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Research paper

Influence of *BDNF* Val66Met genetic polymorphism in Major Depressive Disorder and Body Mass Index: Evidence from a meta-analysis of 6481 individuals

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ABSTRACT

Background: Major depressive disorder (MDD) and obesity are global health problems that frequently co-occur. Among shared etiological factors, genetic variation at the brain-derived neurotrophic factor (*BDNF*) gene is interesting since its implication in energy balance regulation, food intake and synaptic function. Thus, the aim of this study was to investigate the influence of the *BDNF* Val66Met polymorphism in relation to MDD and body mass index (BMI) in two large independent cohorts.

Methods: The sample consisted of 2646 individuals with MDD and 3835 controls from the PISMA-ep and Radiant studies. Linear regressions were performed to test the association between the polymorphism and BMI and the interaction between the polymorphism and MDD on BMI. A meta-analysis across cohorts was conducted.

Results: No association was found between the polymorphism and BMI. However, we found an association with MDD, showing these individuals higher BMI than controls in both cohorts. No differences were found in BMI depending on Val66Met genotype and no interaction between this polymorphism and MDD in relation to BMI was found. Although a tendency towards an interaction was found in the Radiant sample, the results of the meta-analysis did not support this finding.

Limitations: The use of self-reported height and weight measures to calculate BMI values.

Conclusions: We provide evidence for an association between BMI and MDD confirming previous results. Our meta-analysis including two large cohorts showed no interaction between *BDNF*, BMI and MDD. Future studies will be needed to confirm the role of this polymorphism in the relationship between BMI and MDD.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders and a leading cause of disability worldwide. For this reason, it is a major contributor to the global burden of disease (Mathers and Loncar, 2006; Scott et al., 2008).

Several authors have reported that MDD and physical disorders are commonly comorbid, with the presence of one significantly worsening the evolution of the other (Gold et al., 2020). In fact, patients with depression are at higher risk of suffering physical disorders and vice versa (Auton et al., 2015; Farmer et al., 2008; Rivera et al., 2019). In this context, an association between depression and obesity has repeatedly been described, with higher body mass index (BMI) increasing the risk for MDD (Hung et al., 2014). Bearing in mind that obesity is considered a pandemic of the twenty-first century, with more than the double of obese people in the world than 30 years ago (WHO, 2017), it is mandatory to explore the factors and direction of the association between these global health problems (Luppino et al., 2010).

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Among the possible behavioral, sociocultural, and psychological factors influencing this association (Milaneschi et al., 2020; Milaneschi et al., 2019), Preiss et al. (2013) found mediation by educational attainment, physical health, binge eating, body image dissatisfaction and weight and shape concerns. Considering the strong genetic basis of both disorders, biological factors such as genetic variants in candidate genes were explored by Rivera et al. (2012). They analyzed variants in the fat mass and obesity-associated (*FTO*) gene and found a significant interaction between the genotype and depression status in relation to BMI for seven variants. A meta-analysis also performed by Rivera et al. (2017) provided additional support for a significant interaction between *FTO*, depression and BMI, indicating that depression increases the effect of *FTO* gene on BMI.

Among other candidate genes likely involved in both outcomes, the brain-derived neurotrophic factor (*BDNF*) has to be highlighted since it is involved not only in neuronal development and protection, plasticity and synaptic function (Castrén and Monteggia, 2021; Noble et al., 2011) but also in the regulation of energy balance, food intake and feeding behavior (Honarmand et al., 2021; Ieraci et al., 2020). This neurotrophin has antidepressant-like effects in animals, which indicates that it may be implicated in the etiology of mood-related phenotypes (Lin and Huang, 2020; Verhagen et al., 2010). Taking into account its essential participation in body weight control, energy homeostasis and stress regulation, *BDNF* is a key gene to assess in obesity, where all of these processes seem to be altered (Honarmand et al., 2021; Ieraci et al., 2020; Rosas-Vargas et al., 2011). Furthermore, low levels of circulating BDNF have been found in individuals with obesity (Krabbe et al., 2007) as well as an inverse association between the peripheral BDNF concentration and body mass index (BMI) in children and adults (Lommatzsch et al., 2005).

