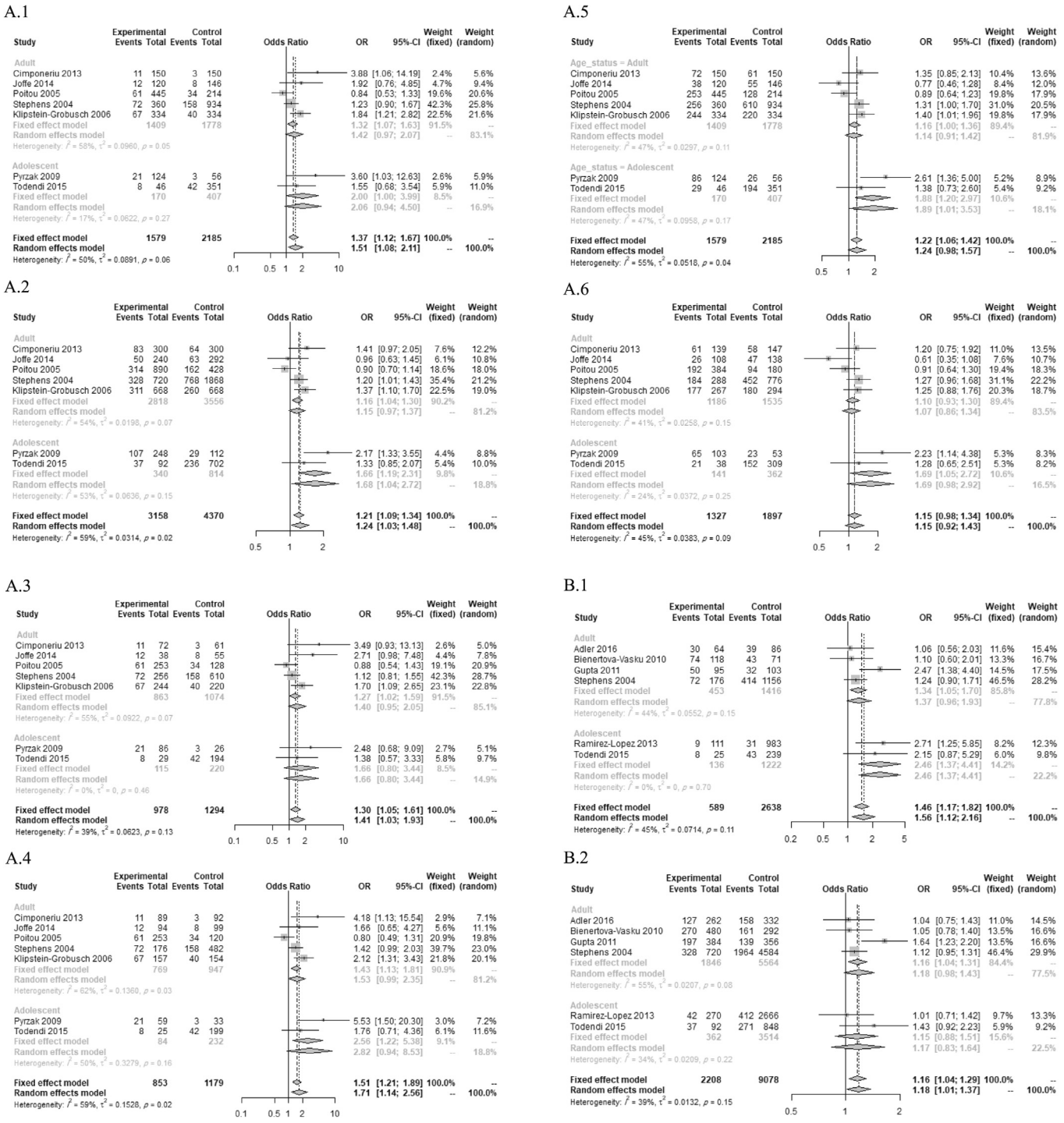


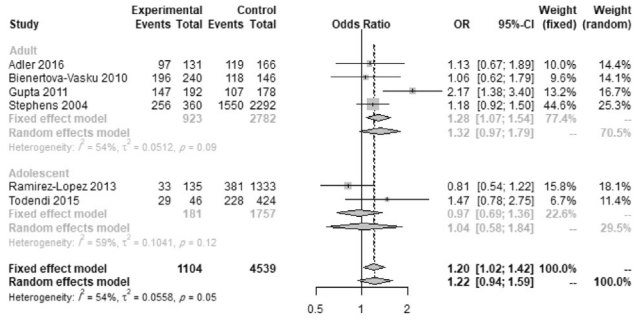
Fig. 3. Forest plots of ORs for the association of rs1800795 polymorphism with risk of obesity (according to all definitions). Figure (A) shows Obese vs. Normal; A.1(CC vs. CG + GG), A.2(C vs. G), A.3(CC vs. CG), A.4(CC vs. GG), A.5 (CC + CG vs. GG), A.6 (CG vs. GG). Figure (B) shows Obese vs. Normal/ Overweight; B.1(CC vs. GG), B.2(C vs. G), B.3(CC + CG vs. CC), B.4(CC vs. CG + GG), B.5 (CC vs. CG), B.6 (CG vs. GG). Figure (C) shows Obese/ Overweight vs. Normal; C.1 (CC + CG vs. CC), C.2(C vs. G), C.3(CG vs. GG), C.4(CC vs. GG), C.5(CC vs. CG), C6(CC vs. CG + GG).

Fig. 3. (*continued*)

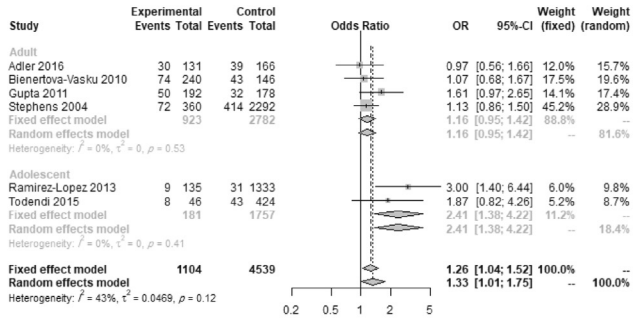
the protective role of this variant as observed in current study.

For rs1800795 variant, there was a previous meta-analysis study [22] with several mistakes which has been described in introduction. In addition, they missed seven studies which should be included in their meta-analysis [16,31,34–36,40,42], which may be related to their incomprehensive search strategy and small number of databases. Unfortunately, they wrongly included 5115 (71%) people, missed 4433 people that must have been included, and only 2095 (29%) people were properly included in their study. These consequently made their analysis completely unreliable. We assessed the effect of rs1800795 polymorphism on the risk of obesity and overweight. In overall our data decisively shows that rs1800795 increases the risk of obesity based on different genetic models. These associations were observed for both BMI and overall definitions of obesity. Subgroup analysis based on age status revealed more significant results. In line with our data, there were also several lines of evidence which demonstrated this polymorphism significantly increases the risk of other inflammatory

