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Association of the Val66met polymorphism and risk of obesity, systematic review and meta-analysis

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ABSTRACT

Single nucleotide polymorphism of brain derived neurotropic factor gene, also known as Val66Met or rs6562, was found to be linked to obesity. However, reports on the link between this gene variant and obesity in Caucasian and Asian populations are inconsistent. A meta-analysis was, therefore, performed to determine the association between Val66Met polymorphism and the risk of obesity. Electronic databases, including Embase, CINAHL, and PubMed, were searched for relevant studies published before November 2018. Random effects model was used to calculate the pooled estimate based on the heterogeneity test results. Data were obtained from 11 studies involving 13,153 individuals with obesity and 18,689 non-obese individuals. The overall estimated odds ratio did not support the proposed association (OR 0.9, 95% CI 0.793–1.136). Stratified analysis, however, showed that Val/Val genotype is associated with increased risk of obesity among adults (OR 1.135, 95% CI 1.001–1.286) but associated with a reduced risk among adolescents (OR 0.61, 95% CI = 0.376, 0.984). The results highlight the role of confounding factors that need to be addressed when making inference.

INTRODUCTION

The prevalence of obesity has reached alarming proportions with more than 39% of adults aged 18 years and above being overweight and 13% as obese in 2014 (WHO, 2014a). Childhood obesity likewise also shows an increasing trend. In 2013, the number of overweight children under the age of 5 years was estimated to be over 42 million (WHO, 2014b). The cost of treating obesity and associated comorbidities, and prevention programs has become onerous to all nations in the world (Wang *et al*., 2011).

The crucial role of gene mutation/polymorphism in obesity is evident from a plethora of published reports. Genome wide-linkage studies provided evidence that around 253 trait loci implicated in obesity-linked phenotypes (Meyre *et al*., 2010).

Accumulating evidence suggests that common genetic variants or single-nucleotide polymorphisms (SNPs) may be a contributing factor to the obesity epidemic. Brain derived neurotropic factor (BDNF) is a type of neurotrophin encoded by the BDNF gene. This protein supports the growth and differentiation of neurons in the central nervous system. Although the function of BDNF is related to long-term memory, neuroplasticity, and growth of neurons (Khalin *et al*., 2015), a polymorphism of its gene was found to be related to obesity, where it was thought to suppress food intake through hippocampal signaling (El-Gharbawy *et al*., 2006; Monteleone *et al*., 2004). The rs6265, also known as Val66Met, is a single nucleotide Polymorphisim (SNP) of *BDNF* gene found to be linked to obesity. The more common G allele encodes for Valine (Val), while the A allele encodes for Methionine (Met). Accordingly, three genotypes emerge, GG (or Val/Val), AA (or Met/Met and GA (or Val/Met).

BDNF Val66met polymorphism has been associated with disorders, such as Schizophrenia (Eisenberg *et al*., 2013; Gratacòs *et al*., 2007; Suchanek *et al*., 2013), depression (Hosang *et al*., 2014), anxiety (Chen *et al*., 2006), eating disorders (Gratacòs *et al*., 2007), and some other disorders like sleeping disorder and tardive dyskinesia (Bachmann *et al*., 2012; Miura *et al*., 2014).

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However, considerable attention has been given to its potential association with obesity among the different populations (Beckers *et al*., 2008; Friedel *et al*., 2005; Hotta *et al*., 2009; Ja'afaruSani *et al*., 2012; León-Mimila *et al*., 2013; Marti *et al*., 2009; Morales-Marín *et al*., 2016; Perkovic *et al*., 2013; Skledar *et al*., 2012; Sustar *et al*., 2016; Thorleifsson *et al*., 2009; Timpano *et al*., 2011; Xi *et al*., 2011).

Generally, SNPs have modest impact on individual susceptibility to common forms of obesity, but due to their high frequency, they may have a large contribution to obesity in a given population (Lyon and Hirschhorn, 2005). The positive link betweenVal66Met and obesity was not ascertained in all published reports. Small sample size of the individual studies may have limited the power and generalizability of the findings. Thus, this meta-analysis was performed to ascertain the association between rs6562 and obesity.

