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Association of Brain-Derived Neurotrophic Factor and Vitamin D with Depression and Obesity: A Population-Based Study

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Abstract
Background: Depression and obesity are widespread and closely linked. Brain-derived neurotrophic factor (BDNF) and vitamin D are both assumed to be associated with depression and obesity. Little is known about the interplay between vitamin D and BDNF. We explored the putative associations and interactions between serum BDNF and vitamin D levels with depressive symptoms and abdominal obesity in a large population-based cohort. ***Methods:*** Data were obtained from the population-based Study of Health in Pomerania (SHIP)-Trend ($n = 3,926$). The associations of serum BDNF and vitamin D levels with depressive symptoms (measured using the Patient Health Questionnaire) were assessed with binary and multinomial logistic regression models. The associations of serum BDNF and vitamin D levels with obesity (measured by the waist-to-hip ratio [WHR]) were assessed with binary logistic and linear regression models with restricted cubic splines. ***Results:*** Logistic regression models revealed inverse associations of vitamin D with depression (OR = 0.966; 95% CI 0.951–0.981) and obesity (OR = 0.976; 95% CI 0.967–0.985). No linear association of serum BDNF with depression or obesity was found. However, linear regression models revealed a *U*-shaped association of BDNF with WHR ($p < 0.001$). ***Conclusion:*** Vitamin D was inversely associated with depression and obesity. BDNF was associated with abdominal obesity, but not with depression. At the population level, our results support the relevant roles of vitamin D and BDNF in mental and physical health-related outcomes.

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Introduction

Depression and obesity are 2 widespread medical conditions with major public health implications [1, 2]. Both conditions are closely linked; recently, a bidirectional association was detected: obesity increases the risk of developing depression by 55%, whereas depressed patients have a 58% increased risk of developing obesity [3]. Little is known about the interplay between BDNF and vitamin D. In a recently published study, obesity was related to a reduced BDNF concentration in the hippocampus and vitamin D treatment increased this concentration [4]. However, that study was conducted in rats only, and therefore results may not apply to humans.

BDNF is, among others, an important growth factor in the central and peripheral nervous system, especially in hippocampal and cortical areas [5]. It plays a key role in adult neurogenesis as well as in the processes of learning and memorizing [5]. Reduced serum BDNF levels have been found to be associated with depressive symptoms or impaired memory performance. Given that BDNF passes the blood-brain barrier and circulating peripheral BDNF levels reflect central BDNF levels [6], BDNF has been suggested as a potential biomarker for different mental health conditions and particularly mood disorders [7, 8]. BDNF is expressed not only in neuronal but also in non-neuronal peripheral tissues [9, 10]. Most of the peripheral BDNF is stored in platelets [11, 12]. Recent evidence suggests that low BDNF levels in patients with depressive disorders mainly result from changes in platelet and megakaryocyte counts [12, 13]. Moreover, previous studies have revealed moderating effects of genetic epistasis between the BDNF Val66Met polymorphism (rs6265) with serotonin transporter 1 functional SNP (rs25531) and childhood adversity on depression susceptibility [14, 15].

The association between BDNF and obesity is only insufficiently understood. Proinflammatory cytokines like tumor necrosis factor are upregulated in adipose tissue of obese individuals and promote neuronal death in the brain [16, 17]. Results from Nakahashi et al. [9] showed that BDNF is involved in neuronal repair processes. Furthermore, BDNF modulates energy homeostasis by interacting with several neuropeptides, including leptin [18]. Leptin is mostly expressed in adipose tissue and regulates, among others, glucose and lipid metabolism [19]. A study from 2006 reported lower serum BDNF levels in 328 obese children and adolescents after adjusting for platelet counts [20]. In contrast, other studies with small sample sizes ($n < 100$) described higher BDNF levels in obese women compared to healthy controls [21–23]. Those previous studies mainly defined obesity based on the body mass index (BMI). Unlike the BMI, which does not provide information on regional body fat distribution [24], the waist-to-hip ratio (WHR) is an index for subcutaneous as well as intra-abdominal adipose tissue. It is more strongly related to cardiovascular diseases and overall mortality than BMI [25, 26].