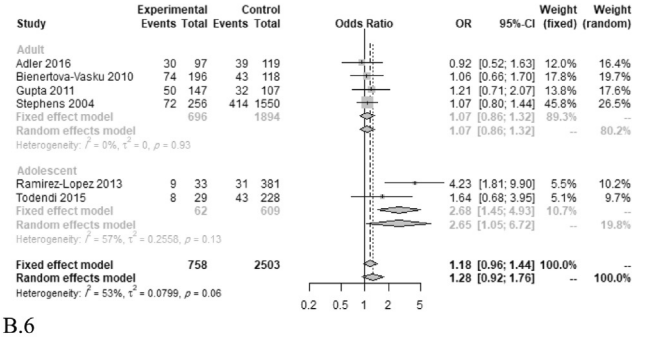
B.3



B.4



B.5



B.6

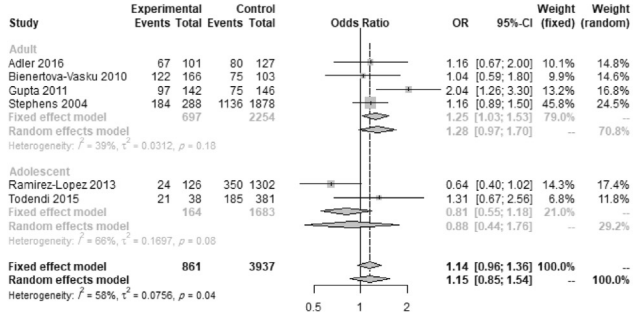
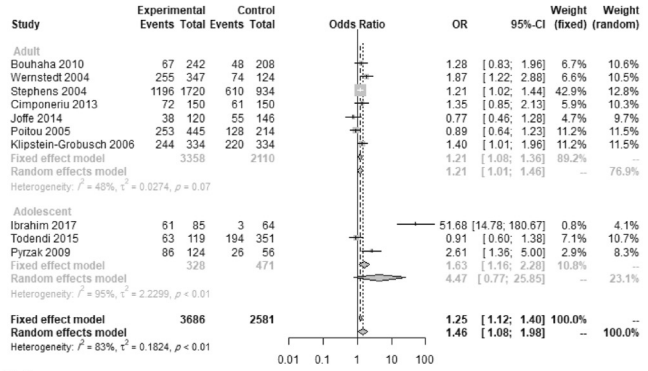


Fig. 3. (*continued*)

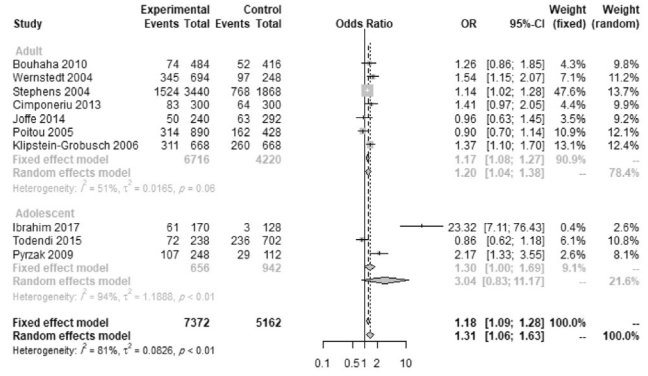
diseases including systemic lupus erythematosus (overproduction of IL-6 is responsible in this disease) [53], T2DM [54], and coronary artery disease [55].

Our study possess following strengths: First, this is the first systematic review, for evaluating the role of IL-6 gene polymorphisms in obesity that helps to better comprehend the relation of inflammatory components with obesity susceptibility. Likewise, the previous meta-analysis in this subject had several limitations. Second, to find out all relevant articles and reduce publication bias we searched four most important databases and other sources such as hand-searching, references of relevant reviews and contacting the corresponding authors. Third, this study was performed without any language limitations, so there was no language bias. Fourth, this study has high power and

