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Abstract: INTRODUCTION: An unhealthy diet is a risk factor for obesity and metabolic abnormalities in psychosis. Increased calorie intake has been associated with psychosocial stress in subjects with early psychosis. The brain-derived neurotrophic factor (BDNF) is a major participant in the regulation of food intake and may play a role in the regulation of the stress response. Therefore, we aimed to investigate whether there is a gene-environment interaction in the relationship between stress and BDNF Val66Met polymorphism in relation to dietary habits and obesity measures in a sample of subjects with early psychosis.

METHODS: We studied 124 early psychotic patients, 36 At-Risk Mental States (ARMS) and 62 healthy subjects (HS). Dietary habits were examined by a dietician. Physical activity, life stress and perceived stress were assessed by validated questionnaires. BDNF Val66Met polymorphism (rs6265) was genotyped. A gene-environment interaction was tested with multiple linear regression analysis while adjusting for covariates.

RESULTS: Both ARMS and PD patients reported more calorie intake, less physical activity and increased perceived stress than HS. Perceived stress was not associated with calorie intake in HS. In ARMS subjects, Met-carriers who presented low-perceived stress were associated with increased caloric intake. Conversely, those who presented high-perceived stress were associated with reduced caloric intake. In PD, perceived stress was associated with increased calorie intake without an effect by BDNF genotype nor a gene-environment interaction.

CONCLUSIONS: Our study suggests that the common Val66Met polymorphism of the BDNF gene modulates the relationship between life stress and calorie intake in subjects at risk for psychosis.

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ABSTRACT

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1. Introduction

People with schizophrenia have a reduced life expectancy compared to the general population (Saha et al., 2007). This increased mortality is mainly caused by cardiovascular disease, as patients with schizophrenia show high rates of metabolic complications and cardiovascular risk factors including central obesity, hypertension, dyslipidaemia, type 2 diabetes and smoking (De Hert et al., 2009). Although antipsychotic treatment is one of the main causes of weight gain and metabolic abnormalities in psychosis (Ryan and Thakore, 2002), life style factors including unhealthy diet and reduced physical activity also play a role (Ratliff et al. 2012; Dipasquale et al. 2013). Dietary habits in subjects with early psychosis are influenced by stressful life events. In a previous study by our group, individuals with a psychotic disorder and increased life stress reported greater calorie intake and increased refined sugar consumption (Manzanares et al., 2014). This is in accordance with other studies in non-psychiatric populations, which have also found that chronic stress is associated with hyperphagia (Adam and Epel, 2007; Wardle et al., 2000).

Psychosocial stress is implicated in the development of psychotic symptoms (Walker et al., 2008). However, individuals likely differ in their vulnerability to stress. A mechanism that could potentially explain between-subject differences is through a gene-environment interaction (van Winkel et al., 2008). Although life stress has been associated with dietary habits in subjects with early psychosis (Manzanares et al., 2014), there are no previous studies addressing whether there is a gene-environment interaction in the relationship between life stress and eating behaviour in early psychotic patients. Genes involved in regulating the adaptive behavioural response to stress represent plausible candidates to be explored in studies addressing why some individuals are more prone to develop dietary changes and metabolic abnormalities. In this sense, the brain-derived neurotrophic factor (BDNF) gene (OMIM 113505) is an excellent target because it has been implicated in several processes including food

intake (Rios, 2013; Rothman et al, 2012; Rosas-Vargas et al, 2011) or the regulation of stress responses (Colzato et al, 2010; Frielingsdorf et al, 2010). Moreover, it is thought to modulate the clinical expression of schizophrenia (Notaras et al, 2015).

