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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

odds ratios (OR) for obesity and its corresponding confidence interval [18–20]. The mean difference (MD) for BMI and its standard deviation (SD) between participants with and without risk alleles was also extracted from studies to be used as the effect size for meta-analysis [18,19,24]. Furthermore, some studies also reported beta and standard error (β±SE) for linear association between risk alleles and BMI [21,23,25]. Hence, we included OR, MD and regression betas (β) in separate meta-analyses. The overall effects were calculated using random effect models, which takes the between study variation into account. Specific sources of heterogeneity between studies were explored using subgroup analysis. Heterogeneity was checked by means of Cochran's Q test and I-squared (I^2). We also explored the extent to which overall estimates might depend on a specific study by conducting sensitivity analysis. Publication bias was examined by visual inspection of funnel plots and by use of Egger's regression asymmetry test and Begg's adjusted rank correlation test. All statistical analyses were performed using STATA (version 11.2, Stata Corp, College Station, TX). $P < 0.05$ was considered as statistically significant.

3. Results

A detailed screening flow is shown in Fig. 1. The general descriptive characteristics of the included studies with odds ratio, β coefficient and mean data are shown in Tables 1–3 respectively.

Overall effects for *BDNF* polymorphisms and BMI were first pooled, and the pooled OR suggested association between *BDNF* polymorphisms and increased obesity risk, assessed by BMI (OR = 1.13, 95% CI = 1.08–1.17, P heterogeneity < 0.001). In the model which was stratified by type of polymorphisms, there were significant links between rs925946 (GG vs TG/TT polymorphism) and BMI (OR = 1.12, 95% CI = 1.08–1.17, P heterogeneity = 0.317), rs10501087 (CC vs CT/TT polymorphism) and BMI (OR = 1.14, 95% CI = 1.04–1.24, P heterogeneity = 0.861), rs6265 (AA vs AG/GG polymorphism) and BMI (OR = 1.13, 95% CI = 1.07–1.19, P heterogeneity = 0.406), rs988712 (TT vs GT/GG polymorphism) and BMI (OR = 1.29, 95% CI = 1.18–1.40, P heterogeneity = 0.602), rs10767664 (TT vs AT/AA polymorphism) and BMI (OR = 1.37, 95% CI = 1.06–1.75, P heterogeneity = 0.004) (Fig. 2).

According to pooled β, overall effects for *BDNF* polymorphisms and BMI suggested that those with *BDNF* polymorphisms had significantly higher BMI (β = 0.05, 95% CI = 0.03–0.07, P heterogeneity < 0.001). In subgroup analysis, a significant result was observed only in the rs925946 polymorphism subgroup. A significantly greater BMI was observed in those with the TG/TT genotype than in those with the GG genotype across studies (β = 0.16, 95% CI = 0.07–0.25, P heterogeneity < 0.001) (Fig. 3).

According to pooled mean, overall effects for the association between *BDNF* polymorphisms and BMI were not significant (Fig. 4).

3.1. Sensitive analysis and publication bias

Articles were removed sequentially to carry out sensitive analysis. Results indicated that no single study considerably diminished the stability of pooled results.

To estimate the publication bias, the Egger's test and Begg's test were performed and the results did not reveal any evidence of clear asymmetry and publication bias. Results of the publication bias assessment in each polymorphism for studies extractingOR included:

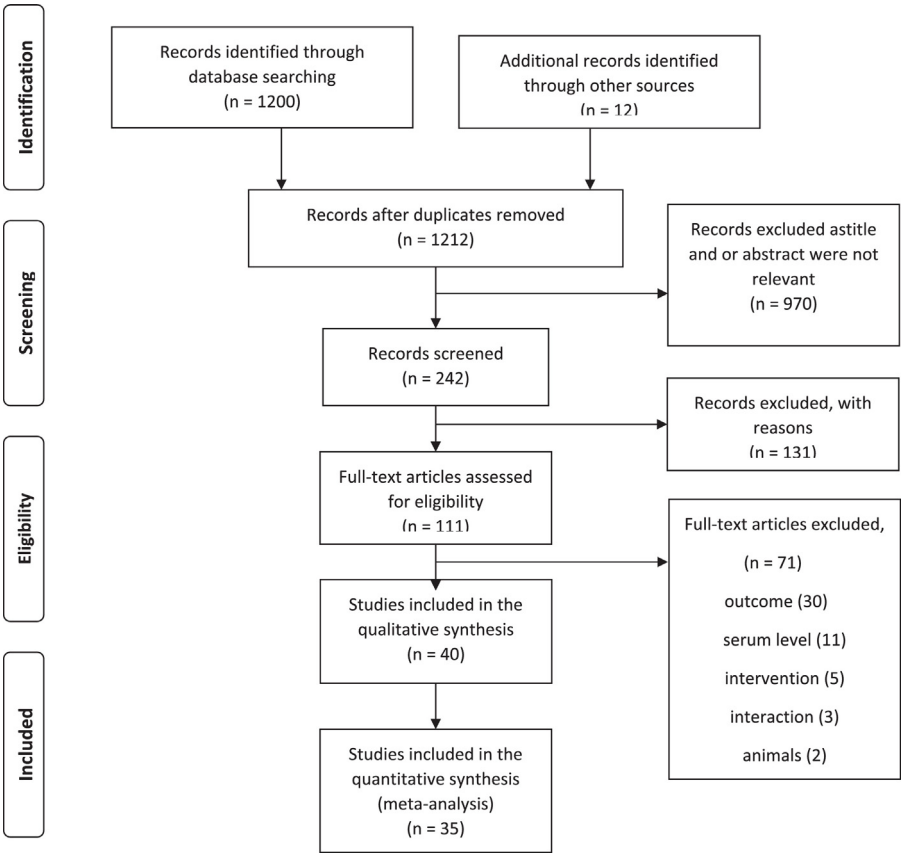

Fig. 1. Literature search for the meta-analysis.

