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UCP2 45bp Ins/Del Gene Polymorphism in Association with Overweight and Obesity: A Meta-Analysis

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Abstract

Uncoupling Protein (UCP) is a mitochondrial inner-membrane protein that is involved in energy homeostasis. In human tissues, UCP2 is widely expressed, acts as an uncoupling agent for oxidative phosphorylation, and is involved in the regulation of metabolism and ATP production. The association between UCP2 45bp Ins/Del gene polymorphism and the risk of overweight and obesity remains controversial and requires further evaluation. A meta-analysis of 12,224 subjects in 20 articles from PubMed, Embase, and China National Knowledge Infrastructure was performed to assess the association of UCP2 45bp Ins/Del gene polymorphism with the risk of overweight and obesity. The results of the meta-analysis showed that the UCP2 45bp Ins/Del gene polymorphism was significantly associated with genetic susceptibility to overweight and obesity only in the recessive model (odds ratio [OR]=1.24, 95% confidence interval [CI]=1.07-1.43, P=0.004), while the rest of the models did not show an association (P>0.05). However, the subgroup analysis of ethnicity showed that, in Asian populations, UCP2 45bp Ins/Del gene polymorphism was associated with genetic susceptibility to overweight and obesity in the allelic (OR=1.18, 95%CI=1.02-1.36, P=0.027), dominant (OR=1.20, 95%CI=1.02-1.41, P=0.030), and heterozygote (OR=1.19, 95%CI=1.01-1.41, P=0.043) models, respectively. No significant associations were found in the Caucasian population (P>0.05), and there was significant heterogeneity between the studies. UCP2 45bp Ins/Del gene polymorphism, which is significantly associated with genetic susceptibility to overweight and obesity in Asian populations, is not significantly associated with genetic susceptibility to obesity in Caucasian populations.

Keywords: Uncoupling proteins (UCPs); Gene polymorphism; Overweight; Obesity; Meta-analysis.

Introduction

With economic development, people's lifestyles have gradually changed, and the number of overweight and obese individuals has increased annually. Since the 1970s, obesity has become prevalent in developed countries, and the number of obese individuals worldwide has increased more than six times in the past 40 years, totaling more than 600 million individuals. Since 1975 and in the next 39 years, the global obesity rate (body mass index ≥30 kg/m^2) increased from 3.2% to 10.8% and from 6.4% to 14.9% in women. If the trend continues, it is expected that, by 2025, 18% of men and 21% of women worldwide will be obese

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[1]. Overweight and obesity are not only important risk factors for metabolic and cardiovascular diseases but are also significantly associated with the risk of certain types of cancer (e.g., liver, kidney, prostate, colon, ovarian, breast), depression, and Alzheimer's disease. Moreover, the death and disability caused by obesity significantly increase the national economic burden, and the problems it poses have become a major challenge worldwide [2,3]. Being overweight and obese are equally important in child and adolescent populations. In the past 30 years, the global situation of obesity in children and adolescents has become critical, with obesity detection rates increasing in many European and American countries and some Asian countries [1]. Overweight and obesity are mainly due to the fact that energy intake is greater than consumption, energy is stored in the body in the form of fat, and many factors can affect the body's energy metabolism, among which genes are a well-known cause.

Uncoupling proteins (UCPs) are thought to be involved in regulating glucose/lipid metabolism and energy homeostasis processes and are essentially a group of mitochondrial anion carrier proteins located in the inner mitochondrial membrane. As a candidate gene for obesity, Fleury et al. were the first to investigate the UCP2 gene. The Homo sapiens UCP2 gene is located on chromosome 11q13 and consists of 8 exons and 7 introns, with a length of 8174. UCP2 is widely expressed in human tissues and is an uncoupling agent for oxidative phosphorylation, which is involved in the regulation of lipid metabolism and ATP production, and disruption of UCP2 expression in the adipose tissue can lead to overweight and obesity [4,5]. UCP2 gene polymorphisms (Aal55Val, 45bp insertion/deletion, and -866G/A) have been extensively studied in relation to overweight and obesity, but showed conflicting results. Among these, information on the biological effects of UCP2 45bp Ins/Del gene polymorphism is still limited. Therefore, this meta-analysis aimed to assess the effects of UCP2 45bp Ins/Del gene polymorphism on the risk of overweight and obesity.

Methods

Search strategy

The following three databases were searched: PubMed, Embase, and China National Knowledge Infrastructure (CNKI). The search terms included "uncoupling protein 2," "UCP2," "polymorphism," "genotype," "alleles," "obesity," "overweight," and "BMI." The deadline for the search was September 3, 2021, for Chinese and English literature published as electronic papers, and reference back was used to find additional literature for inclusion in the study.