BDNF is the most profusely expressed neurotrophin in the central nervous system and is located predominantly within neurons. It is also present in the two major integrative autonomic centres involved in energy homeostasis: the hypothalamus and the dorsal vagal complex. It is involved in growth, differentiation, maturation and survival of neurons, thus it plays an important role in the synaptic plasticity, the augmentation of neurotransmission and the regulation of receptor sensitivity (Nurjono et al., 2012). Moreover, recent evidence indicates that BDNF contributes to energy metabolism, food intake and body weight control by acting as an anorexigenic factor (Lebrun et al., 2006; Rosas-Vargas et al., 2011; Rothman et al., 2012). Animal studies have shown reduced hypothalamic expression of BDNF, increased hyperphagia and risk of obesity in BDNF-deficient mice (Kernie et al., 2000). Infusion of BDNF can transiently reverse the eating behaviour and obesity. There is a functional single-nucleotide polymorphism (SNP) in the BDNF gene, a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met), that has an impact on BDNF protein. Met66 allele carriers have been linked with reduced BDNF activity-dependent secretion and, recently, it has been identified that Met66 but not Val66 should play a role in the regulation of dopaminergic wiring (Notaras et al, 2015) Although there are no studies exploring the role of this polymorphism in the dietary habits in subjects with psychoses, human studies in other clinical populations have reported an increased risk for food restriction (Akkermann et al., 2011; Arija et al., 2010), bulimia (Akkermann et al., 2011) and restrictive type anorexia nervosa (Ribasés et al., 2003) in Met-carriers.

Thus the aim of this study was to investigate whether there is a gene-environment interaction in the relationship between stress and BDNF Val66Met

polymorphism in relation to dietary habits and obesity measures in a sample of subjects with early psychosis.

2. Materials and methods

2.1. Participants

The study sample included 160 individuals who were attending an Early Intervention Service for Psychosis (Hospital Universitari Institut Pere Mata, Reus, Tarragona, Spain): 1) 124 patients with a psychotic disorder (PD, 82 [66.1%] were first episodes of psychosis) with less than 5 years from the onset of the illness; 2) 36 individuals with prodromal psychotic symptoms fulfilling the set criteria for At-Risk Mental States (ARMS) (Yung et al., 2005). Exclusion criteria were: pregnancy, mental retardation, severe head injury or neurological disease, active glucocorticoid treatment, active substance dependence (other than tobacco or cannabis) and type 1 diabetes mellitus. In order to include relatively stable PD patients, clinical assessment was performed when subjects had been treated at the program for at least three months. Finally, we included a control group of healthy subjects (HS, n=62) who were recruited by advertisements and screened to rule out past or current history of psychiatric disorder. Ethical approval was obtained from the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Clinical Assessment

All patients were assessed with the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). The Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT 4 Windows) was used to generate DSM-IV diagnosis for

psychotic disorders (schizophreniform disorder [n=22], schizophrenia [n=20], schizoaffective disorder [n=12]), and psychotic disorder not otherwise specified [n=70]). ARMS subjects were also assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS), to ensure that subjects met criteria for any of the three ultra high risk groups defined by the CAARMS (Yung et al., 2005): 1) attenuated psychosis (n=28), 2) brief limited intermittent psychotic symptoms (n=5), and 3) vulnerability (n=7), that includes subjects with a family history of psychosis in first degree relative or schizotypal personality disorder in identified patient with a 30% drop in Global Assessment of Functioning (GAF) score from premorbid level, sustained for 1 month.

Stressful life events in the previous 6 months were assessed with the Holmes-Rahe Social Readjustment Scale (Holmes and Rahe, 1967). This scale was initially developed to explore the relationship between social readjustment, stress and susceptibility to illness. It explores 43 life events and gives a "stress score" for each item, obtaining a final score by adding the scores of all present life events. This scale has been validated and used in Spanish populations (Roca et al., 2013). Previous studies include the use of this scale to explore the relationship between life events and subclinical psychotic symptoms in the general population (Rössler et al., 2007) or metabolic abnormalities in healthy individuals (Fabre et al., 2013). The 14-item Perceived Stress Scale (Cohen et al., 1983) was used to explore the psychological repercussion of stress. This instrument is a self-report scale that assesses the perception of stressful experiences over the previous month.

Dietary habits were assessed by means of clinical interview conducted by a dietician. Food intake was registered by 24 h recall. Specialized software (Centre d'Ensenyament Superior de Nutrició i Dietètica, University of Barcelona, Santa Coloma de Gramenet, Barcelona, Spain) was used to calculate the daily calorie and nutrient intake. The International Physical Activity Questionnaire-short form (IPAQ-SF) (Craig et al., 2003), was used to calculate the level of physical activity in metabolic equivalents

(MET-min/week). Weight, height, waist circumference and blood pressure were assessed by physical examination. Body Mass Index (BMI) was calculated with the formula weight (kg)/height $(m)^2$.