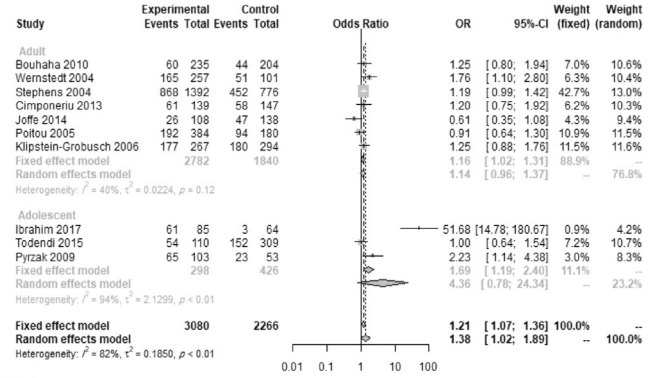
C.1



C.2



C.3



C.4

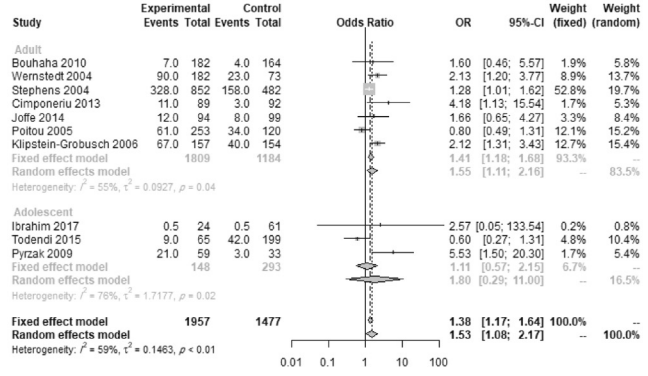
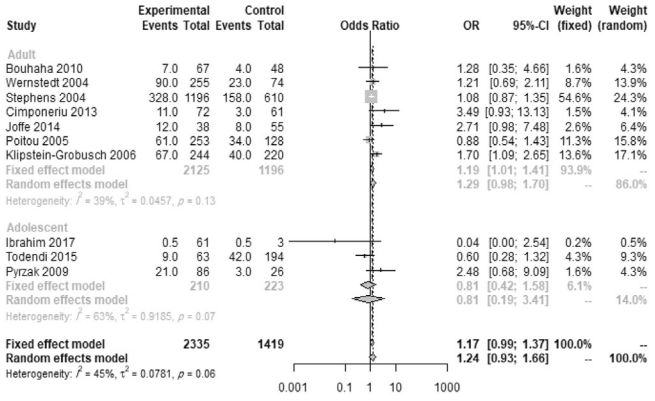


Fig. 3. (*continued*)

strength reliability based on comprehensive search strategy, analyzing obesity with the different rage of BMI, definitions, and ages.

There are also some limitations in our study. First, some studies had to be excluded because of their insufficient data even after email to corresponding author. Second, because of lacking sufficient documents

C.5



C.6

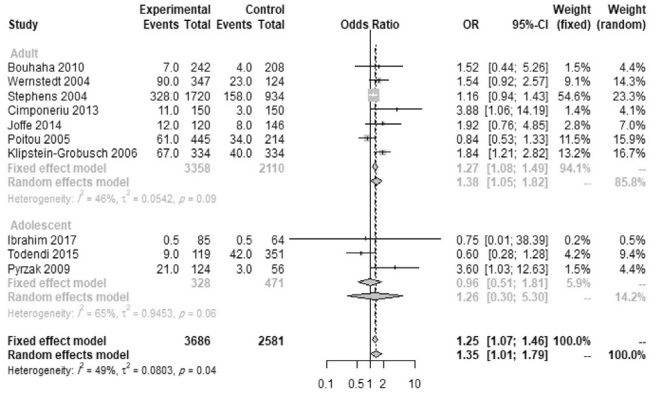


Fig. 3. (*continued*)

and definitions for obesity in some studies we were not able to carry out a strong meta-analysis for all included polymorphisms. Third, due to insufficient data and studies, haplotype analysis for these polymorphisms was not possible. Fourth, it should be noted that in a multifactorial disease like obesity, several factors with different mechanisms are involved. But we only studied one genetic risk effect and many other confounding, cultural and environmental factors were not included in our study.

5. Conclusions

In conclusion this meta-analysis has shown that minor allele (C) of rs1800795 significantly increases the risk of obesity. The minor allele (A) for rs1800797 may also decrease the risk of obesity while rs1800796 and rs2069845 may not be associated, however it cannot be certainly concluded. More observational studies in the future are recommended to reach a conclusion on the role of IL-6 variants in obesity.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.154769.