Inclusion and exclusion Criteria

Studies meeting the following criteria were included in the meta-analysis: (1) case-control, cohort, or cross-sectional studies assessed the association between UCP2 45bp Ins/Del gene polymorphism and overweight and obesity; (2) sufficient information was provided in the text to calculate the frequency distribution of the genotype of interest or that of the allele of interest; (3) subjects were recruited from the same race during the same period; (4) if data were reported repeatedly, the most complete datasets were included; and (5) the genotype distribution of controls obeyed the Hardy–Weinberg equilibrium. Duplicate literature, reviews, abstracts, correspondence, animal studies, non-case-control studies, and non-UCP2 45bp Ins/Del gene polymorphisms in relation to genetic susceptibility to overweight and obesity were excluded from this study.

Quality assessment of included studies

The Newcastle-Ottawa Scale was used to assess the quality of each included study. Scores ≥ 7 were considered high quality.

Data extraction

The articles were evaluated, and data were independently extracted by two authors. Disagreements were resolved by consensus through discussion. The information extracted included the following in order: name of the first author, year of publication, country and ethnicity, number of cases and controls, frequency of cases and control genotypes, and whether the study population consisted of children and adolescents.

Statistical analysis

The Hardy–Weinberg equilibrium of the UCP2 45bp Ins/Del genotype distribution in the control group was tested using the Pearson chi-square test, and a P-value < 0.05 was considered to deviate from the Hardy–Weinberg equilibrium. Literature deviating from the Hardy–Weinberg equilibrium was excluded from the study. A combined odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the association between the UCP2 45bp Ins/Del gene polymorphism and the risk of genetic susceptibility to overweight and obesity in five models (allelic, dominant, recessive, heterozygote, and homozygote models). The significance of the combined OR was determined using the Z-test. I^2 was used to assess the heterogeneity between studies. When a random-effects model was used as the combined method, heterogeneity was considered significant if I^2>50%; otherwise, heterogeneity was considered not significantly different, and a fixed-effects model was used. Subgroup analyses were performed for race in each of the five genetic models. A Begg's funnel plot was used to identify publication bias. All statistical analyses were performed using Stata 16.0 (StataCorp LLC, College Station, TX, USA). P-values <0.05 were considered statistically significant (two-tailed).

Results

Search results

A total of 459 articles were obtained by searching PubMed, Embase, and CNKI databases. After excluding 52 duplicate articles, 407 articles were obtained. A total of 378 articles that were reviews, letters, laboratory studies, or not related to the current study were excluded. Based on the abovementioned inclusion and exclusion criteria, nine full-text articles were excluded. Twenty eligible articles were included in the meta-analysis [6-25] (Figure 1).

Study demographics

A total of 20 relevant papers were included in the meta-analysis, covering 12 countries, including 5750 cases and 6474 controls, and of these 20 papers, five were studies on Asian populations, and 15 were studies on Caucasian populations, with studies published between 1999 and 2020 (Table 1).

Meta-analysis

The results of the meta-analysis showed that the UCP2 45bp

Ins/Del gene polymorphism was significantly associated with genetic susceptibility to overweight and obesity only in the recessive model (OR=1.24, 95%CI=1.07-1.43, P=0.004; Figure 2), while the other models did not show an association (P>0.05). However, the subgroup analysis of ethnicity showed that, in Asian populations, UCP2 45bp Ins/Del gene polymorphism was allelic (OR=1.18, 95%CI=1.02-1.36, P=0.027; Figure 3), dominant (OR=1.20, 95%CI=1.02-1.41, P=0.030; Figure 4), and heterozygote (OR=1.19, 95%CI=1.01-1.41, P=0.043; Figure 5), respectively, which were significantly associated with genetic susceptibility to overweight and obesity in the model. No significant associations were found in the Caucasian population (P>0.05), and there was significant heterogeneity between studies. We also performed subgroup analysis according to whether the subjects were adults and found significant associations only in the recessive (OR=1.19, 95% CI=1.01-1.41, P=0.011; Figure 6) and homozygote (OR=1.24, 95% CI=1.04-1.48, P=0.017; Figure 7) models in the adult group, while no significant associations were found in the other groups (P>0.05) (Table 2).

Influence analysis

To assess the stability of the study results, we performed sensitivity analyses, excluding one study at a time and combining the remaining studies. The results showed that, under all mentioned genetic models, no single study had an excess effect on any pooled effect.

Publication bias evaluation

After excluding the key factors of heterogeneity between studies, no publication bias regarding the association between polymorphisms and overweight and obesity was detected in any of the abovementioned genetic models using funnel plots (Figure 8).

Table 1: Relevant features of the studies included in the meta-analysis.