Antipsychotic treatment and other socio-demographic and clinical variables were requested by semi-structured interview. In our Early Intervention Service, all psychopharmacological treatments (prescription, dosage changes and discontinuation) are registered in an electronic clinical record. We verified antipsychotic treatment at assessment by contrasting information obtained during the clinical records. All patients received second-generation antipsychotics. Of all 36 ARMS individuals, 27 (75%) were not receiving antipsychotic drugs, 7 (19.4%) were on antipsychotic monotherapy (risperidone [n=1], olanzapine [n=3], aripiprazole [n=3]) and 3 were receiving two antipsychotics in combination. Of all 124 PD patients, 72 (58.1%) were on antipsychotic monotherapy (risperidone [n=31], paliperidone [n=13], olanzapine [n=17], quetiapine [n=1], aripiprazole [n=10]), 33 (26.6%) were receiving two antipsychotics in combination and 19 (15.3%) were not receiving antipsychotic drugs.

2.3. DNA extraction and BDNF genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells using the Gentra Puregene Blood Kit (QIAGEN Iberia S.L., L'Hospitalet de Llobregat, Barcelona, Spain) according to the manufacturer's instructions. The extraction was carried out at the Biobank of the Institut d'Investigació Sanitària Pere Virgili (IISPV) (Reus, Tarragona, Spain). DNA was genotyped using a TaqMan SNP genotyping assay for the rs6265 SNP (assay ID C_11592758_10; Life Technologies, Alcobendas, Madrid, Spain). Each 5 µL of PCR reaction mix contained 40 ng of DNA, 2.5 µL of TaqMan Universal PCR Master Mix, 0.25 µL of 20X TaqMan SNP Genotyping Assay and 2.25 µL of DNase-free water. PCR conditions were 10 min at 95°C followed by 40 cycles of

15 s at 95°C and 1 min at 60°C. The reactions were carried out on an ABI 7900HT Fast Real-Time PCR System (Life Technologies, Alcobendas, Madrid, Spain). Five percent of samples were run in duplicate for quality control with 100% concordance.

2.4. Statistical analyses

The Statistical Package for the Social Sciences (SPSS) version 19.0 for Windows (IBM Corporation Software Group, Somers, New York, USA) was used for statistical analysis. T-Student Test or ANOVA was used to compare continuous data between groups. Bonferroni adjustment was used for post-hoc comparisons. Chi-square tests were used to compare categorical data between groups. Pearson correlations were used to explore the association between continuous variables. We conducted a multiple lineal regression analysis to investigate the relationship between stress variables and dietary variables (e.g. calorie intake) while controlling for potential confounders (sex, BMI, substance use) with a confidence interval of 95%. In this analysis, stress measures (e.g. PSS score) and BDNF genes SNP (Met-carriers vs Val/Val homozygotes) were used as independent variables. We also tested the interaction between this SNP and stress measures to explore whether there was a gene-environment interaction. Those significant interaction terms were kept in the final equation. We conducted a multivariate analysis stratified by diagnosis (HS vs ARMS vs PD), so three multiple linear regression analyses were conducted.

3. Results

Socio-demographic and genotype characteristics of samples are described in Table 1. Smoking and cannabis use were more prevalent in PD patients when compared to ARMS and HS. Conversely, alcohol consumption among patients was low

compared to HS. We found significant differences in perceived stress (but not in stressful life events) between diagnostic groups. Among all groups, the ARMS subjects had greater scores in the PSS scale.

Lifestyle variables (dietary habits and physical activity) and obesity measures are described in Table 2. ARMS subjects and PD patients reported an increased energy intake and reduced protein consumption, when compared to HS. Both ARMS subjects and PD patients reported reduced physical activity when compared to HS. Finally, individuals with PD had a greater BMI than other groups.

Diet and stress measures by diagnostic group and genotype are presented in Table 3. We did not find significant differences in each of these variables between Met-carriers or Val homozygotes. However, when we explored the relationship between stress and lifestyle variables or obesity measures by genotype, we found significant differences (Table 4). Perceived stress was associated with a different pattern in calorie intake, depending on genotype and diagnostic group: perceived stress was associated with a reduced caloric intake in ARMS subjects who were Met-carriers, whereas a positive relationship was found in PD patients who were Val homozygous. Perceived stress was associated with food craving in PD patients, independent of genotype, and in ARMS or HS who were Val homozygous. In HS, perceived stress was also associated with increased lipid and fatty acid consumption, reduced protein intake and lower BMI.