Vitamin D deficiency is a considerable global health problem [27, 28]. The latitude and season determine the amount of vitamin D produced by the skin [29], the major source of vitamin D, followed by diet and dietary supplements. Thus, in Europe, for example, but also in North America, circulating 25-hydroxy vitamin D levels have a large seasonal variation [30] with lower levels of vitamin D and higher proportions of vitamin D deficiency observed in winter compared to summer [29]. Several studies including a meta-analysis of 14 studies have suggested that vitamin D deficiency is associated with depressive symptoms [31–33]. A cross-sectional study from Finland reported that vitamin D was inversely associated with depression even after adjusting for lifestyle, sociodemographic, and metabolic factors [34]. Previous studies have also detected an association of low vitamin D levels with depressive disorders and assigned a key role to vitamin D in various physiological processes [35, 36]. Vitamin D receptors are widespread throughout the central nervous system as well as other tissues and influence early childhood brain development and adult brain function [36]. Vitamin D initiates the synthesis of serotonin, a hormone strongly linked to depression [37]. By activating transcription of the serotonin-synthesizing gene [35] vitamin D modifies the production and release of neurotrophic factors via membrane-associated and nuclear vitamin D receptors in neuronal and non-neuronal cells of the central nervous system [36]. In fact, low vitamin D levels promote depressive disorders [35, 38, 39]. Although previous studies have revealed an inverse association between vitamin D and depressive disorders, recent studies report inconsistent results. For instance, a retrospective study with more than 500 participants found no association between low vitamin D levels and depression [40].

Vitamin D deficiency is also associated with obesity [41–43]. For example, inverse associations of vitamin D with total body fat and the presence of the metabolic syndrome in middle aged and elderly subjects have been described [44]. These observations might be related to the reduced bioavailability of vitamin D in obesity, caused by an increased uptake in adipose tissue [45].

In summary, conflicting results regarding the association of BDNF and vitamin D with depression and obesity

have been reported. Additionally, previous studies have been limited by small sample sizes [5, 21–23] or lacking adjustment for confounders like platelets and fibrinogen for associations with BDNF [21–23] and like smoking for associations with vitamin D [31]. We addressed these limitations by investigating a large population-based study of men and women: the Study of Health in Pomerania (SHIP)-Trend. Based on data of this cohort we elaborated the associations of BDNF and vitamin D with depressive symptoms or obesity. We hypothesized that both BDNF and vitamin D are inversely associated with depression and obesity and that BDNF and vitamin D show interactions with depression and obesity. The aim of our study was to investigate these associations in a large population-based sample to extend previously reported findings and to establish a basis for future research. Further knowledge about BDNF and vitamin D in association with depression and obesity may allow methods to prevent disease or support therapeutic options, i.e. vitamin D supplementation.

Materials and Methods

SHIP is a population-based project in northeast Germany that consists of 2 independent cohorts: SHIP and SHIP-Trend. Its objective is to determine the prevalence and incidence of risk factors and diseases and to investigate associations among risk factors and diseases [46, 47]. Both cohorts were selected from the general population in West Pomerania, a region in the northeast of Germany (latitude: 54° north). In both cohorts, only individuals with German citizenship were included. Moreover, participation in the SHIP cohort was an exclusion criterion for participation in the SHIP-Trend cohort.

The present cross-sectional study includes data from the SHIP-Trend baseline examination [46–48], in which vitamin D and BDNF levels were determined. In detail, a stratified random sample of 10,000 adults (net sample size: n = 8,826) aged 20–79 years was drawn from the local population registries. Stratification variables were age, sex, and city/county of residence. Among the invited individuals, 4,420 men and women chose to participate (50.1% response) in the baseline examinations between 2008 and 2012. Further details on the study design, protocols, and sampling methods have been reported elsewhere [46, 47]. All investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent from all participants. The survey and study methods were approved by an institutional review board (SHIP-Trend [BB 39/09]: Ethics Committee of the University of Greifswald).

Interview and Physical Examination

The SHIP-Trend examinations were performed throughout the year. The season of examination was defined as winter (December to May) or summer (June to November). Trained and certified interviewers collected information on medical history, sociodemographic, and health-related factors via a computer-assisted interview. Physical activity and smoking status were assessed by self-report. Participants were defined as physically inactive if they reported less than 1 h of physical activity per week during summer and winter. Women were classified as pre- or postmenopausal based on age and self-reported menstrual cycling. All women younger than 40 years of age as well as women between 40 and 60 years of age, who reported menstrual cycling, were defined as premenopausal, and all other women were defined as postmenopausal. Data on current depressive symptoms were collected using the Patient Health Questionnaire (PHQ-9) [49]. Depression was defined as a PHQ-9 score ≥10 out of 27 achievable points. The PHQ-9 is a self-report measure of depressive disorders. It consists of 9 items that are rated according to how much a symptom has bothered during the last 2 weeks, each on a scale of 0–3. The items match the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria of major depression [50]. We used an item total score which summarizes the scores of the single items, ranging from 0 to 27. A cut-off point of 10 or above represents a good diagnostic method of screening for depressive disorders [49]. Moreover, the PHQ-9 can be used to define depression severity [50]. For this, PHQ-9 scores are categorized into the following 5 groups: none (<5), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (≥19) [50]. In our study the number of subjects with PHQ-9 scores ≥15 was low (n = 63; 1.6%), and therefore we collapsed the 2 upper categories.