Study	Country	Year	Ethnicity	Age	Case			Control			NOS score
					DD	DI	II	DD	DI	II	
Dalgaard et al. [6]	Denmark	1999	Caucasian	adults	371	293	80	432	364	76	8
Evans et al. [7]	Germany	2000	Caucasian	adults	145	130	30	286	198	24	6
Esterbauer et al. [8]	Austria	2001	Caucasian	adults	179	132	29	117	115	24	8
Nieters et al. [9]	Germany	2002	Caucasian	adults	88	58	8	78	57	16	8
Maestrini et al. [10]	Italy	2003	Caucasian	adults	211	124	25	51	42	10	7
Feng et al. [11]	China	2004	Asian	adults	75	27	1	138	31	2	7
Marti et al. [12]	Spain	2004	Caucasian	adults	83	63	11	92	52	6	7
Berentzen et al. [13]	Denmark	2005	Caucasian	adults	277	227	64	356	294	67	8
Hong et al. [14]	China	2005	Asian	children	165	35	1	190	36	4	8
Ochoa et al. [15]	Spain	2007	Caucasian	children	103	71	18	79	76	11	7
Kring et al. [16]	Denmark	2008	Caucasian	adults	104	94	24	166	127	21	8
Liu et al. [17]	China	2012	Asian	adults	463	141	12	696	199	15	7
Papazoglou et al. [18]	Greece	2012	Caucasian	adults	96	55	7	60	27	4	8
Csernus et al. [19]	Hungary	2013	Caucasian	children	338	303	68	339	251	47	7
Oguzkan et al. [20]	turkey	2013	Caucasian	children	46	31	23	65	30	5	7
Say et al. [21]	Malaysia	2014	Asian	adults	181	77	7	505	145	11	7
Gul et al. [22]	Turkey	2017	Caucasian	children	151	96	21	93	68	24	7
Kaabi et al. [23]	Saudi Arabia	2018	Caucasian	adults	58	23	5	30	32	3	7
Surniyantoro et al. [24]	Indonesia	2018	Asian	adults	68	25	7	68	29	3	7
Verdi et al. [25]	Turkey	2020	Caucasian	children	72	29	1	53	29	5	6

Table 2: Pooled measures for the associations of the UCP2 45bp Ins/Del gene polymorphism with overweight and obesity.

Population	Inherited model	Numbers of	Pooled OR (95% CI)				I^2(%)
		cases/controls	FEM	P value	REM	P value	
Overall	Allele	11500/12948	1.08 (1.02, 1.15)	0.011	1.06 (0.95, 1.19)	0.296	67.5
	Dominant	5750/6474	1.07 (0.99, 1.15)	0.096	1.05 (0.92, 1.19)	0.484	59.1
	Recessive	5750/6474	1.24 (1.07, 1.43)	0.004	1.21 (0.97, 1.53)	0.098	46.3
	Heterozygote	5308/6096	1.03 (0.96, 1.12)	0.397	1.02 (0.91, 1.15)	0.704	45.4
	Homozygote	3716/4272	1.24 (1.06, 1.43)	0.005	1.20 (0.93, 1.56)	0.161	54.9

Asian	Allele	2570/4144	1.18 (1.02, 1.36)	0.027	1.18 (1.02, 1.37)	0.025	0
	Dominant	1285/2072	1.20 (1.02, 1.41)	0.03	1.20 (1.01, 1.43)	0.035	6.4
	Recessive	1285/2072	1.27 (0.76, 2.11)	0.358	1.30 (0.77, 2.19)	0.32	0
	Heterozygote	1257/2037	1.19 (1.01, 1.41)	0.043	1.20 (0.99, 1.45)	0.059	12.6
	Homozygote	980/1632	1.31 (0.78, 2.18)	0.303	1.35 (0.80, 2.27)	0.261	0
Caucasian	Allele	8930/8334	1.06 (0.99, 1.14)	0.072	1.03 (0.89, 1.18)	0.706	73.5
	Dominant	4465/4402	1.03 (0.95, 1.12)	0.448	1.00 (0.85, 1.16)	0.971	64.6
	Recessive	4465/4402	1.23 (1.06, 1.43)	0.007	1.20 (0.92, 1.56)	0.171	56.7
	Heterozygote	4051/4059	1.00 (0.91, 1.09)	0.914	0.97 (0.85, 1.11)	0.672	47.8
	Homozygote	2736/2640	1.23 (1.05, 1.44)	0.009	1.18 (0.88, 1.59)	0.275	64.1
Adults	Allele	8356/10138	1.08 (1.01, 1.16)	0.03	1.07 (0.95, 1.21)	0.248	59.7
	Dominant	4178/5069	1.06 (0.97, 1.16)	0.164	1.06 (0.91, 1.22)	0.461	58
	Recessive	4178/5069	1.25 (1.02, 1.48)	0.011	1.24 (1.02, 1.52)	0.031	14.7
	Heterozygote	3868/4787	1.03 (0.94, 1.13)	0.51	1.03 (0.89, 1.19)	0.691	52.1
	Homozygote	2709/3357	1.24 (1.04, 1.48)	0.017	1.23 (0.96, 1.57)	0.1	34.6
Children	Allele	3144/2810	1.08 (0.96, 1.22)	0.189	1.04 (0.76, 1.42)	0.795	81
	Dominant	1572/1405	1.07 (0.92, 1.24)	0.358	1.02 (0.76, 1.37)	0.897	67.6
	Recessive	1572/1405	1.20 (0.92, 1.58)	0.181	1.09 (0.53, 2.23)	0.81	75.1
	Heterozygote	1440/1309	1.05 (0.89, 1.22)	0.582	1.00 (0.81, 1.25)	0.979	34.9
	Homozygote	1007/915	1.23 (0.93, 1.63)	0.152	1.06 (0.49, 2.30)	0.874	77.5