MATERIALS AND METHODS

Search strategy

Two independent researchers conducted the search of the relevant articles in three major databases, Embase, CINHAL, and PubMed, using a different combination of the following keywords that paired "Val66Met," "rs6265," "G196A," "BDNF," and "SNP" with "obesity," and separately, with "BMI." A third researcher cross-checked and validated the articles selected from the databases. Any disagreement was discussed and resolved by the researchers. After the initial screening of the articles for inclusion criteria, a manual search of the lists of extracted articles was done to ensure better coverage of the topic. In addition, the literature search was supplemented by utilizing Google Scholar. Direct contacts were made with four authors to clarify the results. The literature search was updated in November 2018.

Study eligibility and selection criteria

We assessed the quality of each study based on the contents, methodology, and appropriateness for inclusion. Inclusion criteria were as follows: 1) observational studies; 2) studies examining the relationship between *BDNF* Val66Met polymorphism (including genotype and allele frequencies) and the risk of obesity; 3) studies reporting the measure of association as odds ratio (OR); and 4) studies in English. Studies on eating disorders or animal or experimental studies, reviews, meta-analysis, editorials, abstract, and unpublished reports were excluded.

Data extraction

Data including the authors' name, year of publication, country (ethnicity), age (mean and SD), number of participants, genotype, and allele frequency distribution according to the obesity status, measure of association reported as OR and 95% confidence interval (CI) were extracted whenever available.

Statistical analyses

The OR with 95% CI from the selected studies was used to assess the association of obesity and Val66Metpolymorphism. Data from individual studies were extracted for calculation of OR as the effect size of interest. The Val/Val genotype was used as the test group, while Met allele (Met/Met + Val/Met) served as a reference group. Forest plot was used to depict the individual studies and pooled effect size. Random effects model was used to calculate the pooled estimate. Heterogeneity was assessed with Tau-squared, which reflects variance of true effect sizes, and I^2statistic, which reflects the percentage of variation among true effect sizes not due to sampling error (Higgins and Thompson, 2002). A p value of less than <0.05 was indicative of significant heterogeneity among the studies. Publication bias was assessed through funnel plot along with Begg's and Egger's regression statistics. Sensitivity analysis was performed using sequential omission of individual studies in every comparison. All data were entered and analyzed using comprehensive meta-analysis software v.2.

RESULTS

The initial search yielded 912 records. Screening by title resulted in 108 records related to the keywords. After examining abstracts from each of the records, we excluded 31 articles that were unrelated to val66met gene and 27 reports on disorders other than obesity. Another 20 reports were excluded as they were either reviews, meta-analyses, animal studies, and abstracts or being written in a language other than English.

The total number of full-text articles, which were eligible for data extraction, was 30. Out of the 30 studies, 16 studies were excluded as they did not include reports on the association between Val66Met polymorphism (including genotype/allele frequency) and obesity. Further exclusion included studies in which the measure of association was either ambiguous (León-Mimila *et al*., 2013) or rejected by the software due to problematic confidence interval of the odds ratio (Timpano *et al*., 2011; Wu *et al*., 2010) or where the authors did not reply to our queries, leaving 11 eligible studies for the meta-analysis (Fig. 1).

Characteristics of the participating studies

The characteristics of individual studies are shown in Table 1. Most of the studies were conducted on adults except for four studies (Friedel *et al*., 2005; Ja'afaruSani *et al*., 2012; Skledar *et al*., 2012; Xi *et al*., 2011), which were conducted on adolescents. Participants in three of the studies were Asians (Hotta *et al*., 2009; Ja'afaruSani *et al*., 2012; Wang *et al*., 2011) and the rest were Caucasians and or Americans. Perkovic *et al*. (2013) reported data from three different time periods and were considered individually, while Beckers *et al*. (2008) reported data from a sample of female subjects. All studies had reported in frequency tables that allowed for computation of OR except (Thorleifsson *et al*., 2009) who only reported an adjusted OR. In total, 11 studies involving 13,153 individuals with obesity and 18,689 non-obese individuals were included in this analysis.

Association of val66met and obesity

The odds ratio of obesity for Val/Val versus Met carriers of the individual studies showed a wide variation. The overall pooled estimate (OR 0.9, 95%CI 0.793, 1.136) showed no significant association between Val66Met genotype and obesity. However, when studies were stratified according to age group, Val/Val genotype appeared as a risk factor for obesity among adults (OR 1.135, 95% CI =1.001, 1.286), while it was protective among adolescents (OR 0.61, 95% CI = 0.376, 0.984) (Figs. 2–4).