A widely studied common genetic variant in the *BDNF* gene, the Val66Met polymorphism (also known as rs6265), entails protein structural modifications and consequent functional changes in neural circuitries. Specifically, the Met allele has been shown to impair BDNF trafficking and release, possibly hindering neuronal plasticity and other critical processes for a proper brain function (Baj et al., 2013; Egan et al., 2003). Numerous studies have posed this allele as a risk factor for a number of neuropsychiatric disorders including MDD and also for severe obesity in humans (Bath and Lee, 2006; Castrén and Monteggia, 2021; Chen et al., 2008; Neves-Pereira et al., 2002; Xu and Xie, 2016; Youssef et al., 2018). Therefore, the objective of the present study was to investigate the influence of this genetic variant on the association between MDD and BMI in two large independent cohorts.

2. Materials and methods

2.1. Study population

2.1.1. Discovery phase study (PISMA-ep study)

The PISMA-ep is a cross-sectional epidemiological study based on a representative sample of the adult population living in the entire Andalusia region (Spain) (Cervilla et al., 2016). This study aims to establish the prevalence of major psychiatric disorders in Andalusia and to identify genetic and environmental risk factors for such conditions. The exclusion criteria taken into account consisted, among others, of having lived in Andalusia for less than a year, having moved and having a diagnosis of dementia or mental retardation. Information about clinical, psychological, anthropometric measurements and medical conditions were obtained from each participant. Individuals who also agreed to participate in the genetic analysis gave specific informed consent and provided a biological sample. The methodology and characteristics of the PISMA-ep study have been described in more detail elsewhere (Cervilla et al., 2016).

2.1.2. Replication phase study (Radiant study)

The Radiant study includes individuals sourced from several studies described in detail elsewhere: the Depression Network (DeNT) study (Farmer et al., 2004), the Depression Case–Control (DeCC) study (Cohen-Woods et al., 2009), and the Genome-Based Therapeutic Drugs for Depression (GENDEP) study (Uher et al., 2009). The DeNT affected sibling pair linkage study includes cases with recurrent unipolar depression collected at seven European sites and one US site. The DeCC is a case-control study that recruited individuals from three UK sites (Cohen-Woods et al., 2009). All participants in the DeCC and DeNT studies had experienced at least two episodes of major depression of at least moderate severity. The GENDEP study includes individuals with one or more episodes of depression of at least moderate severity recruited from nine European centers (Uher et al., 2009).

All participants included were of European ancestry, both in original and replication phase studies. The local ethics committee at each site approved the studies and written informed consents.

2.2. Diagnosis

2.2.1. PISMA-ep study

A total sample of 3237 individuals, 212 cases with a MDD diagnosis and 3025 psychiatrically healthy controls were included in this study. The Mini-International Neuropsychiatric Interview (MINI) was used to ascertain the diagnosis of MDD following DSM-IV criteria (Pettersson et al., 2018; Sheehan et al., 1998). Interviews were conducted by fully trained psychologists and took place either in the participant's local primary healthcare center or in their homes.

The control group was screened for personal or family history of mental disorders, pharmacological and psychological treatment. They were all screened out for any mental disorder using the MINI (Pettersson et al., 2018; Sheehan et al., 1998). Controls did not have any psychiatric disorder and were all recruited from different primary care centers from the same catchment areas as patients.

2.2.2. Radiant study

A total of 3244 participants (2434 individuals with MDD and 810 controls) were recruited from the Radiant study, which included several studies detailed elsewhere (Cohen-Woods et al., 2009; Farmer et al., 2004; Uher et al., 2009). Diagnosis of MDD was ascertained using the SCAN interview (Wing et al., 1990). The control sample was screened for lifetime absence of any psychiatric disorder using a modified version of the Past History Schedule (McGuffin et al., 1986).