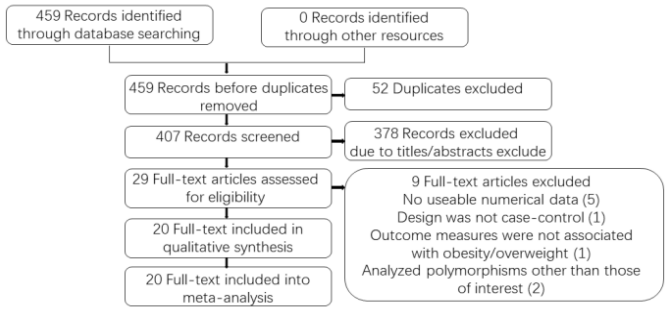

Figure 1: Image showing retrograde pyelography. Ureter appeared to be dilated with? vujo.

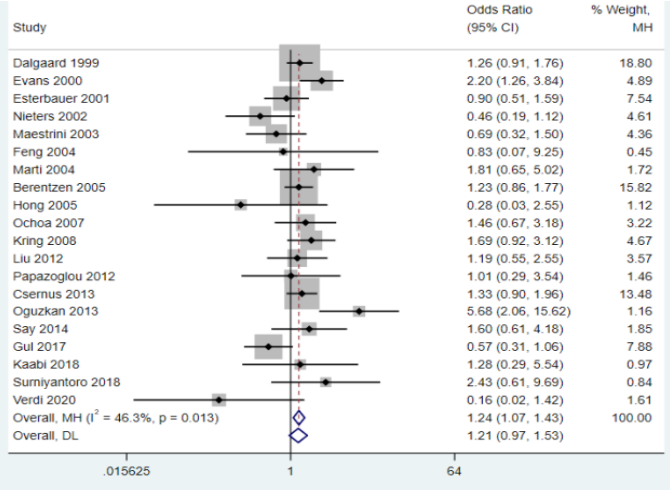

Figure 2

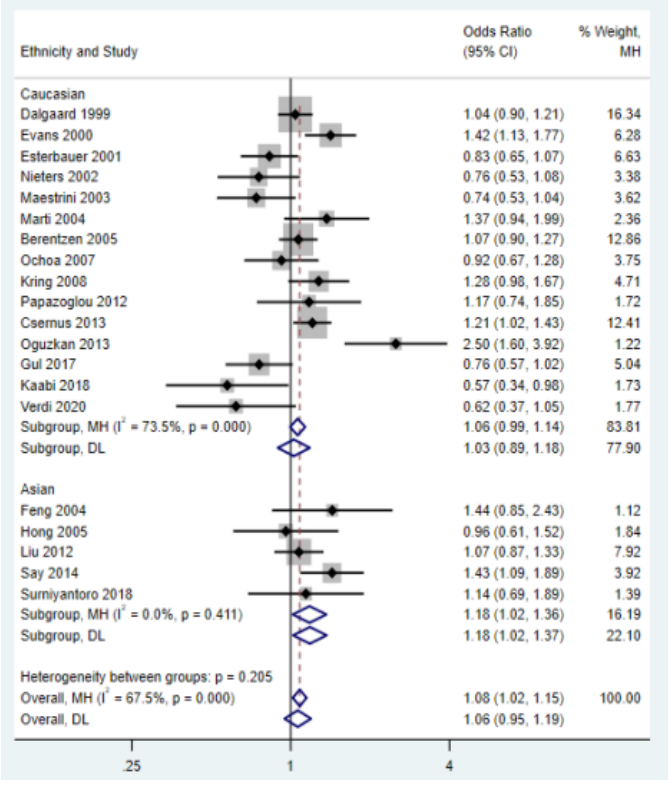

Figure 3

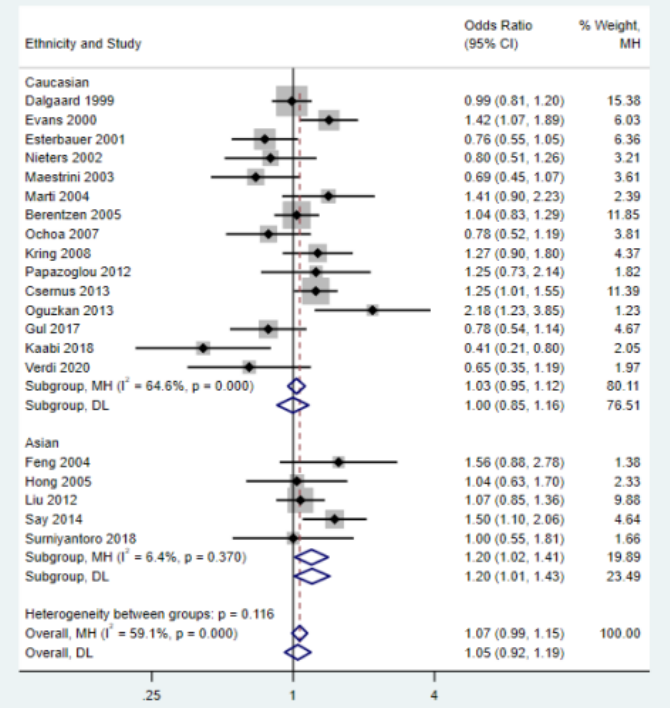

Figure 4

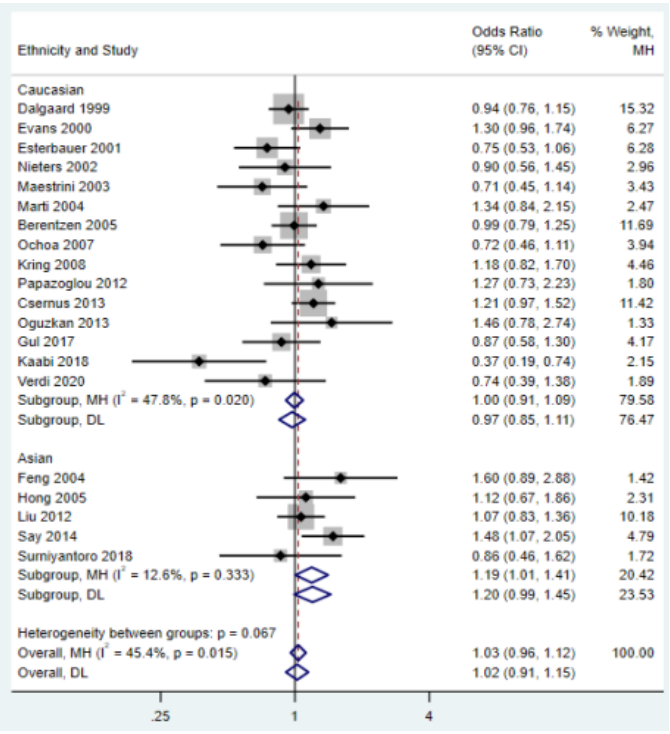

Figure 5

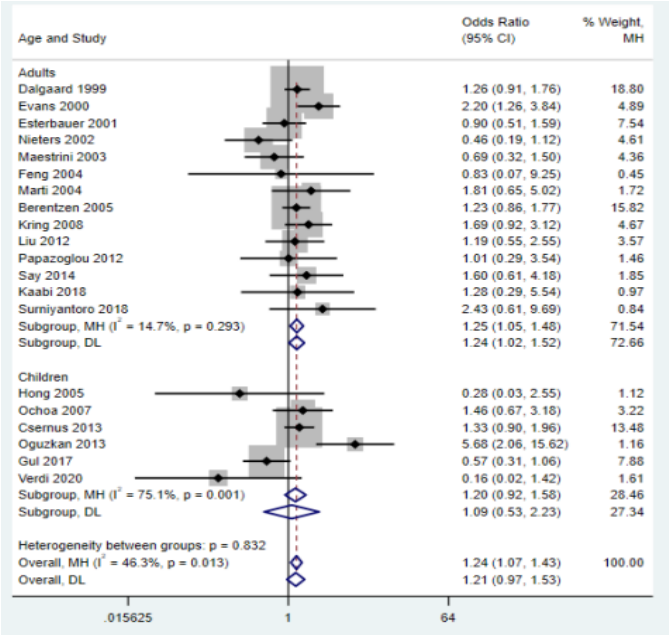

Figure 6

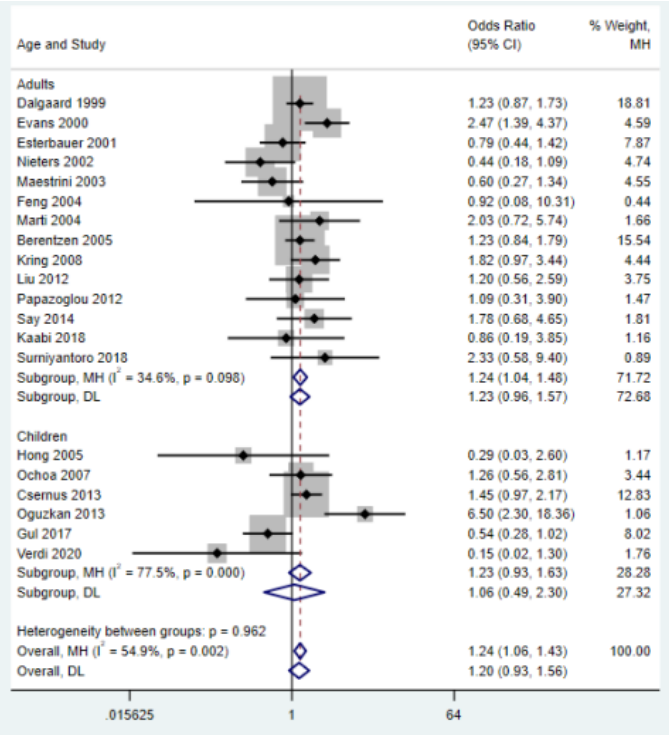

Figure 7

Discussion

UCP2 plays an important role in the development and treatment of overweight and obesity, as an obesity candidate gene involved in the regulation of glucose/lipid metabolism and energy homeostasis. UCP2 affects the susceptibility to obesity and obesity-related diseases by decreasing the activity or expression of these UCPs, thereby increasing oxidative phosphorylation coupling to reduce energy expenditure. Thus, the expression/activity levels of UCP2 influence the relationship between UCP2 gene polymorphisms and obesity [26]. The 3'UTR region of the UCP2 Ins/Del polymorphic gene, which is only 158 bp away from the transcription termination codon, may function by participating in mRNA processing or transcriptional stability, and lower transcript stability may result in lower UCP2 protein translocation [11]. These three polymorphisms are currently the most studied in the UCP2 gene: 45bp Ins/Del in exon 8, missense variant in exon 4 (rs660339, Ala55Val, C/T), and one in the promoter region (rs659366, 866G/A) [12]. The association of one of these 45bp

Ins/Del polymorphisms with overweight and obesity remains highly controversial. Therefore, we systematically summarized 20 eligible case-control studies using the largest sample size available for this meta-analysis to assess the association between UCP2 45bp Ins/Del with genetic susceptibility and overweight and obesity and guide future studies.