All study participants were asked to bring all medications taken in the last 7 days prior to the examination. The drugs were classified according to the anatomical therapeutic chemical classification system (ATC) [51]. Antidepressant drugs were defined as ATC N06A, antidiabetic drugs as ATC A10, lipid-lowering drugs as ATC C10, and antihypertensive drugs as ATC C02, C03, C07, C08, and C09. The physical examination included measurement of anthropometric parameters with calibrated scales. Waist circumference was measured midway between the lower rib margin and the iliac crest on the horizontal plane. Hip circumference was measured at the greatest circumference between the highest point of the iliac crest and the crotch. Both waist and hip circumferences were measured in centimeters. The WHR was calculated from the respective measures (waist circumference divided by hip circumference). We defined obesity according to the German Society for Sports Medicine and Prevention was a WHR >0.85 in females and >1.0 in males [52].

Blood Sampling and Laboratory Measurements

In SHIP-Trend single-occasion blood samples were drawn from the cubital vein of participants in the supine position following standardized procedures. The sampling was performed between 7:30 a.m. and 1:00 p.m. The majority (61.2%) of the study participants provided fasting (>8 h) blood samples, and the remaining samples (38.8%) were obtained from nonfasting subjects. A maximum of 65.5 mL of blood was collected in 13 tubes, including EDTA, citrate, serum, and PAXgene tubes. Directly after sampling, EDTA and serum tubes were cooled down to 4 °C, while citrate tubes were stored at room temperature. Hourly transport to the central laboratory (Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald) was arranged. After arrival at the laboratory, the samples were immediately processed. When necessary, samples were centrifuged at 2,550 *g* for 15 min at 8 °C. The samples were then analyzed or stored at –80 °C in the Integrated Research Biobank (LiCONiC, Lichtenstein). BDNF levels were measured in serum with a quantitative sandwich en-

Table 1. Characteristics of the study population

Characteristics	No depression and no obesity (n = 2,539)	Depression or obesity (n = 1,285)	Depression and obesity (n = 102)	p
Sex				<0.010
Male	53.0	42.6	24.5	
Premenopausal women	24.8	19.7	20.6	
Postmenopausal women	22.1	37.7	54.9	
Age, years	48.0 (36.0–61.0)	57.0 (46.0–67.0)	54.0 (47.0–61.0)	<0.001
Smoking				0.038
Nonsmokers	36.3	36.3	30.4	
Former smokers	35.6	39.6	39.2	
Current smokers	28.1	24.1	30.4	
Physically inactive	51.0	57.2	63.7	<0.001
Antidiabetic drugs	4.6	12.9	14.7	<0.001
Lipid-lowering drugs	10.2	18.5	17.7	<0.001
Antihypertensive drugs	29.2	51.0	53.9	<0.001
Antidepressant drugs	3.5	7.0	22.6	<0.001
Sleep disorders[1]			85.7	
WHR	0.84 (0.80–0.93)	0.92 (0.87–1.01)	0.90 (0.87–1.00)	<0.001
PHQ-9	3.0 (1.0–5.0)	3.0 (1.0–7.0)	12.0 (10.0–15.0)	<0.001
BDNF, pg/mL	21,363 (17,775–25,331)	21,363 (17,250–25,721)	22,487 (16,003–26,763)	0.772
PLT, GPT/L	222 (191–259)	227 (190–264)	231 (187–280)	0.201
Fibrinogen, g/L	2.90 (2.40–3.40)	3.20 (2.70–3.60)	3.30 (2.70–3.80)	<0.001
25(OH)D, ng/mL	23.3 (17.3–29.9)	21.4 (16.4–27.3)	18.7 (14.4–24.9)	<0.001
Season				0.415
Winter	51.8	51.8	45.1	
Summer	48.3	48.3	54.9	

The total number of patients was 3,926. Values are presented as medians (first to third quartiles) or percent. Group differences were tested with Kruskal-Wallis (continuous data) or χ^2 tests (nominal data). BDNF (serum), brain-derived neurotrophic factor; PHQ-9, Patient Health Questionnaire; PLT, platelet count; WHR, waist-to-hip ratio; 25(OH)D, 25-hydroxy vitamin D; no depression, PHQ-9 score <10; depression, PHQ-9 score ≥10; not obese, WHR <0.85 (females) or <1.00 (males); obese, WHR ≥0.85 (females) or ≥1.00 (males). [1] Proportion of participants with sleep disorders, including insomnia or hypersomnia or inability to fall and stay asleep, for at least 2 weeks among 102 subjects with depression and obesity.