We also conducted multiple linear regression analysis that was stratified by diagnosis, in order to explore the relationship between perceived stress and calorie intake while adjusting for confounders (cannabis and tobacco use, sex and BMI) and exploring the gene-environment interaction. In HS, perceived stress was not associated with calorie intake (Figure 1a). In ARMS subjects, BDNF genotype (Met-carriers) was associated with an increased calorie intake (Standardized β= 1.36, p=0.040). However,

a significant negative interaction between perceived stress and Val66Met SNP (Met-carriers) was found (Standardized β= -1.37, p=0.047). Thus, in ARMS subjects, BDNF genotype (Met-carrier in Val66Met SNP) was associated with an increased calorie intake, but that in situations of increased perceived stress, Met-carriers reported reduced calorie consumption (Figure 1b). On the other hand, in PD patients, perceived stress was associated with an increased calorie intake (Standardized β= 0.217, p= 0.021), without an effect by genotype or a gene-environment interaction (Figure 1c).

4. Discussion

In this cross-sectional study exploring the relationship between stress and dietary habits in three diagnostic groups (HS, ARMS subjects and PD patients) in relation to a SNP of the BDNF gene (Val66Met), we found a gene-environment interaction in ARMS subjects only. While in both HS and PD patients this genetic polymorphism did not seem to affect the relationship between stress and energy intake, in ARMS subjects carriers of the Met-allele, a negative relationship between stress and diet was found (a lower calorie intake was reported by those subjects with increased perceived stress).

These findings are in accordance with previous genetic studies that have linked eating disorders, particularly restrictive type anorexia nervosa, with Val66Met Met-allele carriers (Ribasés et al., 2003). Other studies in healthy populations have also found a restricted energy intake in Met-carriers adolescents with maladaptive or problematic eating attitudes and behaviours (Arija et al., 2010), or adolescent girls with food restrictive behaviours (Akkermann et al., 2011). Although BDNF plays an essential role in neuronal survival and differentiation, as well as neuronal plasticity, it is also an anorexigenic factor involved in the regulation of food intake (Lebrun et al., 2006; Rosas-Vargas et al., 2011). Interestingly, in animal models using BDNF knock-out

heterozygous mice with only one functional BDNF allele, a reduction of BDNF expression in the hypothalamus has been demonstrated with associated hyperphagia and obesity (Fox et al., 2013; Kernie et al., 2000).

Of all diagnostic groups, we only found a gene-environment effect in the ARMS group. ARMS subjects showed increased perceived stress, which fits well with other studies in the literature reporting similar findings (Pruessner et al., 2011). The existing clinical differences between ARMS and PD groups, may explain a distinct pattern in the relationship between BDNF gene and perceived stress, in relation to dietary habits. ARMS subjects may be at an early stage of the illness (prodromal), in contrast with the PD patients group, whom would be in a more chronic stage (with greater cumulative stress). So can the different gene-environment effect in ARMS and PD be explained by differences between both diagnostic groups in cumulative stress and allostatic load? Acute stress is associated with anorexia and chronic stress with hyperphagia (Adam and Epel 2007; Kyrou and Tsigos, 2008). In acute stress, corticotrophin releasing hormone (CRH) stimulates pro-opiomelanocortin neurons of the arcuate nucleus which elicit anorexic signals, via α-melanocyte-stimulating hormone release, and suppress neuropeptide Y (NPY), a potent orexigen. In turn, chronic stress and the increase of circulating glucocorticoid concentrations eventually promote the intake of carbohydrates and fat and decrease energy expenditure by suppressing CRH and stimulating NPY hypothalamic secretion. If we consider that ARMS subjects are experiencing prodromal symptoms of psychosis, the reduced calorie intake in vulnerable ARMS subjects (Met-Carriers) may be explained by a lower allostatic load and maintenance of adaptative responses that would mimic the effect of acute stress on apetite). However, in PD an increased allostatic load may induce a lack of adaptation to chronic stress. Increased glucocorticoids stimulate the activation of the eating behaviour through the intake of “comfort food” that may directly reduce the negative effects of chronic stressors in the shell of the nucleus accumbens by

stimulating its pleasure-associated area (Dallman et al., 2005; Oliver and Wardle, 1999).