The analysis showed that the UCP2 45bp Ins/Del gene polymorphism was significantly associated with genetic susceptibility to overweight and obesity only in the recessive model (OR=1.24, 95%CI=1.07-1.43, P=0.004), but race-specific subgroup analysis showed that the UCP2 45bp Ins/Del gene polymorphism was significantly associated with genetic susceptibility to overweight and obesity in Asian populations in the allelic (OR=1.18, 95%CI=1.02-1.36, P=0.027), dominant (OR=1.20, 95%CI=1.02-1.41, P=0.030), and heterozygote (OR=1.19, 95%CI=1.01-1.41, P=0.043) models, and no significant association was found in Caucasian populations.

Brondani's study showed similar findings to this study that polymorphism is significantly associated with increased BMI in Asian populations [27]. However, in a study on Caucasian populations, the findings of Brondani et al. contradicted our findings by suggesting that the UCP2 45bp Ins/Del gene polymorphism was significantly associated with obesity in Caucasian populations [28]. Comparative results from other studies have shown that individuals carrying the II genotype and Ins allele are at higher risk of obesity than those carrying the DD genotype compared to other genotypes or alleles [17,21,29]. Moreover, Ins allele carriers have a higher BMI in some populations [30]. Conversely, Zhang et al. and Surniyantoro et al. showed that 45bp Ins/Del gene polymorphism is not a risk factor for overweight and obesity [24,31]. The nutritional characteristics of populations may influence the relationship between genetic variation and obesity, and food and cultural habits and environmental factors differ for each race, which may influence the association between UCP polymorphisms and obesity [24,32]. Therefore, future