zyme immunoassay technique (Quantikine Human Free BDNF Immunoassay, R&D Systems, Inc., Minneapolis, MN, USA). Two concentrations of control material were measured. The coefficients of variation for BDNF were 14.95% at low levels (129 pg/mL) and 5.81% at high levels (667 pg/mL) of control material. Serum 25-hydroxy vitamin D levels were measured on an IDS-iSYS Multi-Discipline Automated Analyzer (Immunodiagnostic Systems Limited, Frankfurt am Main, Germany). Three concentrations of control material were measured. The coefficients of variation for vitamin D were 11.6 at low, 9.1 at medium, and 10.6% at high levels of control material. The participants' vitamin D status was defined as deficient (vitamin D <20 ng/mL) or sufficient (vitamin D ≥20 ng/mL) according to the recommendation of the German Nutrition Society [53]. Serum creatinine was measured with a modified kinetic Jaffé method (Siemens Dimension Vista; Siemens Healthcare Diagnostics, Eschborn, Germany). The estimated glomerular filtration rate was estimated according to the 4-variable Modification of Diet in Renal Disease formula [54]. Fibrinogen levels were determined in citrate plasma according to Clauss with a BCS-XP analyzer (Siemens Healthcare Diagnostics). Platelets were counted in EDTA whole-blood samples using Sysmex XT2000, XE5000, or SE9000 analyzers (Sysmex, Kobe, Japan) or Advia (Siemens Healthcare Diagnostics).

Selection of the Study Population

We excluded from the SHIP-Trend participants (n = 4,420) all men and women with missing data on exposure, outcome, or confounders (n = 441) for the statistical analyses. From the remaining subjects we excluded all of those (overlap exists) with renal disease, defined as an estimated glomerular filtration rate <30 mL/min/1.73 m^2, or missing information on renal disease (n = 7), suspected hyperparathyroidism, defined as parathyroid hormone levels >120 pg/mL (n = 7), intake of parathyroid hormone or vitamin D supplements (ATC H05AA and A11CC, n = 32), and all pregnant women. The resulting study population consisted of 3,926 participants aged between 20 and 84 years.

Statistical Analyses

Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The general characteristics of our study participants grouped into (1) not depressed and not obese, (2) depressed or obese, and (3) depressed and obese individuals are given in Table 1. Categorical data are given as proportions; continuous data are given as medians (1st to 3rd quartiles). For group comparisons Kruskal-Wallis or χ^2 tests were used. $p < 0.05$ was considered statistically significant.

Table 2. Associations of BDNF or vitamin D serum levels with depression or obesity

Outcome	Model	BDNF				Vitamin D				BDNF × vitamin D interaction	
		OR (95% CI)	*p*	χ^2 (*p*)	R^2	OR (95% CI)	*p*	χ^2 (*p*)	R^2	OR (95% CI)	*p*
Depression	1	0.997 (0.977–1.017)	0.754	0.1 (0.753)	<0.001	0.973 (0.959–0.987)	<0.001	15.5 (<0.001)	0.010	1.002 (1.000–1.004)	0.105
	2	0.992 (0.972–1.013)	0.451	46.8 (<0.001)	0.029	0.976 (0.962–0.990)	<0.001	58.1 (<0.001)	0.036	1.002 (1.000–1.005)	0.057
	3	0.995 (0.974–1.017)	0.681	50.1 (<0.001)	0.031	0.966 (0.951–0.981)	<0.001	70.0 (<0.001)	0.044	1.002 (1.000–1.005)	0.065
Obesity	1	1.000 (0.989–1.011)	0.954	<0.1 (0.950)	<0.001	0.974 (0.966–0 981)	<0.001	47.9 (<0.001)	0.017	1.000 (0.998–1.001)	0.467
	2	0.997 (0.986–1.009)	0.656	353.1 (<0.001)	0.121	0.980 (0.972–0.988)	<0.001	377.1 (<0.001)	0.129	0.999 (0.998–1.000)	0.165
	3	0.995 (0.982–1.007)	0.393	411.8 (<0.001)	0.141	0.976 (0 967–0.985)	<0.001	383.3 (<0.001)	0.131	0.999 (0.998–1.000)	0.117

Results from binary logistic regression models (n = 3,926). Depression was defined as a Patient Health Questionnaire score ≥10. Obesity was defined as a waist-to-hip ratio ≥0.85 (females) or ≥1.00 (males). In the logistic regression models, an increase of 1,000 pg/mL in BDNF and of 1 ng/mL in vitamin D was modeled. Model 1 = unadjusted; model 2 = adjusted for sex, age, physical activity, and smoking and for WHR in depression models; model 3 = model 2 + platelets and fibrinogen in BDNF models or + season in vitamin D models. The overall model fit is given by the χ^2 *(p)* values as well as Nagelkerke's R^2. BDNF, brain-derived neurotrophic factor.