References

[1] C.L. Donohoe, S.L. Doyle, J.V. Reynolds, Visceral adiposity, insulin resistance and cancer risk, Diabetol. Metab. Syndr. 3 (2011) 12.
[2] A.F.M. Afshin, M.B. Reitsma, P. Sur, K. Estep, A. Lee, et al., Health effects of overweight and obesity in 195 countries over 25 years, N Engl. J. Med. 377 (2017) 14.
[3] T. Kelly, W. Yang, C.-S. Chen, K. Reynolds, J. He, Global burden of obesity in 2005 and projections to 2030, Int. J. Obes. 32 (2008) 1431.
[4] X. Pi-Sunyer, The medical risks of obesity, Postgrad. Med. 121 (2009) 12.
[5] S.M. Fruh, Obesity: risk factors, complications, and strategies for sustainable long-term weight management, J. Am. Assoc. Nurse Pract. 29 (2017) 11.
[6] Silvestris GDPaF. Obesity as a major risk factor for cancer. J. Obes. (2013) 11.
[7] N.E. Hassan, S.A. El-Masry, W. Zarouk, R.A. El Banna, R.M. Mosaad, M. Al-Tohamy, et al., Obesity phenotype in relation to gene polymorphism among samples of Egyptian children and their mothers, Genes Dis. 5 (2018) 150–157.
[8] S.I. Berndt, S. Gustafsson, R. Mägi, A. Ganna, E. Wheeler, M.F. Feitosa, et al., Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture, Nat. Genet. 45 (2013) 501.
[9] A.E. Locke, B. Kahali, S.I. Berndt, A.E. Justice, T.H. Pers, F.R. Day, et al., Genetic studies of body mass index yield new insights for obesity biology, Nature 518 (2015) 197.
[10] S.S. Abdelmajed, M. Youssef, M.E. Zaki, N.A.-M. Hassan, S. Ismail, Association analysis of FTO gene polymorphisms and obesity risk among Egyptian children and adolescents, Genes Dis. 4 (2017) 170–175.
[11] E.T.J. Chong, N.F.A. Aziz, P.-C. Lee, Association of IRX3 rs3751723 polymorphism with the risk of overweight and obesity: case-control study and meta-analysis, Meta Gene. 16 (2018) 50–56.
[12] O.E. Ogundele, K.O. Adekoya, A.A. Osinubi, A.A. Awofala, B.O. Oboh, Association of adiponectin gene (ADIPOQ) polymorphisms with measures of obesity in Nigerian young adults, Egypt. J. Med. Human Genet. 19 (2018) 123–127.
[13] Q.-Y. Song, J.-Y. Song, Y. Wang, S. Wang, Y.-D. Yang, X.-R. Meng, et al., Association study of three gene polymorphisms recently identified by a genome-wide association study with obesity-related phenotypes in Chinese children, Obes. Facts. 10 (2017) 179–190.
[14] C. Caër, C. Rouault, T. Le Roy, C. Poitou, J. Aron-Wisnewsky, A. Torcivia, et al., Immune cell-derived cytokines contribute to obesity-related inflammation, fibrogenesis and metabolic deregulation in human adipose tissue, Sci. Rep. 7 (2017) 3000.
[15] A. Ghanemi, J. St-Amand, Interleukin-6 as a "metabolic hormone", Cytokine 112 (2018) 132–136.
[16] P.F. Todendi, E.I. Klinger, M.B. Ferreira, C.P. Reuter, M.S. Burgos, L.G. Possuelo, et al., Association of IL-6 and CRP gene polymorphisms with obesity and metabolic disorders in children and adolescents, Anais da Academia Brasileira de Ciências. 87 (2015) 915–924.
[17] K. Boeta-Lopez, J. Duran, D. Elizondo, E. Gonzales, A. Rentfro, A. Schwarzbach, et al., Association of interleukin-6 polymorphisms with obesity or metabolic traits in young Mexican-Americans, Obes. Sci. Pract. 4 (2018) 85–96.
[18] O.M. Ibrahim, A.A. Gabre, S.F. Sallam, I.R. El-Alameey, R.N. Sabry, E.M. Galal, et al., Influence of interleukin-6 (174G/C) gene polymorphism on obesity in Egyptian children, Open Access Macedonian J. Med. Sci. 5 (2017) 831.
[19] M. Hollensted, T.S. Ahluwalia, C.T. Have, N. Grarup, C.E. Fonvig, T.R.H. Nielsen, et al., Common variants in LEPR, IL6, AMD1, and NAMPT do not associate with risk of juvenile and childhood obesity in Danes: a case–control study, BMC Med. Genet. 16 (2015) 105.
[20] Y. Hamid, C. Rose, S. Urhammer, C. Glümer, R. Nolsøe, O. Kristiansen, et al., Variations of the interleukin-6 promoter are associated with features of the metabolic syndrome in Caucasian Danes, Diabetologia 48 (2005) 251–260.
[21] Z. Yu, S. Han, X. Cao, C. Zhu, X. Wang, X. Guo, Genetic polymorphisms in adipokine genes and the risk of obesity: a systematic review and meta-analysis, Obesity 20 (2012) 396–406.
[22] M. Hu, Z. Yu, D. Luo, H. Zhang, J. Li, F. Liang, et al., Association between-174G > C polymorphism in the IL-6 promoter region and the risk of obesity: a meta-analysis, Medicine 97 (2018).
[23] J. Suazo, S. Smalley, M. Hodgson, G. Weisstaub, A. Gonzalez, J. Santos, Association between genetic polymorphisms of interleukin 6 (IL6), IL6R and IL18 with metabolic syndrome in obese Chilean children, Rev. Med. Chil. 142 (2014) 290–298.
[24] R. Bouhaha, T. Baroudi, H. Ennafaa, E. Vaillant, H. Abid, R. Sassi, et al., Study of TNFα-308G/A and IL6-174G/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population, Clin. Biochem. 43 (2010) 549–552.
[25] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst. Rev. 4 (2015) 1.
[26] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (2009).
[27] Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. < http://www ohri ca/programs/clinical_epidemiology/oxford asp>, 2001.
[28] M.C. Oana, B. Claudia, D. Carmen, P.A. Maria, V. Septimiu, M. Claudiu, The role of IL-6 572 C/G, 190 C/T, and 174 G/C gene polymorphisms in children's obesity, Eur. J. Pediatr. 173 (2014) 1285–1296.
[29] Y. Joffe, L. van der Merwe, J. Evans, M. Collins, E. Lambert, A. September, et al., Interleukin-6 gene polymorphisms, dietary fat intake, obesity and serum lipid concentrations in black and white South African women, Nutrients 6 (2014)