studies on obesity gene polymorphisms should consider environmental factors and dietary habits. Moreover, there are numerous genes associated with obesity [33], and each population has different genetic variants in its gene pool; these factors may also play a role in obesity. Kring et al. concluded that there is a lack of significant correlation between genetic variants and BMI because obesity is a mixed phenotype, and several other proxies for overweight and obesity are available, such as waist circumference, waist circumference for a given BMI, sagittal abdominal diameter, and waist-to-hip ratio [15], which should be considered in future studies. Some researchers have suggested that the effect of insertion polymorphisms may be age-related and associated with late-onset obesity [8]. Therefore, we conducted a subgroup analysis of the study population divided into child and adult groups for age and only found significant associations in the recessive (OR=1.19, 95% CI=1.01-1.41, P=0.011) and homozygote (OR=1.24, 95% CI=1.04-1.48, P=0.017) models in the adult group, while the other groups did not show significant associations. A study by Gul et al. concluded that UCP2 exon 8 Ins/Del had no significant effect on the risk of obesity in adolescents, which is similar to our findings, and that low HDL cholesterolemia may be associated with the Ins allele [12]. Gender-stratified UCP2 45bp Ins/Del gene polymorphism analysis by Surniyantoro et al. and Papazoglou et al. showed that gene polymorphisms had opposite effects on male and female populations, with the II genotype and I allele leading to reduced UCP2 expression and increased body weight in the male population. Conversely, in the female population, the UCP2 45bp Ins/Del gene polymorphism is recessively associated with obesity [22,24].