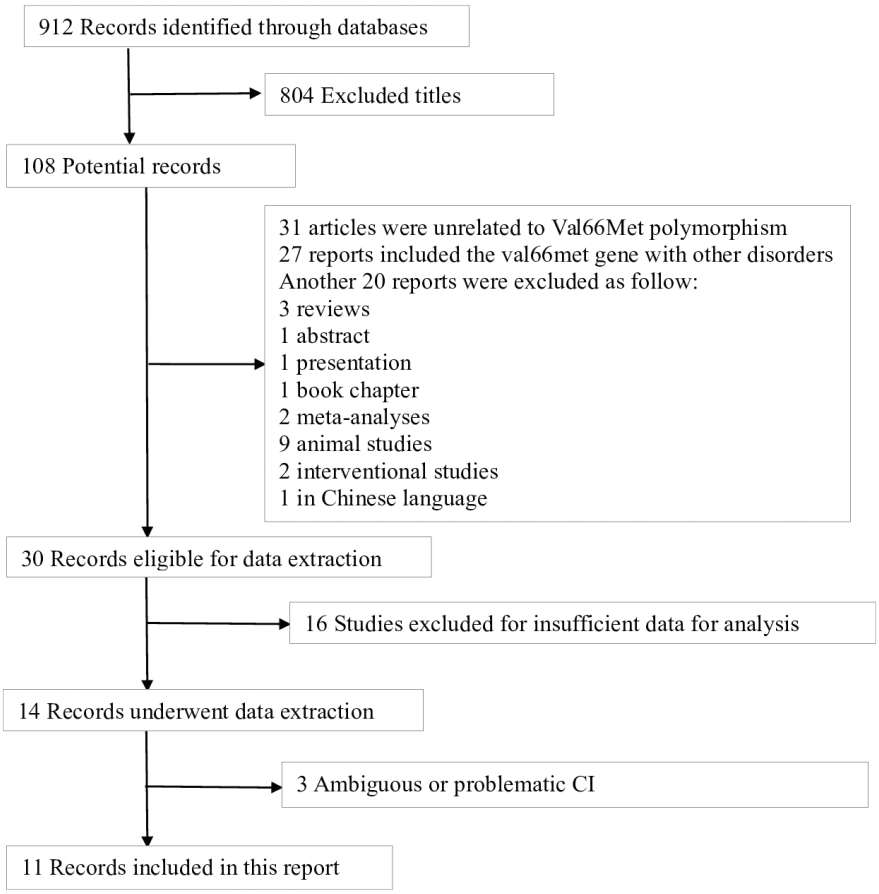

Figure 1. Flow diagram of study selection.

Table 1. Characteristics of individual studies.

	Study name	Year	Country	Study design	n		Mean age and SD		BMI cut off value	Hardy Weinberg equation	IS indexed
					Obese	Non-obese	Obese	Non-Obese			
1	Ja'afaru Sani *et al.*	2012	Malaysia	Cross sectional	132	432	14.85 ± 1.27		30	No deviation	No
2	Marti *et al.*	2009	Spain	Case control	159	154	42.4 ±10.5	38.6 ± 9.0	30	No deviation	Yes
	Nikolac *et al.*	2013	Croatia	Cohort					30	No deviation	Yes
3	Nikolac *et al.*	1972			229	110	43.4 ± 4.4				
4	Nikolac *et al.*	1982			275	64	53.4 ± 4.5				
5	Nikolac *et al.*	2006			282	57	77.2 ± 4.5				
6	Sustar *et al.*	2016	Croatia	Case control	360	138	-		30	No deviation	Yes
7	Morales-Marin *et al.*	2016	USA	Cross sectional	79	60	36.29 ±14.37		30	-	Yes
8	Skeledar	2012	Croatia	Cross sectional	74	226	10.78 ± 4.06		None	No deviation	yes
9	Friedel *et al.*	2004	Germany	Case control	183	96			99th %	No deviation	yes
10	Hotta *et al.*	2009	Japan	Case control	1127	1733	49.1±13.6	48.8±15.8	30	No deviation	yes
11	Becker *et al.*	2008	Belgium	Case control	532	197	37.5 ± 0.4	35.0 ± 0.6	30	No deviation	yes
12	Thorleifsson *et al.*	2009	Iceland	Genome wide association	5996	9255	51.47 (17.43)		30	No deviation	Yes
			Netherlands		331	1432	58.43 (10.28)				
			Denmark		949	2413	47.17 (8.73)				
			European American		591	472	47.13 (12.52)				
			African American		625	231	45.28 (11.75)				
13	Xi *et al.*	2011	Chinese	Cross sectional	1229	1619	11.8 (2.9)	12.5 (3.2)	95th %	No deviation	Yes