Table 1
The generally descriptive characteristics of the included studies according to odd's ratio data.

Frist authors (y)	Country	*BDNF SNP*	Total number (male/ female)	Sample size		Mean age	Characteristics	Mean BMI		OR	95% CI	Adjustment	quality	Main result
				case	control	mean ± SD		case	control					
Gull Rukh et al. [40]	Sweden	rs4923461	N = 29480 M = 11754 F = 17726	16006	13474	58 ± 7.60	1238 diabetic from all population	–	–	1.08	(1.01–1.15)	Age, gender	high	associated with increased risk of both overweight and obesity
Maggie C. Y. Ng et al. [41]	China	rs4923461	N = 605 M = 275 F = 330	139	466	41.20 ± 10.5	Healthy AND diabetic adults	–	–	0.97	(0.90–1.03)	BMI	moderate	Not associated
Maggie C. Y. Ng et al. [41]	China	rs925946	N = 605 M = 275 F = 330	139	466	41.20 ± 10.5	Healthy AND diabetic adults	–	–	1.02	(0.87–1.19)	BMI	moderate	Not associated
Jingwen Zhu et al. [74]	China	rs10501087	N = 2894 M = 1251 F = 1643	1534	1360	58.60 ± 6	Healthy	–	–	1.15	(0.97–1.36)	age, gender, region	high	–
Sigri Beckers et al. [46]	Belgium	rs6265	N = 729 M = 0 F = 729	532	197	–	532 obese without any disease and 197 completely healthy	37.9 ± 0.30	22.1 ± 0.10	1.39	(0.92–2.10)	NA	moderate	associated with increased risk of obesity
Paola Leo' *n*-Mimila et al. [23]	Mexico	rs6265	N = 914 M = 310 F = 604	441	473	40.50 ± 13.4	473 nondiabetic	33.40 ± 2.90	22.80 ± 1.90	1.21	(0.89–1.64)	Age, gender	moderate	associations with obesity
Hong Jiao et al. [34]	Sweden	rs988712	N = 327 M = 59 F = 268	164	163	–	hypertension, type 2 diabetes, dyslipidemia	44.70 ± 4.70	22.20 ± 1.80	1.56	(1.07–2.27)	–	high	associated with obesity
Hong Jiao et al. [34]	Sweden	rs988712	N = 667 M = 131 F = 576	460	247	–	hypertension, type 2 debate, dyslipidemia	44.60 ± 4.60	22.60 ± 1.70	1.42	(1.09–1.85)	–	high	associated with obesity
Hong Jiao et al. [34]	Sweden	rs988712	N = 3518 M = 1674 F = 1844	1814	1704	–	hypertension, type 2 debate, dyslipidemia	37.10 ± 5.40	22.80 ± 1.70	1.27	(1.13–1.42)	–	high	associated with obesity
Hong Jiao et al. [34]	France	rs988712	N = 3666 M = 1354 F = 2312	928	2738	–	hypertension, type 2 debate, dyslipidemia	48.50 ± 7.60	23.80 ± 3.50	1.24	(1.08–1.43)	–	9	associated with obesity
Gudmar Thorleifsson et al. [27]	Iceland	rs6265	N = 22277	8494	13785		838 African-Ame/15251 Iceland/1763Netherland/ 3362 Denmark/1063 Euro-Ame	–	–	1.12	(1.06–1.19)		high	Not associated with obesity
Gudmar Thorleifsson et al. [27]	Iceland	rs925946	N = 22277	8494	13785		838 African-Ame/15251 Iceland/1763Netherland/ 3362 Denmark/1063 Euro-Ame	–	–	1.11	(1.06–1.17)	Age, gender	high	Not associated with obesity
Kikuko Hotta et al. [20]	Japan	rs4074134	N = 2865 M = 1420 F = 1445	1129	1736	49.90 ± 15.10	Obese and normal adults	34.2 ± 5.3	21.7 ± 2.1	1.13	(1.01–1.26)	Age, gender	high	associated with obesity
Kikuko Hotta et al. [20]	Japan	rs4923461	N = 2865 M = 1420 F = 1445	1129	1736	49.90 ± 15.10	Obese and normal adults	34.2 ± 5.3	21.7 ± 2.1	1.13	(1.02–1.26)	Age, gender	high	associated with obesity
Kikuko Hotta et al. [20]	Japan	rs10501087	N = 2865 M = 1420 F = 1445	1129	1736	49.90 ± 15.10	Obese and normal adults	34.2 ± 5.3	21.7 ± 2.1	1.13	(1.02–1.26)	Age, gender	high	associated with obesity