2.3. Phenotypic data

In both studies, self-reported weight and height were obtained to calculate BMI, defined as weight in kilograms divided by height in meters squared (kg/m^2). In the PISMA-ep study, self-reported weight and height were obtained during the interview. In the Radiant study, measures were obtained during the SCAN interview for the individuals with MDD and during telephone interviews for controls in order to calculate their BMI. The reliability of self-report of height and weight was assessed in the GENDEP dataset, where we also had measured height and weight. The correlations for measured versus self-reported height, weight and BMI were 0.97, 0.95 and 0.95, respectively.

2.4. Genotyping

In the PISMA-ep study, a biological sample (saliva) was obtained from each participant using Oragene DNA saliva collection kit (OG-500; DNA genotek Ink). DNA was extracted following standard procedures. The DNA was stored at −80 °C and the concentration was measured by absorbance, using Infinite® M200 PRO multimode reader (Tecan, Research Triangle Park, NC).

The PISMA-ep study samples were genotyped for the *BDNF* rs6265 polymorphism using TaqMan® StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, California, USA) following

manufacturer's instructions. Raw data were analyzed with the system software.

The Radiant sample was genotyped using the Illumina HumanHap610-Quad BeadChips by the Centre National de Génotypage (CNG), Evry, France. All DNA samples were subjected to stringent quality control, and processing was carried out under full Laboratory Information Management System (LIMS) control (Lewis et al., 2010) (Lewis et al., 2010). The genotypic information for the *BDNF* Val66Met polymorphism was extracted to be analyzed in this study.

2.5. Statistical analysis

Pearson's Chi^2 tests were performed to compare distribution of socio-demographic variables, including sex, working status, marital status, educational level and also *BDNF* Val66Met polymorphic variation between MDD cases and controls. Additionally, t-tests were carried out to analyze possible differences in age and BMI means between both groups.

Hardy-Weinberg equilibrium was tested in the entire sample, and then separately in cases and in controls.

Linear regression models for quantitative traits assuming an additive genetic model were carried out to test for the association between BMI and *BDNF* Val66Met polymorphism. In the discovery phase studies, sex and age were included as covariates in the model. In a second step, linear regression models were performed separately in individuals with MDD and controls, including sex and age as covariates. Principal components of variance were not used as a covariate, given that only individuals of Caucasian ancestry were included in this study. Following the same analyses, in the replication phase, case-control status, sex, age and principal components of the variance, to control for possible population stratification, were included as covariates in the regression analyses.

We tested for the interaction between *BDNF* Val66Met polymorphism and MDD on BMI. Sex and age were included as covariates in the regression analyses. We also conducted a meta-analysis by calculating the effect size as the standardized difference in BMI means between the two groups being compared. A fixed-effects meta-analysis was chosen due to the fact that all participants included were of European ancestry, both in original and replication phase studies. Heterogeneity between primary studies was assessed using the I^2 statistic (Higgins et al., 2003).

All statistical analyses were performed using R (version 4.0.3), with RStudio 1.3.959 software. 'stats' R package was used to conducted chi^2 tests, t-tests and linear regression models (https://CRAN.R-project.org/package=stats); 'SNPassoc' R package (https://CRAN.R-project.org/package=SNPassoc) was used in order to determine Hardy-Weinberg equilibrium and 'meta' R package (https://CRAN.R-project.org/package=meta) was used to perform the meta-analysis.

In the discovery sample, we calculated statistical power using QUANTO software version 1.2.4 (http://hydra.usc.edu/gxe/). According to such calculations, our sample size had 80 % power (confidence interval of $p < 0.05$) to detect a gene-by-environment interaction effect of at least 1.8 if we assumed an additive genetic model, a prevalence for MDD of 10 %, a 38 % prevalence for obesity (as reported by (Wang et al., 2011) and a frequency of the hypothesized risk allele (*BDNF* Met66) of 0.22 (as described in Spanish population by (Gutiérrez et al., 2015).