Heterogeneity and sensitivity analysis

Table 2 shows heterogeneity statistics. The variance (Tau-squared) and the proportion of variation of true effect not attributed to random error (I^2statistic) were higher for combined analysis. Nonetheless, the variance and I^2 were reduced after stratification and were the lowest among studies on the adults. Moreover, omission of the study by Ja'afaruSani *et al*. (2012) substantially reduced heterogeneity and variance among adolescent studies. With respect to sensitivity analysis, although the 95% CI and *p* value have only minimally changed with the exclusion of some studies, the magnitude of OR was not appreciably affected (Table 3).

Publication bias

Funnel plot shows some asymmetry (Figs. 5–7) indicating some degree of publication bias. However, Begg's and Egger's *p* values were greater than 0.05.

DISCUSSION

Successful intervention is undoubtedly based on evidence-based practice. Meta-analysis is acknowledged as being amongst the highest levels of evidence (Burns *et al*., 2011). It could also provide a tool for clinicians and public health specialists to design proper interventions that could help curb the escalating incidence of obesity.

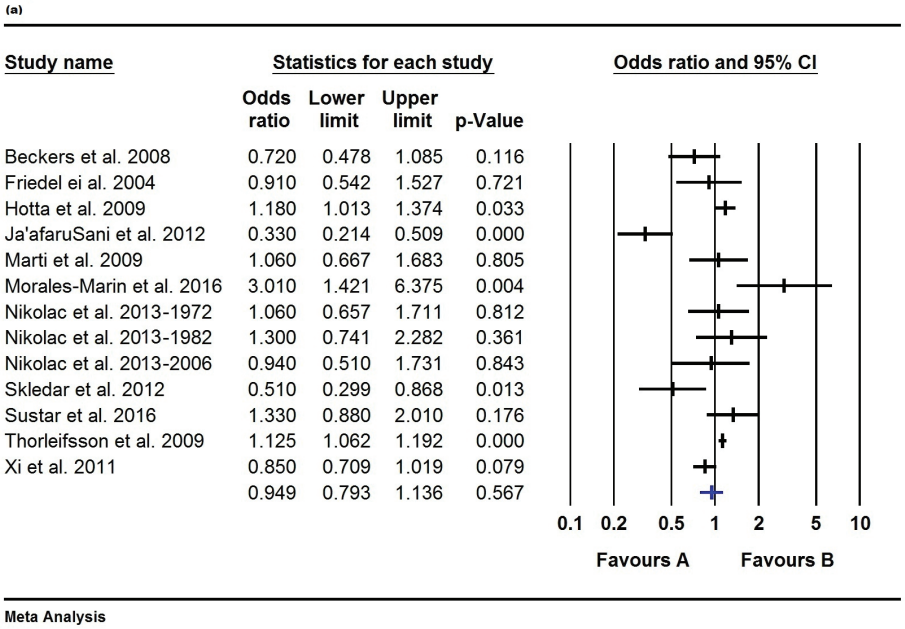

Figure 2. Forest plot-all studies.