2436–2465.
[30] A. Vasků, M. Soucek, M. Goldbergova, J. Vacha, Office blood pressure, heart rate and A (− 596) G interleukin-6 gene polymorphism in apparently healthy Czech middle-aged population, Physiol. Res. 52 (2003) 291–297.
[31] J. Bienertová-Vašků, P. Bienert, M. Forejt, J. Tomandl, Z. Brázdová, A. Vašků, Genotype× nutrient association of common polymorphisms in obesity-related genes with food preferences and time structure of energy intake, Br. J. Nutr. 103 (2010) 352–359.
[32] A. Tekcan, S. Yigit, A. Rustemoglu, C. Gurel, S. Sahin, T. Tasliyurt, The investigation of obesity susceptibility with IL-4 gene intron 3 VNTR and IL-6 gene-597G/A polymorphisms in a Turkish population, Int. J. Human Genet. 13 (2013) 209–213.
[33] H. Chen, X. Weiping, Y. Zhou, R. Zhao, L. Yao, C. Zhang, Distribution of interleukin-6-634C/G promotor gene polymorphism in 8–12-year-old children and its correlation with nutrition, Chinese J. Clin. Nutr. 19 (2011) 394–399.
[34] G. Ramírez-López, E. Portilla-de Buen, J. Sánchez-Corona, J. Salmerón-Castro, F. Mendoza-Carrera, Interleukin-6 polymorphisms are associated with obesity and hyperglycemia in Mexican adolescents, Arch. Med. Res. 44 (2013) 62–68.
[35] G. Adler, K. Skonieczna-Żydecka, A. Madlani, J. Ogonowski, E. Grochans, J. Pierzak-Sominka, et al., Association between depression, parameters of adiposity and genetic polymorphisms of pro-inflammatory cytokines: IL-1α, IL-1β, IL-2 and IL-6 in subjects over 55 years old, Acta Biochim. Pol. 63 (2016).
[36] D. Cimponeriu, C. Serafinceanu, P. Apostol, M. Toma, M. Stavarachi, I. Radu, et al., Potential association of obesity with IL6 G-174C polymorphism and TTV infections, Cent. Europ. J. Biol. 8 (2013) 625–632.
[37] A. Gupta, V. Gupta, A. Singh, S. Tiwari, S. Agrawal, S. Natu, et al., Interleukin-6 G-174C gene polymorphism and serum resistin levels in North Indian women: potential risk of metabolic syndrome, Hum. Exp. Toxicol. 30 (2011) 1445–1453.
[38] C. Poitou, J.-M. Lacorte, M. Coupaye, S. Bertrais, J.-F. Bedel, N. Lafon, 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. 15 (2005) 11–23.
[39] B. Pyrzak, A. Wisniewska, A. Majcher, K. Popko, M. Wasik, U. Demkow, Association between metabolic disturbances and G-174C polymorphism of interleukin-6 gene in obese children, Eur. J. Med. Res. 14 (2009) 196.
[40] J.W. Stephens, S.J. Hurel, J.A. Cooper, J. Acharya, G.J. Miller, S.E. Humphries, A common functional variant in the interleukin-6 gene is associated with increased body mass index in subjects with type 2 diabetes mellitus, Mol. Genet. Metab. 82 (2004) 180–186.
[41] I. Wernstedt, A. Eriksson, A. Berndtsson, J. Hoffstedt, S. Skrtic, T. Hedner, et al., A common polymorphism in the interleukin-6 gene promoter is associated with overweight, Int. J. Obes. 28 (2004) 1272.