We firstly assessed whether BDNF and vitamin D serum levels were related by performing a partial correlation analysis adjusting for sex, age, platelets, and season. Afterwards, we examined the associations of BDNF and vitamin D (continuous exposure variables) with depression or obesity (dichotomous outcome variables) in multivariable binary logistic regression models. In these models we also examined whether the participants' vitamin D status was a potential effect modifier by testing the interaction of BDNF and vitamin D. We additionally used multinomial logistic regression to assess whether increasing BDNF or vitamin D serum levels (continuous exposure variables) are related to higher odds of being not depressed and not obese compared to being depressed and obese (categorized outcome variable). We further assessed the associations between BDNF or vitamin D (continuous exposure variables) and depression severity (categorized outcome variable) in multinomial logistic regression and used multivariable linear regression models to assess the associations between BDNF or vitamin D (continuous exposure variables) and the WHR (continuous outcome variable). To account for nonlinearity, we added restricted cubic splines with 3 knots to the linear regression models. The three knots were prespecified, located at the 5th, 50th, and 95th percentiles, resulting in one component of the spline function, which was named BDNF' or vitamin D', respectively. Whether the overall effect of the exposure was different from zero was tested with a Wald χ^2 test. We report β-coefficients with standard errors SE and *p* values from the linear regression models and OR with 95% CI and *p* values from the logistic regression models. To describe the overall model fit we reported *F* and *p* values as well as the adjusted R^2 for the linear regression models and χ^2 and *p* values as well as Nagelkerke's R^2 for the binary and multinomial logistic regression models. To take confounding into account, we calculated 3 sets for each model with different adjustments. Model 1 was unadjusted; model 2 was adjusted for sex, age, physical inactivity, and smoking and additionally for WHR in models with depression as the outcome; and model 3 was additionally adjusted for platelets and fibrinogen in models with BDNF as exposure or for season in models with vitamin D as exposure. To account for multiple testing, we used the Bonferroni correction to assess statistical significance in the regression models. In total we tested the associations between 2 exposure variables (BDNF and vitamin D) and 5 outcome variables (depression, obesity, depression/obesity group, depression severity, and WHR), yielding a Bonferroni-corrected statistical significance at $p < 0.005$ (i.e., 0.05/10).

Results

Table 1 shows the baseline characteristics of the study sample stratified into not depressed or not obese (n = 2,539), depressed or obese (n = 1,285), and depressed and obese (n = 102) individuals. Women were overrepresented in the depressed or obese group and also in the depressed and obese group. Not depressed and not obese subjects were younger and less often physically inactive and had a lower WHR and higher vitamin D concentrations than subjects in the other 2 groups. Moreover, intake of antidiabetic, lipid-lowering, or antihypertensive medication was substantially less frequent in subjects without depression or obesity than in the other groups. Antidepressant drug intake was highest among depressed and obese individuals, with more than 22% of subjects in

Table 3. Associations of BDNF or vitamin D serum levels with depression and obesity

Model	Outcome	BDNF				Vitamin D			
		OR (95% CI)	p	χ^2 (p)	R^2	OR (95% CI)	p	χ^2 (p)	R^2
1	No depression and no obesity	0.994 (0.963–1.027)	0.731			1.059 (1.032–1.086)	<0.001		
	Depression or obesity	0.993 (0.961–1.026)	0.653	0.26	<0.001	1.032 (1.005–1.059)	0.018	62.1	0.02
	Depression and obesity	Reference		(–0.8783)		Reference		(<0.001)	
		Joint effect	0.878			Joint effect	<0.001		
2	No depression and no obesity	1.008 (0.975–1.041)	0.656			1.046 (1.016–1.076)	0.002		
	Depression or obesity	1.003 (0.970–1.037)	0.866	309.4	0.098	1.031 (1.003–1.060)	0.028	2,757.2	0.652
	Depression and obesity	Reference		(<0.001)		Reference		(<0.001)	
		Joint effect	0.690			Joint effect	0.004		
3	No depression and no obesity	1.004 (0.970–1.040)	0.814			1.061 (1.029–1.095)	<0.001		
	Depression or obesity	0.997 (0.962–1.033)	0.859	368.6	0.116	1.043 (1.013–1.074)	0.005	2,764.3	0.654
	Depression and obesity	Reference		(<0.001)		Reference		(<0.001)	
		Joint effect	0.503			Joint effect	<0.001		

Results from multinomial logistic regression models (n = 3,926). In the multinomial logistic regression models, an increase of 1,000 pg/mL in BDNF and of 1 ng/mL in vitamin D was modeled. The joint effect of the exposure was tested with a Wald χ^2 test. Model 1 = unadjusted; model 2 = adjusted for sex, age, physical activity, and smoking; model 3 = model 2 + platelets and fibrinogen in BDNF models or + season in vitamin D models. The overall model fit is given by the χ^2 (p) values as well as Nagelkerke's R^2. BDNF, brain-derived neurotrophic factor.

reporting a respective medication intake. BDNF concentrations and platelet counts were similar between the 3 groups.