Heterogeneity between studies is a matter of concern, and high heterogeneity was observed in all our analyses of genetic models of the association of the UCP2 45bp Ins/Del gene polymorphism with overweight and obesity. After stratifying the analysis by ethnicity, heterogeneity was significantly lower in the analysis of Asian populations; however, significant heterogeneity remained in the analysis of Caucasian populations, suggesting some other confounding factors in the study on Caucasian populations. The sources of heterogeneity were worth exploring; therefore, a regression analysis was implemented, including covariates such as age, sex, and sample size. However, none of these covariates individually or jointly explained the observed heterogeneity. Study quality, general characteristics of participants, representation of participants, gene-environment interactions, and genotyping methods may contribute to heterogeneity. Without additional information on the metabolic and clinical characteristics of the articles analyzed, the role of these factors in the sources of heterogeneity is difficult to describe accurately.

Therefore, the results of the current meta-analysis should be interpreted with caution. First, the definition of cases is not uniform across studies; in some studies, cases are defined as obese populations, morbidly obese populations, or mixed populations of overweight and obesity. Moreover, in some relevant studies, the threshold values of overweight or obesity were different. Second, due to technical limitations, we only retrieved studies published in English and Chinese, which may lead to certain omissions. Lastly, our analysis revealed significant heterogeneity among studies on Caucasian populations.

Conclusions

Our study showed a significant association between UCP2 45bp Ins/Del gene polymorphism and genetic susceptibility to overweight and obesity in Asian populations but not in Caucasian populations. Factors such as age, sex, environmental factors, and dietary habits may influence the accuracy of this association. To obtain strong evidence, a larger sample size and more adequate information are needed to conduct more detailed analytical studies.

Declarations

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References

1. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19•2 million participants. Lancet. 2016; 387: 1377-1396

2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the

Global Burden of Disease Study. Lancet. 2013; 384: 766-781.

3. M. Blüher. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019; 15: 288-298.

4. H. Oberkofler, Liu YM, Esterbauer H, Hell E, Krempler F, et al. Uncoupling protein-2 gene: reduced mRNA expression in intraperitoneal adipose tissue of obese humans. Diabetologia. 1998; 41: 940-946.

5. Fleury C, Neverova M, Collins S, Raimbault S, Champigny O, et al. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. Nat Genet. 1997; 15: 269-272.

6. Dalgaard LT, Sørensen TI, Andersen T, Hansen T, Pedersen O. An untranslated insertion variant in the uncoupling protein 2 gene is not related to body mass index and changes in body weight during a 26-year follow-up in Danish Caucasian men. Diabetologia. 1999; 42: 1413-1416.

7. D. Evans, Minouchehr S, Hagemann G, Mann WA, Wendt D, et al. Frequency of and interaction between polymorphisms in the beta3-adrenergic receptor and in uncoupling proteins 1 and 2 and obesity in Germans. Int J Obes Relat Metab Disord. 2000; 24: 1239-1245.

8. H. Esterbauer, Schneitler C, Oberkofler H, Ebenbichler C, Paulweber B, et al. A common polymorphism in the promoter of UCP2 is associated with decreased risk of obesity in middle-aged humans. Nat Genet. 2001; 28: 178-183.

9. Nieters, N. Becker, J. Linseisen. Polymorphisms in candidate obesity genes and their interaction with dietary intake of n-6 polyunsaturated fatty acids affect obesity risk in a sub-sample of the EPIC-Heidelberg cohort. Eur J Nutr. 2002; 41: 210-221.

10. S. Maestrini, Podestà F, Di Blasio AM, Savia G, Brunani A, et al. Lack of association between UCP2 gene polymorphisms and obesity phenotype in Italian Caucasians. J Endocrinol Invest. 2003; 26: 985-990.

11. Marti A, Corbalán MS, Forga L, Martinez-González MA, Martinez JA. Higher obesity risk associated with the exon-8 insertion of the UCP2 gene in a Spanish case-control study. Nutrition. 2004; 20: 498-501.

12. Qiwen F, Yan D, Qing S, Huili X, Jingnan Z. Association of uncoupling protein 2 gene polymorphisms with type 2 diabetes in Chinese. Journal of Shanghai Second Medical University. 2004; 108-110.

13. Berentzen T, Dalgaard LT, Petersen L, Pedersen O, Sørensen TI. Interactions between physical activity and variants of the genes encoding uncoupling proteins -2 and -3 in relation to body weight changes during a 10-y follow-up. Int J Obes (Lond). 2005; 29: 93-99.