Another potential explanation of the differences between ARMS and PD groups in the relationship between stress and energy intake is that PD patients were receiving more antipsychotic treatment. It is plausible that the effect of perceived stress on dietary habits may be modified by antipsychotic treatment, which interacts with the dopaminergic and serotoninergic systems (Dallman et al., 2005), that are also involved in the control of eating behaviour. Thus, a potential gene-environment interaction in PD subjects may be obscured by treatment with antipsychotic drugs in this subgroup. Cannabis use is another factor that may partially explain some of the differences in the results between ARMS and PD groups, because PD patients reported more daily cannabis consumption. Cannabinoids promote energy intake by their action at specific brain regions that are important in the control of eating motivation (Kirkham TC, 2009).

Several limitations must be acknowledged. The cross-sectional design of the study does not allow inferring causality in the relationship between life stress and dietary habits. Some variables were retrospectively assessed with questionnaires (Holmes and Rahe, 1967), which may induce a recall bias. BDNF-serotonin transporter gene-gene interactions were not controlled. BDNF and serotonin systems interact with each other to regulate the development and plasticity of neural circuits (Homberg et al., 2014). It is plausible that environmental exposures could trigger the expression of a gene that in turn modifies other genes. Future studies may address whether the effects of BDNF Val66Met polymorphism interact with other genes such as the serotonin transporter gene. Finally the sample size was relatively small, in particular for the ARMS group, thus some negative findings could be influenced by a lack of statistical power.

On the other hand, our study has several strengths among which it should be emphasized that is the first study of the gene-environment interaction in ARMS subjects and PD patients exploring how BDNF polymorphism (Val66Met) affects the diet in correlation with stress life events, adding important information to our previous study that assessed dietary habits and stress measures in ARMS subjects and PD patients groups without considering genetic implications (Manzanares et al., 2014). Besides, a detailed and thorough dietary assessment was conducted by a dietician, who administrated a semi structured interview and registered calorie intake with a special software and a control group of healthy volunteers was included.

Further longitudinal studies are required to describe temporal changes in eating behaviour, before or after the diagnosis of schizophrenia or other PD, in order to elucidate whether these changes are linked to the illness of may be considered a consequence of psychopharmacological treatment. This is important in the design of future preventive interventions that may target improvement of dietary habits and strategies to cope with stress in subjects with early psychosis, particularly in subjects at high risk for psychosis.

A deeper study on this topic and future advances in the understanding of the complex interaction between gene, environment and nutrition may help to find new ways to prevent this illness and lower the costs, raising the quality of life. This issue is important because it could explain why some individuals are more prone to develop dietary changes and metabolic abnormalities. Our study suggests that the BDNF is a candidate gene that may help to identify vulnerable people with stress-related dietary habits in the field of early psychosis, and highlights the need to continue exploring the potential role of neurotrophins in the interplay between stress and diet in individuals who are at risk for psychosis.

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Figure 1. Scatter plot of the relationship between perceived stress and calorie intake in healthy subjects (1a), at-risk mental states (1b) and patients with a psychotic disorder (1c). Regression lines for each Val66Met genotype group (Val/Val vs Met-carriers) are presented. A gene-environment effect was observed in ARMS individuals (1b).

Table(s)

Table 1. Clinical, stress and genetic variables of the sample.