Kikuko Hotta et al. [20]	Japan	rs6265	N = 2865 M = 1420 F = 1445	1129	1736	49.90 ± 15.10	Obese and normal adults	34.2 ± 5.3	21.7 ± 2.1	1.11	(1.00–1.23)	Age, gender	high	associated with obesity
Camilla Helene Sandholt et al. [18]	Denmark	rs4923461	N = 18014 M = 9330 F = 8120	12359	3339	–	Obese and overweight BMI ≥ 25	–	–	1.14	(1.05–1.23)	Age, gender	high	associated with increased risk of overweight
Camilla Helene Sandholt et al. [18]	Denmark	rs925946	N = 18014 M = 9330 F = 8120	12359	3339	–	Obese and overweight BMI ≥ 25	–	–	1.15	(1.06–1.24)	Age, gender	high	associated with increased risk of overweight
Xueyao Han et al. [19]	China	rs4074134	N = 2724	630	2094	53 ± 10	obese = BMI > 28	–	–	0.79	(0.68–0.92)	Age, gender	high	associated with BMI & waist circumference
Kiara R. Timpano et al. [45]	USA	rs6265	N = 301 M = 122 F = 179	–	–	–	Obsessive Compulsive Disorder	–	–	2.18	(1.16–4.11)	Not mentioned	moderate	Associated with BMI
J Hong et al. [45]	China	rs10767664	N = 1040	540	500	19.60 ± 3.70	Young healthy and obese	35.23 ± 4.65	19.90 ± 1.90	1.31	(1.09–1.59)	Age, gender matched	high	significantly associated with obesity risk
Khalid K. Alharbi et al. [80]	Saudi Arabia	rs10767664	N = 450	246	204	23	–	–	–	1.92	(1.32–2.80)	–	moderate	associated with increased risk of obesity
Konstantinos Rouskas et al. [42]	Greece	rs6265	N = 979 M = 435 F = 544	510	469	47.1 ± 12.35	–	37.59 ± 6.47	23.71 ± 0.95	1.23	(0.97–1.56)	Age, gender	high	Not related with obesity
Konstantinos Rouskas et al. [42]	Greece	rs925946	N = 979 M = 435 F = 544	510	469	47.1 ± 12.35	–	37.59 ± 6.47	23.71 ± 0.95	0.77	(0.96–1.21)	Age, gender	high	Not related with obesity
Shengxu Li et al. [17]	UK	rs925946	N = 20431 M = 10005 F = 10426	–	–	–	Healthy	–	–	1.16	(1.08–1.24)	Age, gender	high	Associated with increased risks of obesity and overweight
Lavinia Paternoster et al. [38]	UK	rs10767664	N = 5373	2633	2740	–	–	–	–	1.07	(0.98–1.18)	Age	moderate	Associated with BMI but not obesity
Ioanna Ntalla et al. [79]	Greece	rs10767664	M = 707 M = 311 F = 396	218	489	–	–	–	–	1.72	(1.00–2.95)	Age, gender	moderate	Associated with risk of obesity
Matea Nikolac Perkovic et al. [37]	Croatia	rs6265	N = 339 M = 149 F = 190	229	110	77.2 ± 4.5	Healthy adult	28.9 ± 1.65	23.0 ± 1.6	0.94	(0.58–1.53)	Not mentioned	moderate	Not related with obesity or overweight
Matea Nikolac Perkovic et al. [37]	Croatia	rs6265	N = 339 M = 149 F = 190	229	110	77.2 ± 4.5	Healthy adult		23.0 ± 1.6	0.77	(0.44–1.36)	Not mentioned	moderate	Not related with obesity or overweight
Matea Nikolac Perkovic et al. [37]	Croatia	rs6265	N = 339 M = 149 F = 190	229	110	77.2 ± 4.5	Healthy adult		23.0 ± 1.6	1.07	(0.58–1.96)	Not mentioned	moderate	Not related with obesity or overweight

Table 2
The generally descriptive characteristics of the included studies according to β coefficient data.

Frist authors (y)	Country	*BDNF SNP*	Sample size			Mean age	Characteristics	Mean BMI	β ± SE	Adjustment	quality	Main result
			population	male	female							
Kikuko Hotta et al. [44]	Japan	rs6265	1279	556	723	51 ± 11.80	Obesity and/or Metabolic abnormalities	–	0.50 ± 0.22	Age, gender	high	Associated with obesity
Kikuko Hotta et al. [44]	Japan	rs925946	1279	556	723	51 ± 11.80	Obesity and/or Metabolic abnormalities	–	0.81 ± 0.54	Age, gender	high	Not associated with obesity
F. Takeuchi et al. [25]	Japan	rs6265	18264	9076	9188	58.00± 8.70	Diabetic/ Cardiovascular disease	23.06± 3.06	5.41	Age separately by gender	moderate	Associated with obesity
Yukinori Okada et al. [70]	Japan	rs2030323	62245	32865	29380	61.30 ± 12.90	Different diseases	22.70 ± 3.59	0.46 ± 0.00	Not mentioned	high	Associated with BMI
Alaitz poveda et al. [71]	Spain	rs4923461	372	147	255	–	Healthy	–	−0.80 (−0.27–0.12)	Age and gender	moderate	Not associated with obesity
Gull Rukh et al. [40]	Sweden	rs4923461	29480	11754	17726	58.00 ± 7.60	1238 diabetic from all population	25.80 ± 4.10	0.14 ± 0.04	Age and gender	high	Associated with obesity
Damien C. Croteau-Chonka et al. [72]	Philippines	rs4923461	1792	0	1792	48.40± 6.10	Not mentioned	24.30± 4.40	0.02 ± 0.00	Age	moderate	Associated with BMI and weight
Fernando Martínez-García et al. [33]	Spain	rs925946	1425	718	707	54.40 ± 19.30	Urban population with 19% obese	26.40 ± 4.20	−0.07 ± 0.16	Age and gender	high	Not associated with BMI
Fernando Martínez-García et al. [33]	Spain	rs10501087	1425	718	707	54.40 ± 19.30	Urban population with 19% obese	26.40 ± 4.20	0.08 ± 0.17	Age and gender	high	Not associated with BMI
Fernando Martínez-García et al. [33]	Spain	rs925946	869	322	543	46.20 ± 13.80	Rural population with 36% obese	28.60 ± 5.20	0.12 ± 0.24	Age and gender	high	Not associated with BMI
Fernando Martínez-García et al. [33]	Spain	rs10501087	869	322	543	46.20 ± 13.80	Rural population with 36% obese	28.60 ± 5.20	0.03 ± 0.26	Age and gender	high	Not associated with BMI
Maggie C. Y. Ng et al. [41]	China	rs4923461	605	275	330	41.20 ± 10.50	Healthy adults	22.90 ± 3.30	−0.06 ± 0.06	Not mentioned	moderate	Not associated with anthropometric measurements
Maggie C. Y. Ng et al. [41]	China	rs925946	605	275	330	41.20 ± 10.50	Healthy adults	22.90 ± 3.30	0.53 ± 0.14	Not mentioned	moderate	associated with anthropometric measurements
Maggie C. Y. Ng et al. [41]	China	rs4923461	6013	2741	3272	56.80 ± 13.30	Type 2 diabetic patients	25.10 ± 3.90	−0.02 ± 0.02	Not mentioned	moderate	Not associated with anthropometric measurements
Maggie C. Y. Ng et al. [41]	China	rs925946	6013	2741	3272	56.80 ± 13.30	Type 2 diabetic patients	25.10 ± 3.90	0.02 ± 0.00	Not mentioned	moderate	associated with anthropometric measurements
Florianne Bauer et al. [73]	Netherlands	rs1488830	1700	0	1700	57.22 ± 6.06	Healthy female	25.90 ± 4.02	0.04 ± 0.17	energy	high	Not associated with BMI
Florianne Bauer et al. [73]	Netherlands	rs925946	1700	0	1700	57.22 ± 6.06	Healthy female	25.90 ± 4.02	0.320 ± 0.15	energy	moderate	Associated with BMI
Jingwen Zhu et al. [74]	China	rs10501087	2894	1251	1643	58.60 ± 6.00	Healthy	24.50 ± 3.60	0.180 ± 0.09	Age, gender and region	high	Associated with BMI
Xueyao Han et al. [19]	China	rs4074134	1113	316	797	53.00 ± 10.00	Healthy	25.30 ± 3.20	−0.049	Age, gender	high	Associated with BMI
Paola Leo' *n*-Mimila et al. [47]	Mexico	rs6265	945	–	–	–	Healthy	–	.030 ± 0.08	Age, gender	moderate	Not associated
Elizabeth K. Speliotes et al. [21]	European	rs10767664	249796	–	–	–	–	–	0.190 ± 0.03	Not mentioned	moderate	Associated with BMI
Kiara R.Timpano et al. [45]	USA	rs6265	301	122	179	–	–	–	0.150 ± 2.34	Not mentioned	moderate	Not associated
Camilla Helene Sandholt et al. [18]	Germany	rs4923461	18014	–	–	–	Three population	–	0.290 ± 0.09	Age, gender	High	Associated with BMI