The logistic regression models revealed no association between BDNF and depression or obesity, while vitamin D was inversely associated with both outcomes in all models (Table 2). Thus, increasing vitamin D levels was associated with decreased odds of depression or obesity. The fully adjusted multinomial logistic regression model (Table 3) also revealed no associations with BDNF but associations with vitamin D. We found that a 1 ng/mL increase in vitamin D levels was related to a 6.1% higher odds of being not depressed and not obese versus being depressed and obese ($p < 0.001$). We further observed 4.3% higher odds of being either depressed or obese versus being depressed and obese with a 1 ng/mL increase in vitamin D levels ($p = 0.005$). However, this association was on the threshold of statistical significance after correction for multiple testing. The results from the previous 2 analyses were supported by the observations regarding depression severity. There was no association between BDNF and depression severity but there was one between vitamin D and depression severity (Table 4). In the fully adjusted model 3, an increase in vitamin D of 1 ng/ml was associated with an OR of 1.076 (95% CI 1.037–1.116, $p < 0.001$) for having a PHQ-9 score <5 compared to a PHQ-9 score ≥15. Overall, the associations of vitamin D with depression or depression severity remained significant after correction for multiple testing, and only the odds for moderate versus moderately severe or severe depression missed the Bonferroni-corrected statistical significance threshold.

We found a very weak partial correlation between BDNF and vitamin D (partial correlation coefficient 0.006, $p < 0.001$) but the interaction of BDNF and vitamin D missed statistical significance in the model for depression (Table 2; model 1: $p = 0.105$, model 2: $p = 0.057$, and model 3: $p = 0.065$). Interactions of BDNF and vitamin D on obesity were also not statistically significant (Table 2; model 1: $p = 0.467$, model 2: $p = 0.165$, and model 3: $p = 0.117$).

Finally, we assessed the associations of BDNF and vitamin D with WHR (Table 5; Fig. 1). We found significant nonlinear associations of BDNF or vitamin D with WHR. Regarding BDNF, the fully adjusted model showed a *U*-shaped association with a nadir at 23,000 pg/mL of BDNF. Regarding vitamin D, the fully adjusted model demonstrated a linear decrease in WHR starting at vitamin D concentrations of about 25 ng/mL and a constant WHR when the vitamin D level was below this threshold. These associations were also robust to the correction for multiple testing.

Table 4. Associations of BDNF or vitamin D serum levels with PHQ-9

Model	PHQ-9 score	BDNF				Vitamin D			
		OR (95% CI)	*p*	χ^2 (*p*)	R^2	OR (95% CI)	*p*	χ^2 (*p*)	R^2
1	<5	1.012 (0.971–1.055)	0.562			1.076 (1.040–1.114)	<0.001		
	5–9	1.026 (0.984–1.070)	0.228			1.063 (1.026–1.100)	<0.001		
	10–14	1.017 (0.971–1.065)	0.479	5.8	0.002	1.054 (1.015–1.093)	0.006	33.9	0.011
	≥15	Reference		(0.120)		Reference		(<0.001)	
		Joint effect	0.120			Joint effect	<0.001		
2	<5	1.020 (0.979–1.064)	0.346			1.068 (1.032–1.106)	<0.001		
	5–9	1.028 (0.985–1.073)	0.199			1.056 (1.020–1.093)	0.002		
	10–14	1.019 (0.972–1.068)	0.431	140.8	0.043	1.048 (1.010–1.087)	0.014	164.6	0.050
	≥15	Reference		(<0.001)		Reference		(<0.001)	
		Joint effect	0.423			Joint effect	<0.001		
3	<5	1.016 (0.972–1.062)	0.488			1.076 (1.037–1.116)	<0.001		
	5–9	1.028 (0.983–1.075)	0.232			1.059 (1.020–1.099)	0.003		
	10–14	1.019 (0.970–1.071)	0.451	152.3	0.047	1.042 (1.001–1.084)	0.045	185.0	0.056
	≥15	Reference		(<0.001)		Reference		(<0.001)	
		Joint effect	0.271			Joint effect	<0.001		

Results from multinomial logistic regression models (n = 3,926). In the multinomial logistic regression models, an increase of 1,000 pg/mL in BDNF and of 1 ng/mL in vitamin D was modeled. The joint effect of the exposure was tested with a Wald χ^2 test. Model 1 = unadjusted; model 2 = adjusted for sex, age, physical activity, and smoking, and for WHR in depression models; model 3 = model 2 + platelets and fibrinogen in BDNF models or + season in vitamin D models. The overall model fit is given by the χ^2 (p) values as well as Nagelkerke's R^2. BDNF, brain-derived neurotrophic factor; PHQ-9, Patient Health Questionnaire.