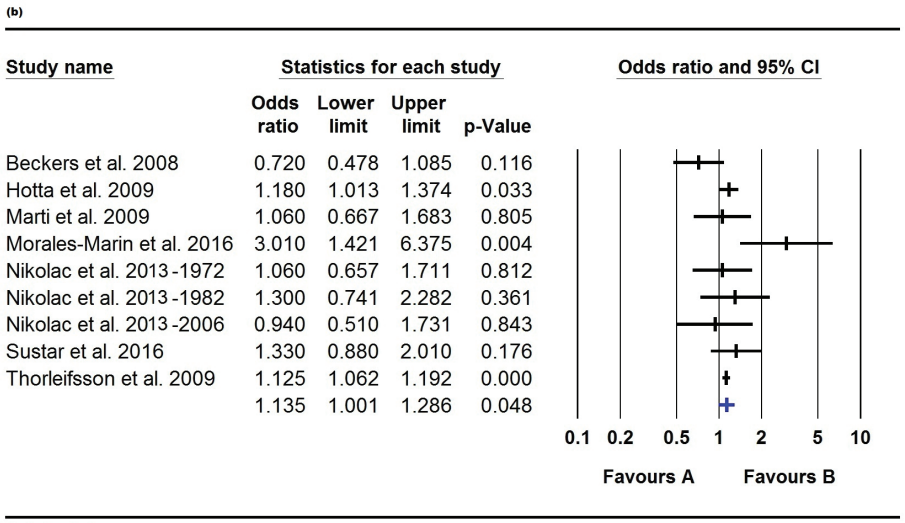

Figure 3. Forest plot-adults.

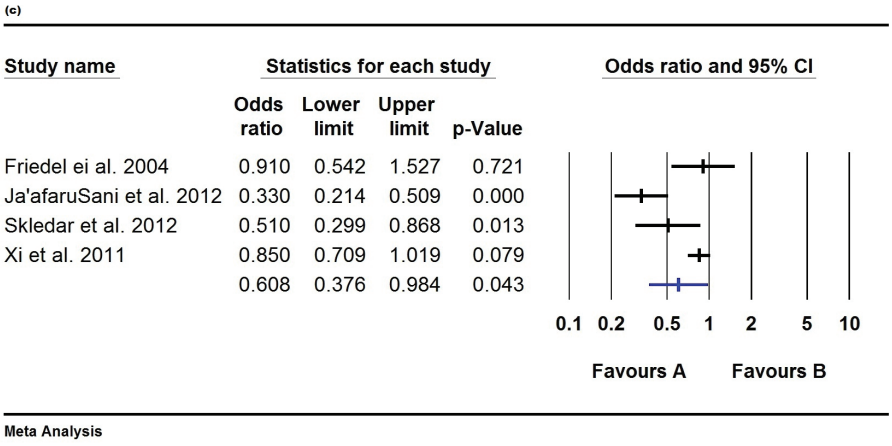

Figure 4. Forest plot- adolescents.

Table 2. Heterogeneity indices.

Population	Pooled OR 95% CI	Tau-squared	I^2
All	0.949 (0.79,1.14)	0.065	79.73
Adult	1.14 (1.01,1.29)	0.010	37.73
Children	0.61 (0.38,0.98)	0.193	83.85
Children*	0.776 (0.583,1.032)	0.028	40.47

*Ja'afaru Sani *et al.* removed.

Table 3. Sensitivity analysis.

	All		Adults		Adolescents	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Beckers *et al*., 2008	0.97 (0.81,1.17)	0.758	1.16 (1.06,1.26)	0.001		
Hotta *et al*., 2009	0.92 (0.74,1.15)	0.478	1.13 (0.94,1.36)	0.208		
Marti *et al*., 2009	0.94 (0.78,1.14)	0.529	1.14 (0.99,1.31)	0.063		
Morales-Marin *et al*., 2016	0.91 (0.76,1.08)	0.277	1.12 (1.07,1.18)	0.000		
Nikolac *et al*., 2013-1972	0.94 (0.78,1.14)	0.530	1.14 (0.99,1.31)	0.062		
Nikolac *et al*., 2013-1982	0.93 (0.77,1.12)	0.452	1.13 (0.98,1.29)	0.082		
Nikolac *et al*., 2013-2006	0.95 (0.79,1.14)	0.585	1.14 (1.01,1.31)	0.048		
Sustar *et al*., 2016	0.92 (0.76,1.12)	0.404	1.12 (0.98,1.28)	0.104		
Thorleifsson *et al*., 2009	0.93 (0.73,1.18)	0.552	1.14 (0.93,1.4)	0.191		
Friedel *et al*., 2004	0.95 (0.79,1.15)	0.604			0.54 (0.28,1.01)	0.053
Ja'afaruSani *et al*., 2012	1.03 (0.89,1.19)	0.666			0.78 (0.58,1.03)	0.082
Skledar *et al*., 2012	0.99 (0.83,1.18)	0.887			0.64 (0.35,1.17)	0.147
Xi *et al*. 2011	0.96 (0.79,1.17)	0.701			0.53 (0.29,0.96)	0.035
Overall	0.95 (0.79,1.14)	0.567	1.13 (1.001,1.29)	0.048	0.61 (0.38,0.98)	0.043

In this study, the results of meta-analysis support the association of obesity with Val66Met polymorphism that is confounded by age.