Camilla Helene Sandholt et al. [18]	Germany	rs925946	18014	–	–	–	Three population	–	0.350 ± 0.89	Age, gender	High	Associated with BMI
Karani S. Vimaleswaran et al. [10]	USA	rs10767664	–	–	–	–	A risk allele substitute with T original allele	–	0.040 ± 0.00	Not mentioned	high	Associated with BMI
Rachel A. Murphy et al. [39]	USA	rs10767664	1662	–	–	–	Cohort Health ABC	–	0.020	Age and gender	moderate	Not associated
Rachel A. Murphy et al. [39]	USA	rs10767664	3216	–	–	–	Cohort AGES-Reykjavik	–	0.040	Age and gender	moderate	Not associated
Rachel A. Murphy et al. [39]	USA	rs10767664	1139	–	–	–	American African of health ABC	–	0.000	Age and gender	moderate	Not associated
Shengxu Li et al. [17]	UK	rs925946	20431	10005	10426	–	Healthy	26.30 ± 3.70	0.217 ± 0.04	Age and gender	moderate	Associated with BMI
Jian Gong et al. [75]	USA	rs1519480	17513	5875	11638	–	–	–	−0.009 ± 0.00	Age, gender and study site	high	Not associated
Jian Gong et al. [75]	USA	rs1519480	17513	5875	11638	–	–	–	−0.011 ± 0.00	Age, gender and study site	high	Not associated
Tiina Jaaskelainen et al. [76]	Finland	rs10767664	459	153	306	55.20 ± 7.00	BMI > 25 inclusion criteria	31.30 ± 4.50	1.096 ± 0.43	Age, gender and study site	high	Associated
Jimmy Z. Liu et al. [77]	Australia	rs925946	11536	–	–	–	–		0.031 ± 0.02	Not mentioned	moderate	Not associated
M. Islam et al. [78]	Pakistan	rs10767664	1755	–	–	–	Some of them diabetic	–	−0.040 ± 0.03	age, gender, ethnicity and clustering of household member	moderate	Not associated
Ioanna Ntalla et al. [79]	Greece	rs10767664	707	311	396	13.42 ± 0.88	–	–	0.320 ± 0.23	Age and gender	moderate	Not associated
R. Di Paola et al. [23]	Italy	rs10767664	764	379	385	62.5 ± 9.7	diabetic	31.0 ± 5.6	0.041	age, gender, smoking habit and exercise	moderate	Not associated with BMI
Alexandra Jean Mayhew et al. [48]	Canada	rs6265	1850	643	1207	–	diabetic	30.83 ± 6.44	−0.089 ± 0.27	Age and gender	moderate	Not associated with BMI
Alexandra Jean Mayhew et al. [48]	Canada	rs1401635	1850	643	1207	–	diabetic	30.83 ± 6.44	0.264 ± 0.22	Age and gender	moderate	Not associated with BMI

Table 3
The generally descriptive characteristics of the included studies according to mean data.