3. Results

3.1. Participants

3.1.1. PISMA-ep study

Among 212 MDD cases, 150 (70.75 %) were women and 62 (29.25 %) were men whereas in the control group, 1456 (48.13 %) were women and 1569 (51.87 %) were men. Distribution of sexes was found to differ significantly between both groups, with an excess of women in the group of cases ($\chi^2 = 39.66$, $p = 3.02 \times 10^{-10}$). In addition, controls were significantly younger than cases (mean age ± s.d.: 42.75 ± 15.05 years and 49.14 ± 15.16 years, respectively; $t = -5.929$, $p = 1.05 \times 10^{-8}$). Also, differences between groups were found for educational level ($\chi^2 = 34.84$, $p = 5.00 \times 10^{-4}$). Table 1 shows the sample's main socio-demographic characteristics.

3.1.2. Radiant study

The sample included 3244 individuals, 2434 MDD cases (1700 women and 734 men; mean age ± s.d.: 45.22 ± 12.16 years) and 810 psychiatrically healthy controls (61.1 % were women and 38.9 % were men with a mean age of ± s.d.: 39.89 ± 13.70 years). There were significant differences between groups for the distribution of sexes and age, being cases significantly older than controls ($t = -10.374$, $p = 2.20 \times 10^{-16}$) and with an excess of women in the group of cases ($\chi^2 = 21.18$, $p == 9.37 \times 10^{-6}$) (Table 2).

3.2. Association between BMI and MDD

3.2.1. PISMA-ep study

Significant differences between MDD cases and controls were found in the BMI average ($t = -5.01$, $p = 1.07 \times 10^{-6}$). Individuals with depression showed higher BMI values in comparison to controls (28.09 (SD = 5.83) and 26.04 (SD = 4.37), respectively).

3.2.2. Radiant study

We found significant differences in the BMI average between cases and controls ($t = -9.56$, $p = 2.20 \times 10^{-16}$). Individuals with depression showed higher BMI values in comparison to controls (26.40 (SD = 5.52) and 24.33 (SD = 4.50), respectively).

3.3. Association between BDNF Val66Met polymorphism and MDD

3.3.1. PISMA-ep study

BDNF Val66Met genotype frequencies were found to be in Hardy Weinberg equilibrium in the whole sample ($\chi2 = 0.2727$; df = 2; p = 0.873) and both in MDD cases ($\chi2 = 1.4892$; df = 2; p = 0.4749) and controls ($\chi2 = 0.7587$; df = 2; p = 0.684), supporting absence of genotyping artifacts. The analysis of the association between this polymorphism and MDD revealed that there were no statistically significant differences in the distribution of allele and genotype frequencies ($\chi2 = 0.047$; df = 1; p = 0.827; $\chi2 = 2.168$; df = 2; p = 0.338; respectively) when comparing cases with controls even after adjusting the analyses by sex, age and BMI (See Table 3 for a detailed description of allelic and genotypic frequencies distribution).

Table 1
Socio-demographic profile of the discovery sample (PISMA-ep).

		Cases N %		Controls N %	
MDD		212	6.55	3025	93.45
Mean age (SD)		49.14 (15.16)		42.75 (15.05)	
Sex	Male	62	29.25	1569	51.87
	Female	150	70.75	1456	48.13
Marital Status	Single	40	18.87	803	26.55
	Married/cohabiting	117	55.19	1914	63.27
	Separated	16	7.55	109	3.60
	Divorced	17	8.01	94	3.11
	Widowed	22	10.38	105	3.47
Education	Illiterate	6	2.83	29	0.96
	Basic education	46	21.70	343	11.34
	Primary grade	91	42.92	1198	39.60
	Secondary or higher	69	32.55	1455	48.10
Working status	With job	50	23.58	1392	46.02
	Unemployed	67	31.60	787	26.02
	Retired	27	12.74	343	11.34
	Disabled	9	4.25	37	1.22
	Homework	50	23.58	269	8.89
	Full-time student	9	4.25	196	6.48

SD, standard deviation; MDD, Major Depressive Disorder.