	Healthy Subjects N=62	ARMS N=36	Psychotic Disorder N=124	P value
Sex				
Male	32 (51.6)	26 (72.2)	81 (65.3)	0.082
Female	30 (48.4)	10 (27.8)	43 (34.7)	
Ethnic Group				
Caucasian	59 (95.2)	32 (88.9)	95 (76.6)	0.204
Black	0 (0)	0 (0)	1 (0.8)	
Gipsy	0 (0)	0 (0)	5 (4.0)	
Asian	0 (0)	0 (0)	1 (0.8)	
Arabian	1 (1.6)	1 (2.8)	10 (8.1)	
Latinoamerican	2 (3.2)	3 (8.3)	12 (9.7)	
Civil Status				
Single	43 (69.4)	29 (80.6)	99 (79.8)	0.207
Lives with couple/Married	19 (30.6)	6 (16.7)	22 (17.7)	
Divorced	0	1 (2.8)	3 (2.4)	
Work Status				
Employed/ Student	55 (88.7)	24 (66,7)	44 (35,5)	<0.001
Unemployed	7 (11.3)	12 (33,3)	80 (64.5)	
Drug Use				
Tobacco				
No	41 (66.1)	20 (55.6)	33 (26.6)	<0.001
Occasionally	5 (8.1)	1 (2.8)	4 (3.2)	
Daily	16 (25.8)	15 (41.7)	87 (70.2)	
Cannabis				
No	49 (79.0)	26 (72.2)	70 (56.5)	<0.001
Occasionally	11 (17.7)	5 (13.9)	12 (9.7)	
Daily	2 (3.2)	5 (13.9)	42 (33.9)	
Alcohol				
No	5 (8.1)	12 (33.3)	41 (33.1)	<0.001
Occasionally	56 (90.3)	23 (63.9)	66 (53.2)	
Daily	1 (1.6)	1 (2.8)	17 (13.7)	
Stress measures				
PSS	18.7 (32.5)	32.5 (11.)	24.8 (9.0)	<0.001[a,b,c]
SLE (Holmes-Rahe score)	107.1 (96.7)	150.5 (83.9)	158.1 (118.0)	0.052
BDNF (rs6262) genotype				
Val/Val	34 (54.8)	20 (55.5)	72 (58.0)	0.908
Val/Met	25 (40.3)	14 (38.9)	43 (34.7)	
Met/Met	3 (4.8)	2 (5.5)	9 (7.3)	

Data are mean (SD) or N (%).

Significant ANOVA post-hoc comparisons are highlighted: [a] HS vs ARMS; [b] HS vs PD; [c] ARMS vs PD

Abbreviation: ARMS= At-Risk Mental State; PSS= Perceived Stress Scale; SLE= Stressful life events; Val= Valine; Met= Methionine.

Table(s)

2. Lifestyle variables and obesity measures among diagnostic groups.

	Healthy Subjects N=62	ARMS N=36	Psychotic Disorder N=124	P value
Dietary Intake (24h recall):				
Total energy (Kcal)	1741.6 (424.3)	2424.1 (863.0)	2509.4 (653.3)	<0.001[a,b]
Lipids (%)	35.9 (6.0)	36.6 (10.3)	37.6 (6.8)	0.318
Proteins (%)	20.3 (4.9)	15.6 (4.5)	16.11 (3.5)	<0.001[a,b]
Carbohydrates (%)	43.4 (6.3)	46.4 (11.4)	45.7 (8.0)	0.121
Saturated fatty acids (%)	10.9 (2.9)	13.1 (5.1)	12.5 (3.3)	0.003
Refined sugar (%)	18.4 (6.4)	21.1 (11.9)	20.1 (6.6)	0.197
Food craving (FCQ-S)	28.3 (10.5)	32.0 (12.7)	33.6 (14.3)	0.038
Physical activity (IPAQ)				
MET-min/week	2954.7 (2227.3)	1289.5 (1144.1)	1672.5 (1370.3)	<0.001[a,b]
Obesity measures				
BMI (kg/m^2)	22.2 (3.8)	22.2 (3.5)	24.3 (4.6)	0.002[b,c]
Weight classification by BMI				
Underweight (<18.5 kg/m^2)	5 (8.2)	4 (11.1)	5 (4.1)	0.012
Normal (18.5-24.9 kg/m^2)	46 (75.4)	22 (61.1)	77 (62.6)	
Overweight (25-29.9 kg/m^2)	7 (11.5)	10 (27.8)	28 (22.8)	
Obesity(≥30 kg/m^2)	3 (4.9)	0	13 (10.6)	

Data are mean (SD) or N (%).

Significant ANOVA post-hoc comparisons are highlighted: [a] HS vs ARMS; [b]HS vs PD; [c]ARMS vs PD

Abbreviation: ARMS= At-Risk Mental State; IPAQ= International Physical Activity Questionnaire; FCQ-S= Food Craving Questionnaire-State; IPAQ= International Physical Activity Questionnaire; MET: Metabolic Equivalent of Task; BMI= Body mass index.

Table(s)

Table 3. Diet and stress measures. Stratified analysis by diagnosis and BDNF Val66Met polymorphism.