Frist authors (y)	Country	*BDNF SNP*	Total number (male/female)	Sample size[a]			Age	Mean BMI[a]			Mean difference ± SD or CI	Number of risk allele GG-GA	Adjustment	quality	Main result
				11	12	22		11	12	22					
Xian-YongMa et al. [81]	USA	rs6265	N = 1340 M = 395 F = 945	922	313	24	57.20 ± 7.40	31.00 ± 0.3	31.80 ± 1.00	30.10 ± 1.50	−1.1(−1.7, 0.5)	1235	age, smoking status, alcohol use, gender, education, medication use for depression, and physical activity, and population admixture	moderate	Not associated with obesity After adjustment for gender, significantly associated with BMI, hip & weight
John Gunstad et al. [82]	USA	rs6265	N = 481 M = 243 F = 238	290	173	18	18–82	24.62 ± 4.77	24.92 ± 4.88	22.28 ± 3.77	−2.45(−5.18, 0.28)	463	Gender	moderate	Not associated with BMI
Yin Yao Shugart et al. [36]	UK	rs6265	N = 3631	3468		163	60–79	27.63 ± 5.02		26.72 ± 4.78	−0.911(−1.70, −0.12)	3468	Gender and age	moderate	associated with BMI
Yin Yao Shugart et al. [36]	UK	rs6265	N = 6478	6253		225	60–79	23.04 ± 3.87		22.45 ± 3.65	−0.57(−1.08, −0.054)	6253	Gender and age	moderate	associated with BMI
Kikuko Hotta et al. [44]	Japan	rs6265	N = 1279 M = 556 F = 723	207	609	462	50.80 ± 11.75	29.60 ± 6.30	28.70 ± 5.30	28.60 ± 5.90	29 ± 31.14	816	age, gender and BMI	high	Not associate with obesity
Kikuko Hotta et al. [44]	Japan	rs925946	N = 1279 M = 556 F = 723	3	100	1175	50.80 ± 11.75	36 ± 10.70	29.50 ± 6.10	28.90 ± 5.70	30 ± 39.57	103	age and gender	high	Not associated with obesity
Kyung-Won Hong et al. [26]	Korea	rs6265	N = 20270 M = 8998 F = 11272	6045	10057	4167	54.10 ± 8.40	24.60 ± 3.10	24.40 ± 3.10	24.30 ± 3.10	24 ± 9.62	16102	age, living area, and gender	moderate	Associated with BMI
Camilla Helene Sandholt et al. [18]	Denmark	rs4923461	N = 5873 M = 2929 F = 2944	268	2025	3580	46 ± 8	25.90 ± 4.60	26 ± 450	26.40 ± 450	26 ± 20.35	2293	age and gender	moderate	associated with increased risk of overweight and borderline with obesity
Camilla Helene Sandholt et al. [18]	Denmark	rs925946	N = 5873 M = 2929 F = 2944	2753	2495	552	46 ± 8	26 ± 4.50	26.40 ± 4.50	26.90 ± 4.60	26 ± 20.29	5248	age and gender	moderate	associated with overweight and obesity
Xueyao Han et al. [19]	China	rs4074134	N = 2723 M = 997 F = 1726	932	1320	471	–	26.10 ± 3.20	25.70 ± 3.10	25.70 ± 3.20	26 ± 9.9	2252	age and gender	moderate	associated with obesity
Idoia Marque's-Iturria et al. [24]	Spain	rs6265	34	28	6		12–40	34.22 (27.47–49.69)	31.74 (27.60–36.58)				–	obese	Met allele(A) assosiated with BMI
Idoia Marque's-Iturria et al. [24]	Spain	rs6265	27	17	10		12–40	22.07 (19.53–24.97)	21.65 (19.89–24.87)				–	thin	Met allele (A) assosiated with BMI

[a] rs6265 (G = 1/A = 2), rs925946 (G = 1/T = 2), rs4074134 (G = 1/A = 2).

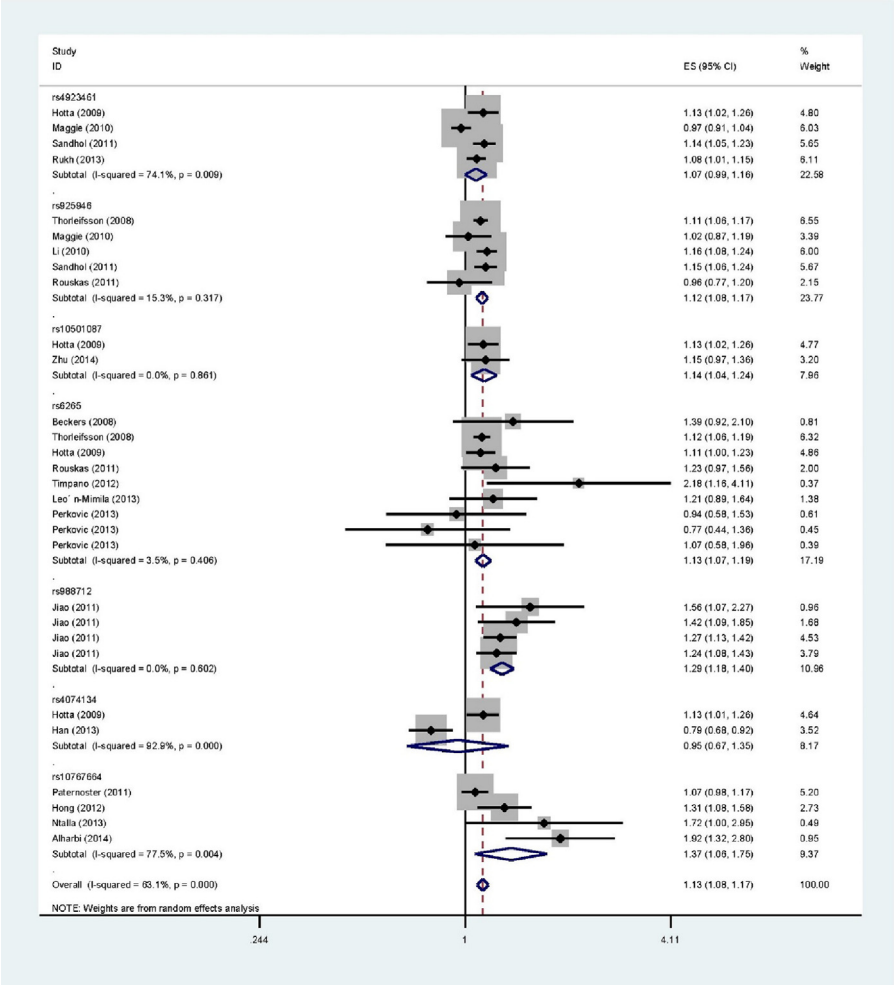

Fig. 2. Forest plot of overall OR stratified by *BDNF* gene polymorphisms and BMI.

rs4923461: Begg's test P = 0.497, Egger's test P = 0.461, rs6265: Begg's test P = 0.532, Egger's test P = 0.520, rs925946: Begg's test P = 0.142, Egger's test P = 0.238, rs10501087: Begg's test P = 0.317, Egger's test P = 0.068, rs4074134: Begg's test P = 0.497, Egger's test P = 0.055.