14. Qingrong H. Association of uncoupling protein 2 gene polymorphisms with obesity in children and adolescents. Chinese Journal of Endocrinology and Metabolism. 2005; 545-546.

15. Ochoa MC, Santos JL, Azcona C, Moreno-Aliaga MJ, Martínez-González MA, et al. Association between obesity and insulin resistance with UCP2-UCP3 gene variants in Spanish children and adolescents. Mol Genet Metab. 2007; 92: 351-358.

16. Kring SI, Larsen LH, Holst C, Toubro S, Hansen T, et al. Genotype-phenotype associations in obesity dependent on definition of the obesity phenotype. Obes Facts. 2008; 1: 138-145.

17. X. Liu, Zhang B, Liu X, Shen Y, Li J, et al. A 45-bp insertion/deletion polymorphism in uncoupling protein 2 is not associated with obesity in a Chinese population. Biochem Genet. 2012; 50: 784-796.

18. Papazoglou D, Papathanasiou P, Papanas N, Papatheodorou K, Chatziangeli E, Nikitidis I, et al. Uncoupling protein-2 45-base pair insertion/deletion polymorphism: is there an association with severe obesity and weight loss in morbidly obese subjects? Metab Syndr Relat Disord. 2012; 10: 307-311.

19. Csernus K, Pauler G, Erhardt E, Lanyi E, Molnar D. Uncoupling protein-2 gene polymorphisms are associated with obesity in Hungarian children. Acta Paediatr. 2013; 102: e200-204.

20. Oguzkan-Balci S, Col-Araz N, Nacak M, Araz M, Sabanci H, et al. Mitochondrial uncoupling protein 2 (UCP2) gene polymorphisms are associated with childhood obesity and related metabolic disorders. J Pediatr Endocrinol Metab. 2013; 26: 277-283.

21. Say YH, Ban ZL, Arumugam Y, Kaur T, Tan ML, et al. Uncoupling protein 2 gene (UCP2) 45-bp I/D polymorphism is associated with adiposity among Malaysian women. J Biosci. 2014; 39: 867-875.

22. Gul, Ateş O, Özer S, Kasap T, Ensari E, et al. Role of the Polymorphisms of Uncoupling Protein Genes in Childhood Obesity and Their Association with Obesity-Related Disturbances. Genet Test Mol Biomarkers. 2017; 21: 531-538.

23. Kaabi YA. The Deletion Polymorphism in Exon 8 of Uncoupling Protein 2 is Associated with Severe Obesity in a Saudi Arabian Case-control Study. Indian J Endocrinol Metab. 2018; 22: 200-203.

24. Surniyantoro HNE, Sadewa AH, Hastuti P. Uncoupling Protein 2 (UCP2) as Genetic Risk Factor for Obesity in Indonesia is Different in Gender Stratification. Kobe J Med Sci. 2018; 64: E64-e72.

25. Verdi H, Kınık ST, Baysan-Çebi HP, Yalçın YY, Yazıcı-Güvercin AC, et al. Uncoupling protein gene UCP1-3826A/G, UCP2 Ins/Del and UCP3-55C/T polymorphisms in obese Turkish children. Turk J Pediatr. 2020; 62: 921-929.

26. Azzu V, Brand MD. The on-off switches of the mitochondrial uncoupling proteins. Trends Biochem Sci. 2010; 35: 298-307.

27. Brondani LA, Assmann TS, de Souza BM, Bouças AP, Canani LH, et al. Meta-analysis reveals the association of common variants in the uncoupling protein (UCP) 1-3 genes with body mass index variability. PLoS One. 2014; 9: e96411.

28. Brondani LA, Assmann TS, de Souza BM, Bouças AP, Canani LH, et al. Association of the UCP polymorphisms with susceptibility to obesity: case-control study and meta-analysis. Mol Biol Rep. 2014; 41: 5053-5067.

29. Hashemi M, Rezaei H, Kaykhaei MA, Taheri M. A 45-bp insertion/deletion polymorphism of UCP2 gene is associated with metabolic syndrome. J Diabetes Metab Disord. 2014; 13: 12.

30. Jia JJ, Zhang X, Ge CR, Jois M. The polymorphisms of UCP2 and UCP3 genes associated with fat metabolism, obesity and diabetes. Obes Rev. 2009; 10: 519-526.

31. Zhang M, Wang M, Zhao ZT. Uncoupling protein 2 gene polymorphisms in association with overweight and obesity susceptibility: A meta-analysis. Meta Gene. 2014; 2: 143-159.

32. Luan JA, Wong MY, Day NE, Wareham NJ. Sample size determination for studies of gene-environment interaction. Int J Epidemiol. 2001; 30: 1035-1040.

33. Kim HJ, Lee SY, Kim CM. Association between gene polymorphisms and obesity and physical fitness in Korean children. Biol Sport. 2018; 35: 21-27.