The random effects model was used to calculate the pooled estimate on assumption of variation among the studies included in this review (Borenstein *et al*., 2007). The analysis included different study designs and on mixed populations. Thus, I^2 statistic showed that there was a considerable amount of variation among studies that is not attributed to random error. Heterogeneity is inevitable in meta-analysis (Huedo-Medina *et al*., 2006) and it might indicate the presence of a factor with differential impact, as was the case in this study. Stratified analysis by age group reduced the true variance (tua-squared) and also reduced the I^2 whereby apparently identifying a source of heterogeneity. It identified age as an important factor to be considered when making an inference. In addition, it also showed that omission of the study performed by Ja'afaruSani *et al*. (2012) did not significantly influence the pooled estimate, but affected the measure of heterogeneity. The claim that a significant association of Met allele and obesity is only applicable to female gender was not evident in Ja'afaruSani et al's study. This might question the validity of such results. In general, with

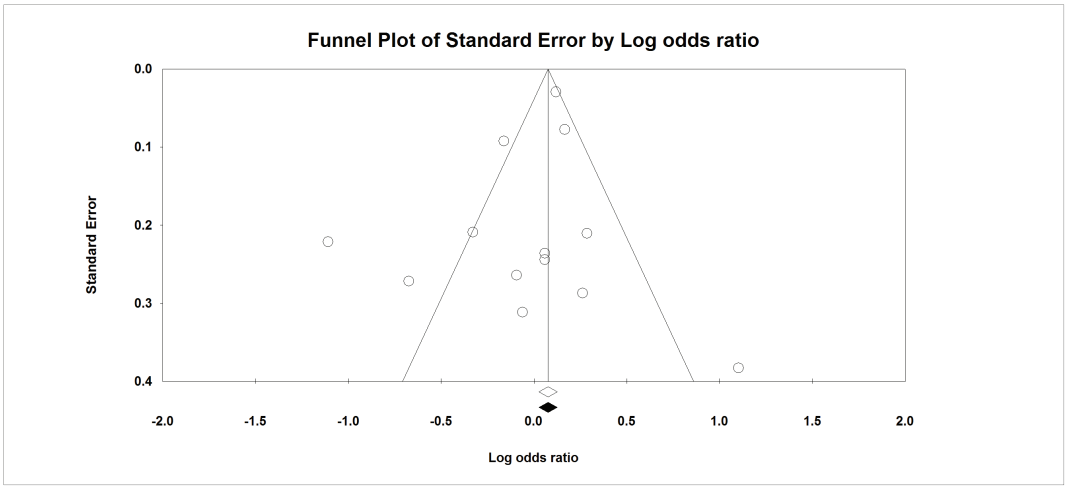

Figure 5. Funnel plot-all.

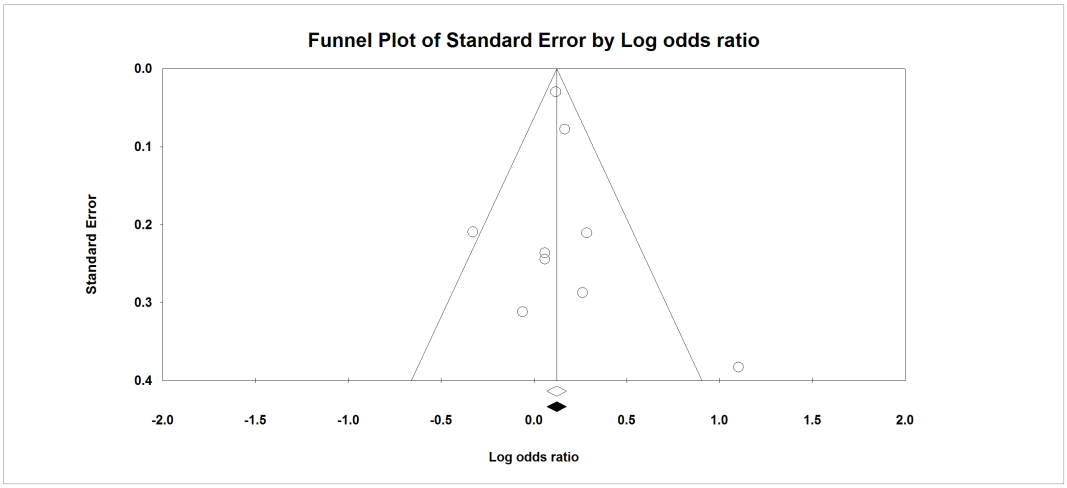

Figure 6. Funnel plot-adults.