Results of the publication bias assessment in each polymorphism for studies that reported β were as follows:

rs4923461: Begg's test P = 0.851, Egger's test P = 0.740, rs6265: Begg's test P = 0.497, Egger's test P = 0.681, rs925946: Begg's test P = 0.835, Egger's test P = 0.25, rs10501087: Begg's test P = 0.117, Egger's test P = 0.104, rs10767664: Begg's test P = 0.327, Egger's test P = 0.378, rs1519480: Begg's test P = 0.317

4. Discussion

To the best of our knowledge, no previous meta-analysis study has been conducted to assess the association of the *BDNF* gene variants with BMI. In our study, the overall OR and β indicated a significantly positive association between *BDNF* polymorphisms and obesity risk. When stratified by SNPs, the results showed that some *BDNF* polymorphisms such as rs925946, rs10501087, rs6265 and rs988712 significantly increased the risk of obesity indicating that these polymorphisms might be involved in the pathogenesis of obesity. Due to the nature of the SNP, we expect these polymorphisms to be the functional variants causing this association.

Except for rs6265, all other three SNPs stated above are located upstream of *BDNF* gene, itself. Interestingly, there is a natural antisense transcript which is transcribed from the human *BDNF* locus in the opposite direction [,28,29]. According to dbSNP database [30], rs988712, rs925946 and rs10501087 are all located within the intronic regions of this non-coding RNA, *BDNF*-AS (Fig. 5). Evidences indicate that *BDNF*-AS transcripts could have an important role in the regulation of *BDNF* expression in human [29]. Although, these three SNPs are within intronic regions of *BDNF*-AS itself, they can influence the expression of the genes that host them. Intronic regions contain several functional elements including intron splice enhancers and silencers that regulate alternative splicing and trans-splicing elements [31].

Due to the nature of the SNPs, we may hypothesize that these polymorphisms may be functional variants or in linkage disequilibrium (LD) with functional ones causing this significant association with obesity.

According to a study by Thorleifsson et al. [27], rs6265 and rs10501087 are in strong LD with $r^2 = 0.85$ and D' = 1. This study reports a GWAS results in 25,344 Icelandic, 2998 Dutch, 1890 European Americans and 1160 African American subjects and combined the results with Diabetes Genetics Initiative on further 3024 Scandinavians.

In 2009, Zhao et al. [32] genotyped 25 SNPs including some in *BDNF* gene in a cohort consisted of 6078 children of European ancestry in order to determine the genetic components of pediatric BMI. They reported r^2 between rs4074134, rs4923461 and

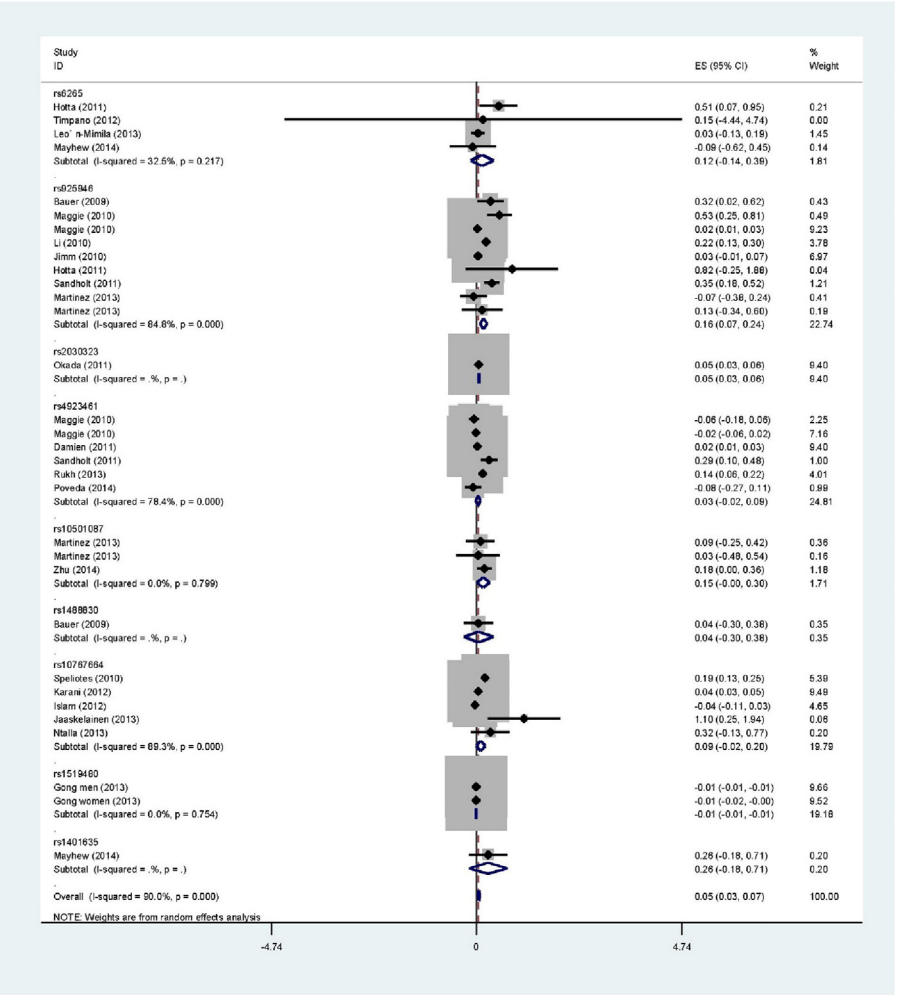

Fig. 3. Forest plot of overall β coefficient stratified by *BDNF* gene polymorphisms and BMI.

rs10501087 = 1 and r^2 between rs4074134 and rs925946, rs6265 = 0.14 and 0.85 respectively.

