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Review article

Association of Brain-derived neurotrophic factor gene polymorphisms with body mass index: A systematic review and meta-analysis

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ABSTRACT

Background: Many studies with inconsistent results have assessed the association of Brain-derived neurotrophic factor (*BDNF*) gene polymorphisms with prevalence of obesity and overweight. This review aims to provide a summary of the literature evaluating the relation between *BDNF* genotype and body mass index (BMI).
Methods: A systematic search through PubMed, Scopus, Science direct, Ovid and Cochrane was performed. We included observational studies with cross-sectional and case-control design, which investigated relationship between all kinds of *BDNF* polymorphisms with BMI, as a representative index of obesity and overweight. Newcastle–Ottawa Scale was used to assess the quality of included articles.
Results: Thirty five studies were included in quantitative synthesis. Analyses were performed separately using OR, β coefficient and mean. Significant association were documented between rs925946 and BMI (OR = 1.12, 95% CI = 1.08–1.17, P heterogeneity = 0.317), rs10501087 and BMI (OR = 1.14, 95% CI = 1.04–1.24, P heterogeneity = 0.861), rs6265 and BMI (OR = 1.13, 95% CI = 1.07–1.19, P heterogeneity = 0.406), rs988712 and BMI (OR = 1.29, 95% CI = 1.18–1.40, P heterogeneity = 0.602). According to pooled β coefficient analysis, significant result was only observed in the rs925946 polymorphism subgroup. Pooled mean analysis showed that overall effects for the association between *BDNF* polymorphisms and BMI were not statistically significant.
Conclusion: This meta-analysis suggests that some polymorphisms in *BDNF* gene including rs925946, rs10501087, rs6265 and rs988712 can be considered as genetic determinants of obesity.

Contents

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1. Introduction

Prevalence of obesity is increasing in both developed and developing countries, challenging scientists to overcome this problem [1]. The World Health Organization (WHO) reported that almost half or more than half of the population in USA (61.1%), Europe (54.8%), and Eastern Mediterranean (46.0%) are overweight or obese (body mass index (BMI) $\geq$ 25 or BMI $\geq$ 30 kg/m^2, respectively); meanwhile the prevalence was reported to be lower in Africa (26.9%), South-East Asia (13.7%), and the Western pacific (25.4%) [2]. Obesity is a major risk factor for several disorders and chronic diseases [3]. Articles show in both developed and developing countries, Obesity can result in serious problems such as hypertension, cardiovascular disease, insulin resistance and dyslipidemia [4]. Furthermore, obesity poses a financial burden to societies. Based on a systematic review, 0.7% to 2.8% of total healthcare expenditure of each country belongs to health services towards obesity. Moreover, obese individuals are faced with almost 30% higher medical costs than their normal weight peers [5].

The increasing prevalence of obesity and overweight could be attributed to lifestyle changes due to urbanization leading to reduced physical activity and increase in calorie intake through consumption of high-density foods [6]. In addition to environmental factors, genetic factors contribute to the prevalence of obesity. Various genotypes are implicated in differences in energy expenditure, resting metabolic rate, thermic effect of food, and cost of energy during exercise [7]. Many genome-wide association studies (GWAS) have assessed genetic contribution in different ethnicities to find common genetic variants and their association with biological problems such as asthma, cardiovascular disease, type 2 diabetes and obesity [8–11].

Brain-Derived Neurotrophic Factor (*BDNF*), a key protein in central nervous system (CNS), involves in proliferation, differentiation, survival, and death of neuronal cells [12]. Recent studies have reported changes of circulating *BDNF* in major depression, bipolar, Alzheimer, Huntington, and Parkinson diseases [13]. In addition, because of *BDNF* attendance in hypothalamus (the center of appetite), investigators have evaluated a hypothesis that polymorphisms of the *BDNF* gene might affect obesity and energy balance as well [14–16]. Different studies have inconsistent results regarding the association of *BDNF* gene polymorphisms with prevalence of obesity and overweight. There are various *BDNF* single nucleotide polymorphisms (SNP) including: rs6265, rs925946, rs4923461, rs10767664, rs10501087, rs988712, rs4074134, rs2030323, rs10835211, rs7481311, rs1519480, and rs1488830. Several GWAS have shown that showed these variants might be associated with weight, BMI and several related traits [17–20] However, results from previous studies remain contradictory. Therefore, to increase statistical power and achieve a more precise estimation of the effects, we conducted a systematic review and meta-analysis to provide a summary of the literature evaluating the relation between *BDNF* gene variances and BMI.

2. Methods and materials

2.1. Search strategy

A systematic search through PubMed, Scopus, Science direct, Ovid and Cochrane was performed up to November 2015. We furthermore screened reference lists of published articles to identify probable related papers. The following keywords were used in our search strategy: 'Brain-derived neurotrophic factor', 'BDNF', and all polymorphisms of BDNF included 'rs6265', 'Val66Met', 'rs925946', 'rs4923461', 'rs10767664', 'rs10501087', 'rs988712', 'rs4074134', 'rs2030323', 'rs10835211', 'rs7481311', 'rs1519480', and 'rs1488830' in combination with 'body mass index', 'BMI', 'overweight', 'obesity', 'body fat', 'fat mass', 'waist circumference', 'abdominal fat', 'WC', 'weight' and 'adiposity'. All keywords were selected from the medical subject headings database [21].

2.2. Inclusion criteria

We included observational studies including cross-sectional and case-control designs which investigated the relationship between all kinds of *BDNF* polymorphism and BMI as a representative marker of obesity and overweight. We conducted this systematic review in adult human population ($\geq$18 year), either single sex or both male and female participants. Papers reporting odds ratio, Beta, and mean of BMI in relation to *BDNF* SNPs were included. Additionally, we were able to analyze compatible articles that considered same risk allele as obesity related factor.

2.3. Exclusion criteria

We excluded articles with the same population [22]. Furthermore, articles which did not reports on standard deviation or standard error were eliminated from meta-analysis but remained in the systematic review table [10,23–25]. Some studies could not be completely included because the value of Beta was considerably different from other papers [26,27] or considered a different risk allele for some polymorphisms from the frequent risk allele reported in papers (this is the case for rs6265, rs925946 [20] and rs6265 [26]).

2.4. Data extraction

Two authors independently extracted information from included articles. Generally, extracted data included characteristics of the study (e.g. first author's last name, publication date, country and polymorphisms of *BDNF*), demographics of participants (e.g. mean of age, sample size and BMI), outcome measures (e.g. OR, beta or mean), main result and adjusted variables.

2.5. Quality assessment

Newcastle–Ottawa Scale was used to assess the quality of articles. This check-list evaluates articles based on three domains including selection, comparability and outcome with 0–10 minimum to maximum scores. Studies receiving 0–4 points, 5–7 points and 8–10 points out of 10 were considered having low, moderate and high quality, respectively.

2.6. Statistical analysis

The eligible studies had reported the association between *BDNF* polymorphisms and obesity in three different forms. A number of observations reported the number of obese and healthy participants with and without *BDNF* risk allele. Therefore, we calculated