Table 5. Associations of BDNF or vitamin D serum levels with WHR

Model	BDNF						Vitamin D					
	exposure	β coefficient	SE	*p*	*F* value (*p*)	R^2	exposure	β coefficient	SE	*p*	*F* value (*p*)	R^2
1	BDNF	-4.55×10^{-3}	5.65×10^{-4}	<0.001	42.6	0.021	Vitamin D	1.57×10^{-3}	4.13×10^{-4}	<0.001	31.1	0.015
	BDNF'	9.60×10^{-6}	1.77×10^{-6}	<0.001	(<0.001)		Vitamin D'	-3.84×10^{-6}	6.27×10^{-7}	<0.001	(<0.001)	
	Overall			<0.001			Overall			<0.001		
2	BDNF	-1.74×10^{-3}	3.86×10^{-4}	<0.001	681.3	0.548	Vitamin D	2.73×10^{-4}	2.81×10^{-4}	0.332	685.1	0.550
	BDNF'	5.09×10^{-6}	1.21×10^{-6}	<0.001	(<0.001)		Vitamin D'	-1.30×10^{-6}	4.26×10^{-7}	0.002	(<0.001)	
	Overall			<0.001			Overall			<0.001		
3	BDNF	-1.75×10^{-3}	3.89×10^{-4}	<0.001	546.6	0.556	Vitamin D	1.01×10^{-4}	2.89×10^{-4}	0.728	601.2	0.550
	BDNF'	4.71×10^{-6}	1.20×10^{-6}	<0.001	(<0.001)		Vitamin D'	-1.20×10^{-6}	4.28×10^{-7}	0.005	(<0.001)	
	Overall			<0.001			Overall			<0.001		

Results from linear regression models with restricted cubic splines with 3 knots (*n* = 3,926). In the regression models, an increase of 1,000 pg/mL in BDNF and of 1 ng/mL in vitamin D was modeled. BDNF' and vitamin D' denote the spline components. The overall effect of the exposure was tested with a Wald χ^2 test. Model 1 = unadjusted; model 2 = adjusted for sex, age, physical activity, and smoking; model 3 = model 2 + platelets and fibrinogen in BDNF models or + season in vitamin D models. The overall model fit is given by the F and *p* values as well as the adjusted R^2. BDNF, brain-derived neurotrophic factor; WHR, waist-to-hip ratio.