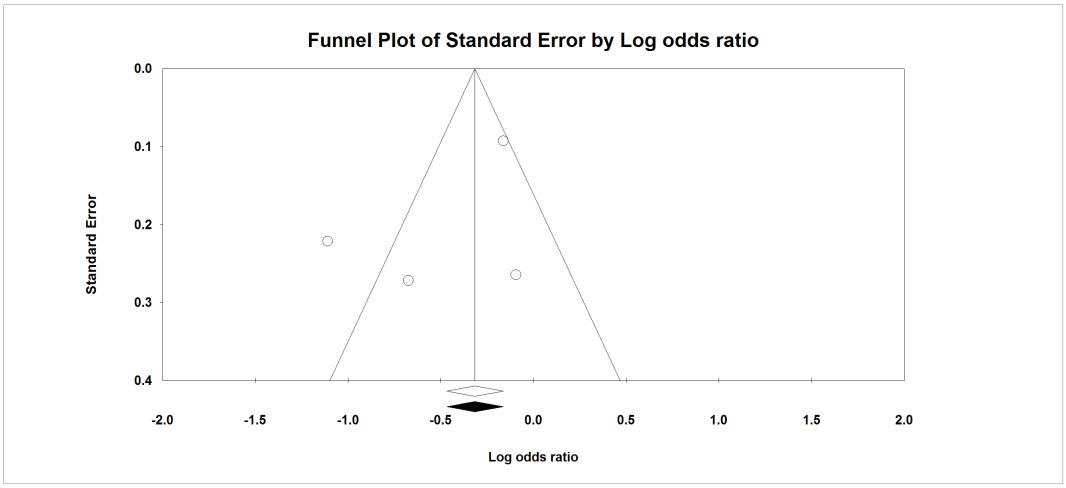

Figure 7. Funnel plot-adolescents.

a limited number of studies, publication bias may be anticipated (Copas and Shi, 2000). However, such bias was not evident in our study as the studies included in this analysis have shown contradicting results.

BDNF was found to regulate body weight by suppressing appetite in mice (Lapchak and Hefti, 1992; Pelleymounter *et al*., 1995). Studies in human and rodents have further confirmed the dominant role of BDNF and TrKB in the control of energy balance. In mice, global BDNF down regulation increased feeding and body weight (Kernie *et al*., 2000; Rios, 2013; Xu *et al*., 2003). Selective deletion of BDNF in the ventromedial and dorsomedial hypothalamus caused hyperphagia and obesity in adult mice (An *et al*., 2015; Kernie *et al*., 2000; Rios *et al*., 2001).

Adding to the impact of *BDNF* gene mutation on body weight, the polygenic nature of obesity itself makes it difficult to identify a single most influential gene. Nonetheless, the genetic differences of obesity have been replicated from different world populations (Lyon and Hirschhorn, 2005). This signifies the complex interaction of several factors in the causation of obesity including an individual's phenotype and disease risk factors other than BDNF.

It is relevant to acknowledge that the magnitude of effect size plays an important role in deciding whether the result is applicable for prognostic or diagnostic purposes (Chen *et al*., 2010). Jakobsdottir *et al*'s (2009) logical illustration pointed out that a good genetic marker should be a good classifier (large enough) to discriminate between cases and control, which means high specificity of the applied markers. Nonetheless, the estimated OR in this study was not sizable and it is in tandem with most genetic studies.

Although we had taken all necessary precautions to ensure reliability of the results, few limitations were inevitable. First, we could not perform gender specific or age specific analysis due to lack of such information from participating studies. Several studies have reported sexual dysmorphism with particular reference to several factors implicated in obesity. Thus, there is a need to look into this aspect. Second, we only were able to perform analysis with recessive model due to the nature of extracted data. Last, most of the data emerged from Caucasian populations. This might be attributed to a high frequency of gene mutation in the Caucasians compared to the Asians. In conclusion, our findings add to evidence of genetic contribution to obesity and highlight the impact of age as a factor that might influence the interpretation.

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CONFLICT OF INTEREST

Authors declare that they have no conflicts of interest.

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