Table 2
Discovery and replication sample characteristics.

	PISMA-ep		Radiant	
	Cases	Controls	Cases	Controls
Sample size, N	212	3025	2434	810
Sex, %				
Male	29.25	51.87	30.16	38.89
Female	70.75	48.13	69.84	61.11
Mean age (SD), years	49.14 (15.16)	42.75 (15.05)	45.22 (12.16)	39.89 (13.70)
Mean body mass index (SD), kg/m^2	28.09 (5.83)	26.04 (4.37)	26.40 (5.52)	24.33 (4.50)

BMI, Body Mass Index; SD, standard deviation.

Table 3
BDNF Val66Met allele and genotype frequencies in MDD cases and controls both in discovery and replication phase samples.

	PISMA-ep		Radiant	
	Cases	Controls	Cases	Controls
Allele frequencies				
Met	92 (21.70 %)	1278 (21.12 %)	986 (20.25 %)	311 (19.20 %)
Val	332 (78.30 %)	4772 (78.88 %)	3882 (79.75 %)	1309 (80.80 %)
	$\chi2 = 0.048$; df = 1; p = 0.827		$\chi2 = 0.849$; df = 1; p = 0.357	
	Cases	Controls	Cases	Controls
Genotype frequencies				
Met/Met	13 (6.13 %)	127 (4.20 %)	93 (3.82 %)	30 (3.70 %)
Met/Val	66 (31.13 %)	1024 (33.85 %)	800 (32.87 %)	251 (30.99 %)
Val/Val	133 (62.74 %)	1874 (61.95 %)	1541 (63.31 %)	529 (65.31 %)
	$\chi2 = 2.168$; df = 2; p = 0.338		$\chi2 = 1.065$; df = 2; p = 0.587	

3.3.2. Radiant study

Genotype frequencies for the *BDNF* Val66Met polymorphism were found to be in Hardy Weinberg equilibrium in the whole sample ($\chi2 = 0.283$; df = 2; p = 0.868) and both in MDD cases ($\chi2 = 0.353$; df = 2; p = 0.838) and controls ($\chi2 = 0$; df = 2; p = 1), supporting absence of genotyping artifacts. There were no statistically significant differences in the distribution of allele and genotype frequencies ($\chi2 = 0.849$; df = 1; p = 0.357; $\chi2 = 1.065$; df = 2; p = 0.587; respectively) when comparing MDD cases with controls even after adjusting the analyses by sex, age, 10 principal components, and BMI (see Table 3).

3.4. Association between BDNF Val66Met polymorphism and BMI

3.4.1. PISMA-ep study

No statistically significant results were found in BMI values depending on the genotype carried (β = −0.2524, p = 0.067). These results remained robust after adjusting by sex, age and depression status (β = −1.496, p = 0.135). When analyzing cases and controls separately, no evidence of association was found between BMI and *BDNF* Val66Met in any group (β = −0.4614, p = 0.471 in cases and β = −0.1715, p = 0.189 in controls) (see Table 4).

3.4.2. Radiant study

We did not find statistically significant differences in BMI values depending on the genotype carried (β = −0.04985, p = 0.7659) even after adjusting by sex, age, 10 principal components, or depression status (β = −0.051, p = 0.7540). Moreover, no evidence of association was found between BMI and *BDNF* Val66Met when MDD cases (β = −0.2093, p = 0.2852) and controls (β = 0.4096, p = 0.1417) were analyzed separately (Table 4).

3.5. Interaction between BDNF Val66Met polymorphism and MDD on BMI

3.5.1. PISMA-ep study

When we tested if there was an interaction effect between genotype and affected status in relationship to BMI no statistically significant results were found (β = −0.2865, p = 0.565) taking into account sex and age as covariates (see Fig. 1 A).

3.5.2. Radiant study

We found a significant trend of interaction between genotype and affected status in relationship to BMI (β = −0.7821, p = 0.0533) considering sex, age and 10 principal components as covariates in the model (see Fig. 1 B).