By genotyping 2294 Spanish individuals [33], Martínez-García et al. revealed a strong LD between rs6265 and rs10501087 (r^2 = 0.82), but not between these two and rs925946 (with r^2 = 0.09 and 0.1, respectively).

Jiao et al. [34] genotyped different cohorts of European and Scandinavians in a step-wise manner. Neither of rs6265 and rs10501087 showed a strong LD with rs988712 in their cohort, with r^2 0.57–0.59.

In an another study conducted on the Han Chinese population, no LD was observed between rs6265 and rs988712 [35]

In conclusion, as different studies report a strong LD between rs6265 and rs10501087 [27,33], we may hypothesize that these two SNPs are not independent genetic markers. There is a controversy of r^2 reported between rs6265 and rs925946, so we cannot definitely conclude about LD between these two SNPs. As far as we searched in databases, there were only two papers reporting r^2 of rs988712 with other SNPs [34,35]. Both reported no LD between rs988712, rs6265 and rs10501087.

As is known, genes play an important role in obesity. In the recent years, several obesity-related genes have been discovered. *BDNF* is involved in regulation of food intake. In addition, it plays a role in obesity and locomotor activity. Several studies have demonstrated an association between *BDNF* gene polymorphisms and BMI [18,20,36]. However, other studies did not find a significant associations [17,33,37,38].

A number of studies have shown the association between *BDNF* polymorphisms in some populations [24,25,34,39]. However, results from these previous studies remain contradictory. The discrepancies might be due to the small sample size, differences in ethnicity, age and severity of obesity, differences in sample selection and definition of phenotype, moderate genetic effects, variation in study duration, low power and other characteristics.

One population-based cohort of 29480 individuals showed that genetic factors play an important role in obesity and its comorbidities. It indicated that *BDNF* rs4923461 significantly increased the risk of obesity [40]. A Danish study showed a link between the *BDNF* rs4923461 A-allele and increased risk of overweight, with per allele OR of 1.15 (1.07–1.24), and partially with obesity with per allele OR of 1.14 (1.05–1.23) [18]. A Study on Japanese participants confirmed these results. It suggested that rs4923461 and rs6265 SNPs which were identified by a GWAS in the Caucasians, confer susceptibility to obesity in Japanese participants as well [20]. However, another study including 7705 Chinese individuals did not support any association of *BDNF* rs4923461 and rs925946 polymorphisms with obesity [41].

From the population-based European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk cohort, 12 SNPs were assessed in 20431 individuals. Rs925946 in the *BDNF* locus tended

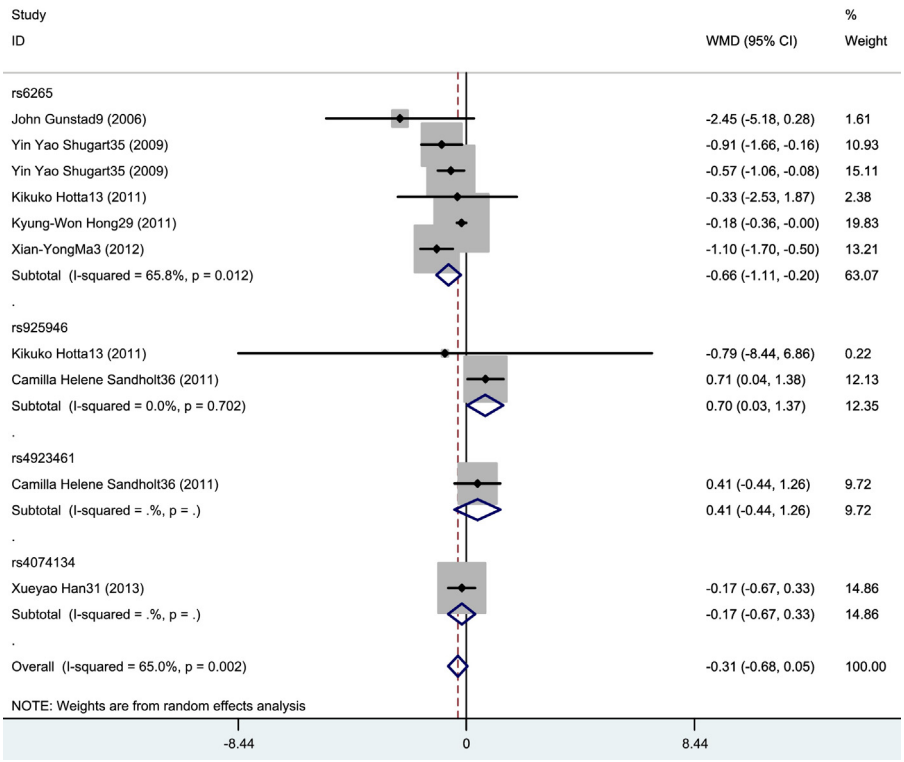

Fig. 4. Forest plot of overall mean stratified by *BDNF* gene polymorphisms and BMI.