[42] K. Klipstein-Grobusch, M. Möhlig, J. Spranger, K. Hoffmann, F.U. Rodrigues, A.M. Sharma, et al., Interleukin-6 g.− 174G > C promoter polymorphism is associated with obesity in the EPIC-potsdam study, Obesity 14 (2006) 14–18.
[43] T. Deng, C.J. Lyon, S. Bergin, M.A. Caligiuri, W.A. Hsueh, Obesity, inflammation, and cancer, Annu. Rev. Pathol. 11 (2016) 421–449.
[44] L.R. Howe, K. Subbaramaiah, C.A. Hudis, A.J. Dannenberg, Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer, Clin. Cancer Res. 19 (2013) 6074–6083.
[45] B. Sun, M. Karin, Obesity, inflammation, and liver cancer, J. Hepatol. 56 (2012) 704–713.
[46] P. Dandona, A. Aljada, A. Bandyopadhyay, Inflammation: the link between insulin resistance, obesity and diabetes, Trends Immunol. 25 (2004) 4–7.
[47] D.R. Hodge, E.M. Hurt, W.L. Farrar, The role of IL-6 and STAT3 in inflammation and cancer, Eur. J. Cancer 41 (2005) 2502–2512.
[48] A.A. Teixeira, B.M.R. Quinto, M.A. Dalboni, C.J.D.O. Rodrigues, M.C. Batista, Association of IL-6 polymorphism-174G/C and metabolic syndrome in hypertensive patients, BioMed. Res. Int. 2015 (2015) 6.
[49] L.A. Hefler, C. Grimm, T. Lantzsch, D. Lampe, S. Leodolter, H. Koelbl, et al., Interleukin-1 and interleukin-6 gene polymorphisms and the risk of breast cancer in caucasian women, Clin. Cancer Res. 11 (2005) 5718–5721.
[50] S. Wang, Z. Ding, J. Tang, G. Li, The association of interleukin-6 gene polymorphism and risk of colorectal cancer in Chinese patients, Trans. Cancer Res. 7 (2018) 401–410.
[51] Y. Du, L. Gao, K. Zhang, J. Wang, Association of the IL6 polymorphism rs1800796 with cancer risk: a meta-analysis, Genet. Mol. Res. 14 (2015) 13236–13246.
[52] L. Qi, R.M. van Dam, J.B. Meigs, J.E. Manson, D. Hunter, F.B. Hu, Genetic variation in IL6 gene and type 2 diabetes: tagging-SNP haplotype analysis in large-scale case–control study and meta-analysis, Hum. Mol. Genet. 15 (2006) 1914–1920.
[53] N.M. Asano, H.D. Angelo, H.A. da Silva, M.M. Maia, O.G. Lins, P.E. Souza, Interleukin-6 promoter polymorphisms− 174 G/C in Brazilian patients with systemic lupus erythematosus, Hum. Immunol. 74 (2013) 1153–1156.
[54] M.N. Plataki, M.I. Zervou, G. Samonis, V. Daraki, G.N. Goulielmos, D.P. Kofteridis, Association of the interleukin-6 rs1800795 polymorphism with type 2 diabetes mellitus in the population of the Island of Crete, Greece, Genet. Test. Mol. Biomar. 22 (2018) 448–452.
[55] H. Hou, C. Wang, F. Sun, L. Zhao, A. Dun, Z. Sun, Association of interleukin-6 gene polymorphism with coronary artery disease: an updated systematic review and cumulative meta-analysis, Inflamm. Res. 64 (2015) 707–720.