3.6. Meta-analysis

The meta-analysis performed of both studies reinforced the non-statistical significance of the differences in BMI means in MDD cases for additive models of the *BDNF* Val66Met polymorphism, both in the heterozygote and in the homozygote for the risk allele (SMD = 0.06, 95%CI = −0.02 to 0.19, *p*-value = 0.19; SMD = 0.08, 95%CI = −0.23 to 0.38, p-value = 0.86, respectively) (see Fig. 2).

4. Discussion

The aim of this study was to investigate the influence of the *BDNF* Val66Met polymorphism in relation to BMI in two large independent cohorts of individuals with MDD and controls. To our knowledge, this is the first study examining the relationship between the *BDNF* Val66Met polymorphism, BMI and MDD concurrently.

We examined whether BMI was associated with MDD and a statistically significant association was found both in the discovery and replication phase samples. These results were in accordance with those reported by Jokela et al. (2012) and Opel et al. (2015), as well as with the results of several longitudinal meta-analyses that robustly evidenced how obesity increases the risk of developing depression and vice versa (Luppino et al., 2010; Mannan et al., 2016a; Mannan et al., 2016b).

On the other hand, given the strong genetic basis underlying both disorders (Amare et al., 2017; Gharipour et al., 2020), we hypothesized that shared genetic risk factors could be contributors of such association, as previously suggested by other authors (Afari et al., 2010). Concretely, we analyzed genetic variation at the *BDNF* gene since this neurotrophin is found to be altered in several mental illnesses and obesity-related

Table 4
Association results of *BDNF* Val66Met polymorphism and BMI.

		Whole sample			Cases			Controls		
Study	N	β	SE	p	β	SE	p	β	SE	p
PISMA-ep	3237	−0.190	0.130	0.766	−0.461	0.639	0.471	−0.171	0.131	0.189
Radiant	3244	−0.051	0.163	0.754	−0.209	0.196	0.285	0.410	0.279	0.142

BMI, Body Mass Index; N, sample size; S.E, standard error.