	Healthy Subjects N=62		ARMS N=36		Psychotic Disorder N=124	
	Val/Val N=34	Met Carriers N=28	Val/Val N=20	Met Carriers N=16	Val/Val N=72	Met Carriers N=52
Dietary intake (24h recall)						
Total energy (Kcal)	1762.5 (468.4)	1716.3 (370.7)	2329.5 (904.1)	2542.4 (821.9)	2476.7 (626.5)	2554.8 (692.3)
Lipids (%)	36.2 (6.1)	35.5 (5.9)	36.7 (10.9)	36.4 (10.0)	36.8 (6.3)	38.7 (7.3)
Proteins (%)	19.2 (5.2)	21.6 (4.2)	15.5 (4.6)	15.8 (4.5)	15.9 (3.7)	16.4 (3.2)
Carbohydrates (%)	43.9 (7.1)	42.7 (5.1)	46.3 (12.1)	46.6 (10.9)	46.8 (8.1)	44.2 (7.7)
Saturated fatty acids (%)	11.1 (2.8)	10.6 (2.9)	12.8 (4.3)	13.4 (6.1)	12.8 (3.5)	11.9 (2.8)
Refined sugar (%)	19.1 (6.3)	17.6 (6.3)	20.0 (13.2)	22.5 (10.3)	20.8 (6.8)	19.0 (6.3)
Food craving (FCQ-S)	27.7 (9.6)	29.1 (11.6)	34.5 (13.6)	28.9 (11.2)	34.3 (14.7)	32.6 (13.9)
Stress measures						
PSS	19.3 (8.0)	18.0 (6.6)	32.4 (13.0)	32.7 (8.6)	25.2 (8.7)	24.2 (9.3)
SLE (Holmes-Rahe score)	112.7 (106.9)	100.3 (84.5)	172.0 (90.2)	124.9 (70.0)	176.5 (124.6)	133.3 (104.8)

Abbreviation: Val/Val= homozygous for valine at codon 66; ARMS= At-Risk Mental State; PSS= Perceived Stress Scale; SLE= Stressful life events; FCQ-S= Food Craving Questionnaire-State.

Data are mean (SD)= Standard Deviation

Table(s)

Table 4. Correlations between lifestyle variables and stress measures. Stratified analysis by diagnosis and BDNF Val66Met polymorphism.

	Healthy Subjects N=62				ARMS N=36				Psychotic Disorder N=124			
	Val Homozygous N=34		Met Carriers N=28		Val Homozygous N=20		Met Carriers N=16		Val Homozygous N=72		Met Carriers N=52	
	SLE (HR)	PSS	SLE (HR)	PSS	SLE (HR)	PSS	SLE (HR)	PSS	SLE (HR)	PSS	SLE (HR)	PSS
Dietary intake (24h recall)												
Total energy (Kcal)	-0.257	0.018	0.050	0.081	0.059	0.119	-0.303	-0.594* (0.015)	0.137	0.262* (0.033)	0.255	0.242
Lipids (%)	0.126	0.048	-0.029	0.558* (0.004)	0.151	-0.294	-0.362	-0.404	-0.142	-0.019	-0.056	-0.083
Proteins (%)	-0.118	-0.254	0.083	-0.444* (0.026)	-0.287	-0.408	0.203	0.168	-0.046	-0.228	-0.394* (0.007)	-0.255
Carbohydrates (%)	-0.079	0.072	0.060	-0.260	0.128	0.332	0.206	0.193	0.140	0.176	0.245	0.198
Saturated fatty acids (%)	-0.100	0.119	-0.247	0.444* (0.026)	0.182	-0.235	-0.156	-0.187	-0.084	0.059	0.012	0.016
Refined sugar (%)	-0.216	-0.186	-0.252	-0.308	-0.144	0.151	0.132	0.127	0.189	0.107	0.230	0.281
Food craving (FCQ-S)	0.366* (0.047)	0.489* (0.005)	0.114	0.196	0.252	0.546* (0.016)	0.192	0.380	0.112	0.327* (0.008)	0.464* (0.001)	0.430* (0.003)
Physical Activity (IPAQ)	0.192	0.148	0.174	0.206	0.225	-0.343	0.413	-0.005	0.135	-0.365* (0.003)	-0.215	-0.115
BMI	0.175	0.237	-0.011	-0.457* (0.032)	-0.006	0.340	0.094	-0.341	-0.104	-0.079	-0.021	-0.086

*Significant P values are shown.