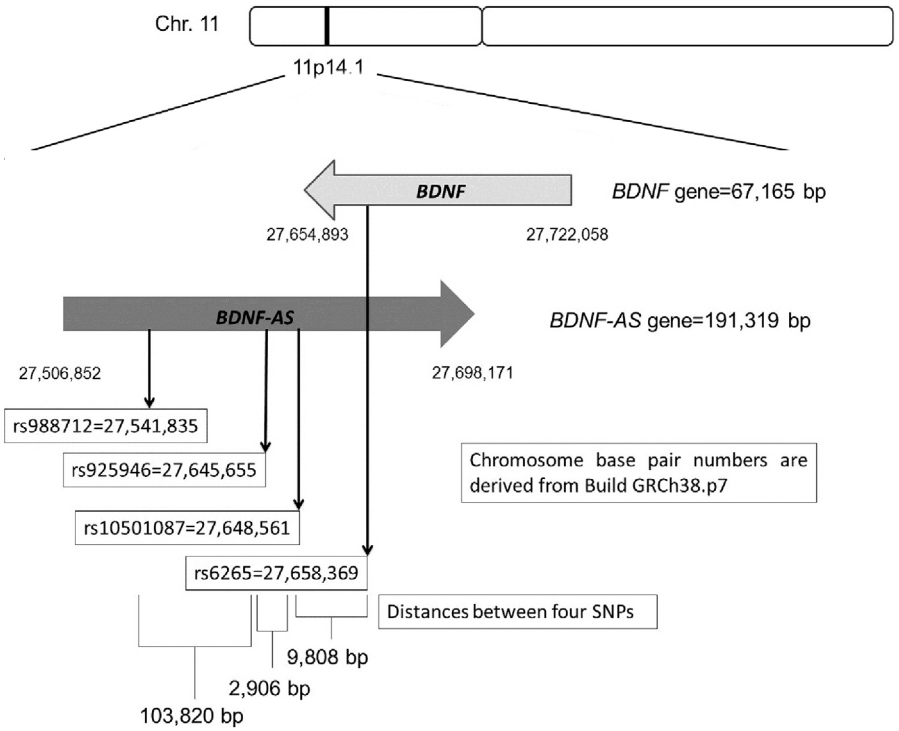

Fig. 5. Structure and chromosome locations of the human *BDNF* (right) and *BDNF-AS* (left) genes. The numbers below the gene boxes indicate their chromosome locations in base pairs (bp) based on Build GRCh38.p7. Polymorphisms are shown in open boxes with their genomic locations indicated.

to have a stronger positive associations with BMI and increased risk of obesity [17].

A genome-wide association [21] study with 305846 SNPs typed in 25344 Icelandic, 2998 Dutch, 1890 European Americans and 1160 African American subjects was performed and combined the results with previously published results from the Diabetes Genetics Initiative (DGI) on 3024 Scandinavians. Forty-three variants in 19 chromosome regions were selected for follow-up in 5586 Danish individuals and the results were compared with a genome-wide study on obesity-related traits from the GIANT consortium. Results indicated that rs925946 and rs6265 increase the risk of obesity [27]. However, the Greek adult population study did not reproduce such an association [42].

In the GWA analysis of Swedish subjects, *BDNF* rs988712 was associated with obesity in five out of six investigated case-control cohorts. They identified a novel susceptibility locus for obesity near KCNMA1 (rs2116830) and confirmed the association with *BDNF* (rs988712) [27] by GWA analysis [34].

Hong et al. genotyped 23 BMI-associated genetic variants identified from a recent GWAS in Caucasians from European ancestry with minor allele frequencies more than 0.05 in HapMap Han Chinese in Beijing, China. Six loci including *BDNF* rs10767664 showed consistent associations with obesity in Chinese and Caucasians [43].

GWAS reported a significant association between *BDNF* rs6265 gene and BMI [27,44,45], while other studies did not find any significant relation between *BDNF* rs6265 and obesity [37,46–48]. Most studies evaluated the correlation of *BDNF* rs6265 with eating disorders, and found either a significant association [49], or no association [50] between the Met allele and eating disorders.

The mechanisms underlying the effect of *BDNF* polymorphisms on obesity are unknown. *BDNF* is a member of the nerve growth factors that is necessary for survival of striatal neurons in the brain. It is also an important mediator of energy balance and is regulated by the *MC4R* gene [51,52].

Animal studies have implied the anorectic and satiating properties of *BDNF* that when administered centrally, induces appetite suppression and weight loss [53–56]. *BDNF* binds to its tropomyosin-related kinase B (TrkB) receptor [54] and modulates energy metabolism, food regulation and BMI by central as well as peripheral actions, and regulates physical activity, hyperactivity, anxiety, and hyperphagia [55–57]. In addition, mutations in the genes coding for *BDNF* and TrkB are responsible for obesity and eating disorders [54–57]. According to these findings, lower serum or plasma *BDNF* levels were found in obese [58–62], compared to normal weight participants. However, some studies showed opposite results [63,64].

Kernie et al. reported obesity, eating behaviour alterations, increased body weight and adipocyte cellular hypertrophy developed in *BDNF* heterozygous 'knockout' mice [14]. These results confirm the fact that *BDNF* increases extracellular serotonin levels [65–67] and its expression is under estrogen control [68,69]. Thus, *BDNF* variants are associated with anorexia nervosa and may lead to increases in the neurotrophin levels, function or stability. *BDNF* could directly affect food consumption and control of body weight, as it is expressed in the hypothalamic center.

>We must note that there are some limitations in our meta-analysis. First, different techniques were used to genotype DNA samples in eligible studies may increase heterogeneity. Second, gene–environment or gene–gene interactions may affect the results and conceal the potential inaccuracy. However, the major strength of this study is stratification by different SNPs. In addition, we extracted data separately according to OR, β and mean and distinctly analysed them.

5. Conclusion

This meta-analysis suggests that some polymorphisms in *BDNF* gene including rs925946, rs10501087, rs6265 and rs988712 could be genetic risk factors for obesity. Therefore, these polymorphisms may be potential obesity biomarkers in the early diagnosis or gene therapy targeting of obesity and weight disturbances.

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