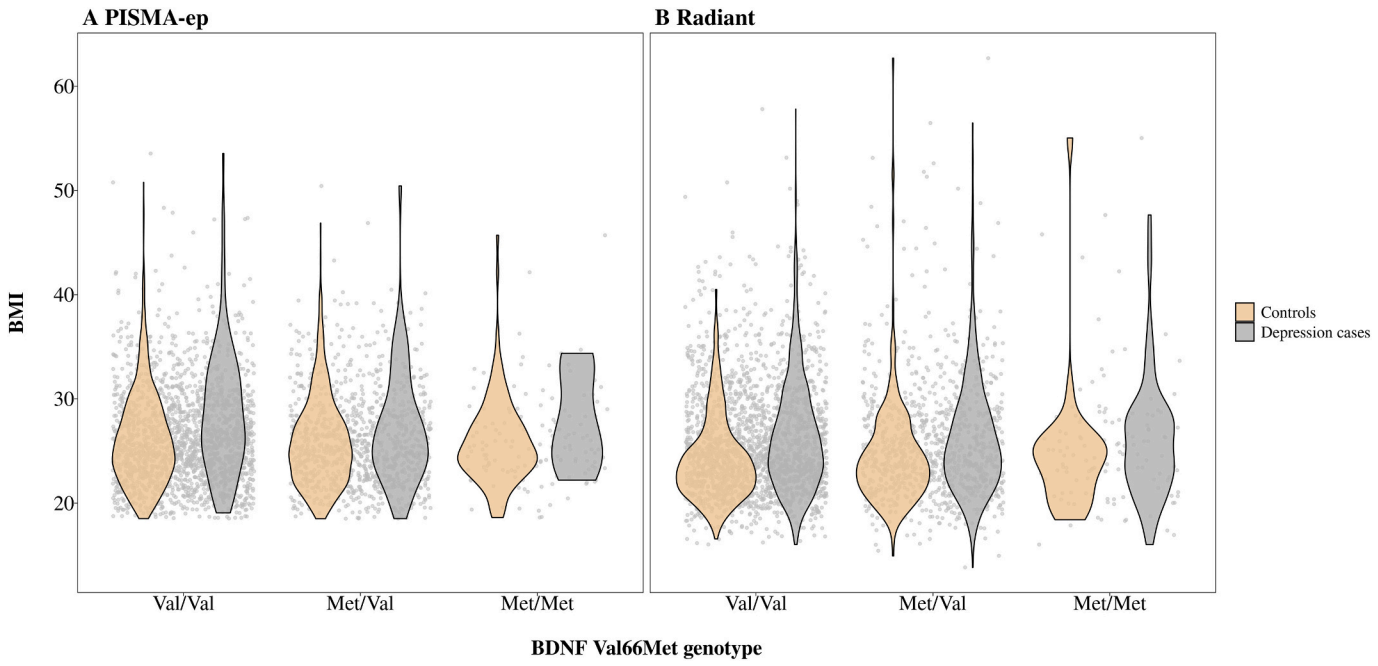

Fig. 1. BMI distribution in MDD cases and controls according to *BDNF* Val66Met genotype in A) PISMA-ep sample & B) Radiant sample.

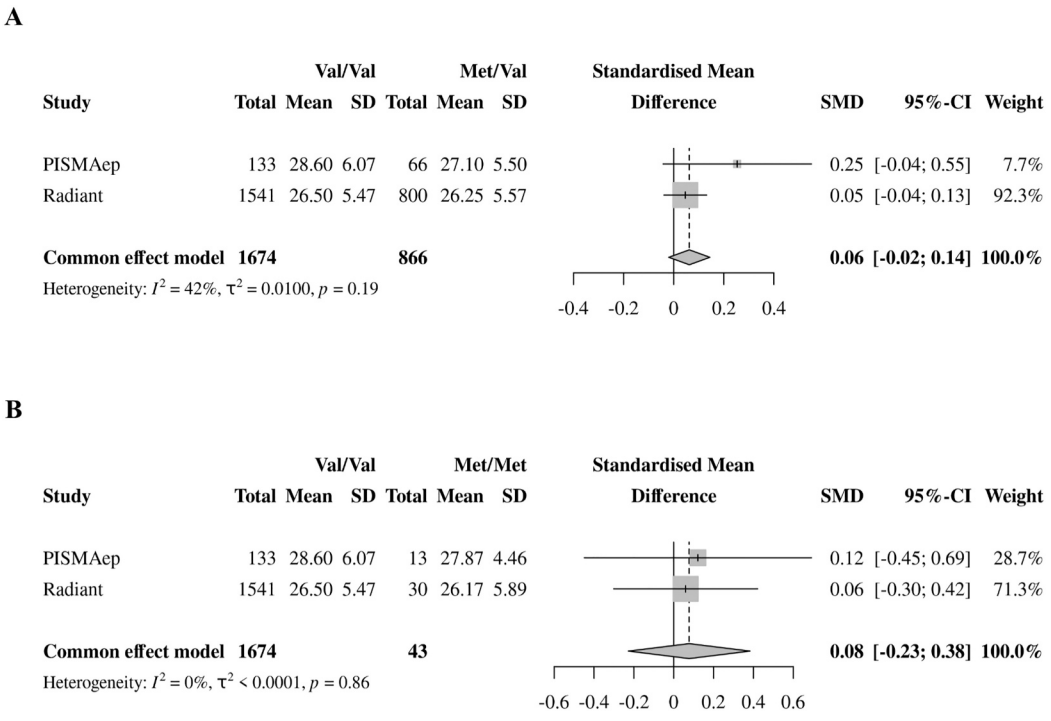

Fig. 2. Forest plots of the standardized mean difference (SMD) of the effect of *BDNF* Val66Met polymorphism on BMI in MDD cases. A) Val/Val vs. Met/Val and B) Val/Val vs. Met/Met. SD standard deviation, CI confidence interval.