Abbreviation: ARMS= At-Risk Mental State; SLE (HR)= Stressful life events (Homes-Rahe score); PSS= Perceived Stress Scale; IPAQ= International Physical Activity Questionnaire; FCQ-S= Food Craving Questionnaire-State; BMI= Body mass index.

Figure 1

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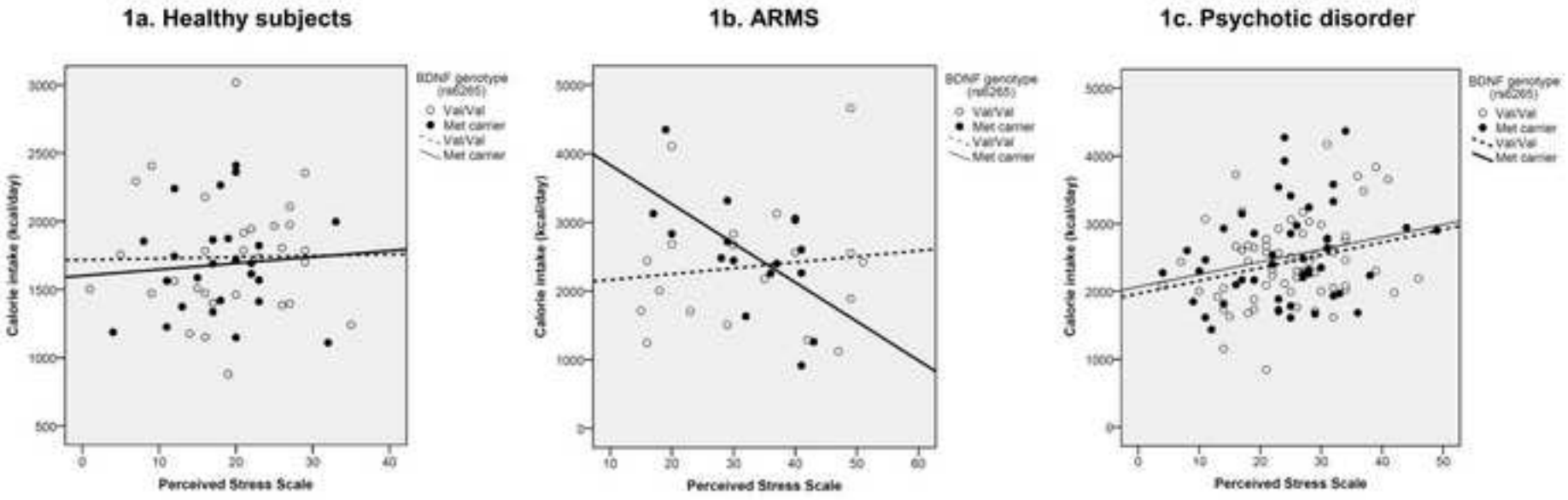

HIGHLIGHTS

We studied healthy subjects, at-risk-mental-states (ARMS) and psychotic disorders (PD).

We explored gene-environment effects in the relationship between stress, diet and BDNF gene.

Val66Met single nucleotide polymorphism (SNP) of the BDNF gene was genotyped.

Perceived stress was associated with greater calorie intake in PD, without an effect by the BDNF gene.

In ARMS who were Met66 carriers, perceived stress was associated with lower calorie intake.

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Contributors

Javier Labad and Rebecca Reynolds designed the study and wrote the protocol. Javier Labad performed the statistical analysis. Giulia Gattere and Alexander Stojanovic-Pérez managed the literature searches. Giulia Gattere wrote the first draft of the manuscript, which was supervised by Javier Labad, Lourdes Martorell and Rebecca M Reynolds. Rosa Monseny, Maria José Algora and Laura Ortega participated in the recruitment and obtained clinical data related to stress measures, dietary habits and physical examination. Montse Solé, Itziar Montalvo and Ángel Cabezas administered the psychiatric interviews. Alexander Stojanovic-Pérez, Giulia Gattere, Lourdes Martorell and Elisabet Vilella performed the genetic analyses. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Javier Labad has received honoraria for lectures or advisory boards from Janssen-Cilag, Otsuka and Lundbeck. Itziar Montalvo has received honoraria for lectures from Janssen-Cilag, Otsuka and Lundbeck. All other authors do not have potential conflicts of interest.

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