phenotypes (Arija et al., 2010). We specifically tested if the Val66Met polymorphism, widely associated with structural and functional brain changes (Forde et al., 2014; Wang et al., 2014), was associated with MDD. Our results were in line with the ones reported by Tsai et al. (2003) and with the results of the meta-analyses conducted by Gyekis et al. (2013) and Verhagen et al. (2010), who did not found any significant association between the polymorphism and depression. It is worth mentioning that there may be some discrepancies regarding this relationship since the sex-stratified analyses conducted by Verhagen et al. (2010) revealed that carrying the Met allele increased the risk for MDD in men but not in women. Moreover, some studies found that the Val66Met polymorphism could be moderating life stress in MDD (Hosang et al., 2014; Zhao et al., 2018). These variable results highlight the importance of performing future meta-analyses of studies analyzing such association in order to increase the statistical power to obtain a reliable conclusion.

When we examined the association between the polymorphism and BMI we found no significant association, as previously reported by Arija

et al. (2010) and Monteleone et al. (2006). Conversely, this polymorphism was associated with obesity in several studies such as the one conducted by Martínez-Ezquerro et al. (2017) in a Mexican pediatric population or a more recent one conducted by Honarmand et al. (2021) in women from the Northwest of Iran. These inconsistent findings may be understood considering that both conditions have a polygenic basis (Flint and Kendler, 2014; Hinney et al., 2010). The polygenic architecture of obesity and MDD complicates the finding of specific variants with a sizable phenotypic effect on these phenotypes. Thus, individual *BDNF* genetic variants by itself may have a small effect on the phenotype and they might produce a detectable phenotypic effect only in combination with other predisposing variants.

Even though the results of our interaction analyses were not significant in the discovery sample, we found a tendency towards an interaction in the Radiant study. However, the results obtained from the meta-analysis of both studies showed no significant difference in BMI means in cases with MDD for the different genotypes. Since the increase in BMI or the risk of MDD are determined by genetic and environmental factors, it would be ideal also to include some environmental exposures to represent the complex nature of these outcomes. Given all this, we propose that future research should be approached on the likely environmental, genetic, social and cultural factors underlying the relationship between these disorders since it can lead to more effective prevention and treatment strategies for both conditions (Afari et al., 2010).

The main limitation of this study could be the use of self-reported height and weight measures to calculate BMI values. However, in a previous study, Rivera et al. (2012) used both self-reported and non-self-reported measures and did not find differences due to this factor, which prevented us from having reported mistaken results.

In addition, it is probable that the conclusions about the association between MDD and the Val66Met polymorphism and about the interaction between this polymorphism and MDD on BMI may be different when considering the heterogeneity of depression definition criteria (Cannon and Keller, 2006). In line with recent research, the definition of more similar clinical subtypes or endophenotypes of depression may help to elucidate its relationship with the polymorphism because endophenotypes are thought to be genetically simpler and more directly related to etiological factors than dichotomous diagnostic categories (Milaneschi et al., 2020; Ormel et al., 2019). Also, the use of endophenotypes would facilitate increasing the sample size considerably thus overcoming the sample size limitation.

In conclusion, our results show an association between BMI and MDD confirming the results from previous studies. However, our study does not support the implication of the *BDNF* Val66Met polymorphism in the reported relationship between higher BMI values and MDD.

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Role of the funding source

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CRediT authorship contribution statement

JC designed and coordinated the PISMA-ep study. JC, MR, BG and EM obtained the financial support for the project leading to this publication. MR, EM, BG and JC were involved in the study design and acquisition and data interpretation. MR led the study and supervised the analyses. BG and EM contributed to the coordination and genotyping of the PISMA-ep samples. JC helped with the phenotypic and clinical data. PR, AMP-G and JAZ-R conducted the statistical and genetics analyses. PR and AMP-G wrote the first draft of the manuscript. All authors discussed the results, provided critical feedback, and approved the submission. All authors were involved in drafting the manuscript or revising it critically for important intellectual content, and approved the final version of the manuscript to be published.

Declaration of competing interest

None.

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