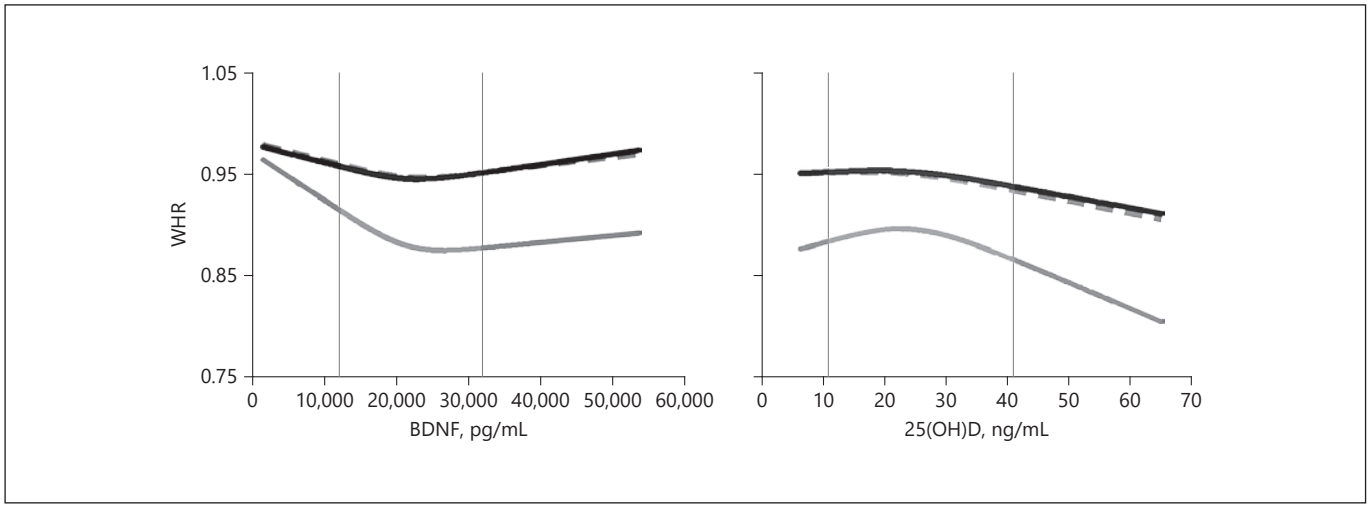

Fig. 1. Associations of brain derived neurotrophic factor (BDNF) or vitamin D with waist-to-hip ratio (WHR). Regression lines from 3 linear regression models with restricted cubic splines (3 knots). The grey solid lines represent the results from model 1 (unadjusted), the grey dashed lines represent the results from model 2 (adjusted for sex, age, physical activity, and smoking status), and the black solid lines represent the results from model 3 (model 2 + platelets and fibrinogen in BDNF models or + season in vitamin D models). The grey shaded areas indicated the central 95% range of the BDNF or vitamin D distribution, respectively. 25(OH)D, 25-hydroxy vitamin D.

Discussion

In the present cross-sectional study we investigated the associations of BDNF and vitamin D with depression, measured with the PHQ-9 [50], and obesity, measured with the WHR [52], in 3,926 adult individuals from the general population. While BDNF was not associated with depression, we revealed a *U*-shaped association of BDNF with WHR. Moreover, inverse associations of vitamin D with depression and obesity were found.

Our hypothesis about an inverse association of BDNF and depression was not confirmed. Indeed, there was no statistically significant association between BDNF and depression or depression severity. A meta-analysis from 2014 [7] reported an inverse association of BDNF and depression but pointed out that evidence for this association was less than initially thought. Besides, these authors questioned the influence of BDNF released from peripheral tissues on the investigated association of BDNF and depression [7]. Similarly, Chacón-Fernández et al. [13] and Serra-Millàs [55] investigated the influence of BDNF released from platelets and megakaryocytes and proposed that alterations in serum BDNF levels result from changes in platelets [13, 55]. However, adjusting for platelet counts did not significantly change the results of this study. Another aspect of this result might be that pro-BDNF, the precursor of mature BDNF, is biologically active, too [56, 57]. Pro-BDNF plays an important role in multiple physiological processes and partially shows effects different from those of mature BDNF [8]. Hence, we recommend distinguishing between pro-BDNF and BDNF for future studies. Another aspect for the lack of an association between BDNF and depression may be found in the small proportion (1.6%) of moderately severe or severely depressed individuals. We cannot exclude that associations between BDNF and PHQ-9 are present in severely ill patients, who are found in clinical samples.

Regarding BDNF, we did not detect an inverse association with WHR, as hypothesized, but we did find a *U*-shaped association. Previously, an inverse association between BMI or body fat mass and BDNF was observed in children after adjusting for platelets, age, and pubertal status [20]. Other studies suggested a positive association between BDNF and BMI: Monteleone et al. [21] investigated this association in women with anorexia nervosa and obesity. Likewise, Nakazato et al. [23] considered 30 young women (age range: 14–34 years) with anorexia nervosa and bulimia nervosa, 10 of whom took antipsychotic drugs [23]. All of these studies [20, 21, 23, 58] did not adjust for platelets, had a small sample size,

and investigated diseased individuals only. Therefore, these results cannot be transferred to the general population or be compared to our results. Huang et al. [58] found no association between BDNF and obesity but they did find one between BDNF and interleukin 6 in 31 obese and non-obese individuals [58]. The authors mention that increasing BDNF levels may have a neuroprotective effect in inflammation caused by obesity [58]. This might be one explanation for our results of high BDNF levels in subjects with a high WHR. A study including 144 individuals found no correlation between BDNF and interleukin 6, and the authors query the findings of Huang et al. [58, 59]. However, the mechanisms of a potential association of BDNF with obesity are not sufficiently determined to date. In rodents, BDNF was found to control appetite by melanocortin signaling, thereby influencing obesity [60]. Additionally an association between BDNF gene variants and obesity was postulated in another study [61]. An fMRI pilot study in 48 healthy individuals found a positive correlation of serum BDNF with connectivity in the (pre-)motor hub. Especially in older adults BDNF levels were associated with physical activity and learning capacities [62]. However, existing results regarding the association of BDNF and physical activity are conflicting, as studies show that endurance training is not related to BDNF levels in elderly persons [63]. Future studies are needed to confirm our results regarding the association of BDNF with obesity and to reveal causation.

Our study revealed a very weak correlation between BDNF and vitamin D. Furthermore we did not find an interaction of BDNF and vitamin D on depression. This is in line with previous studies that found associations of BDNF and vitamin D or vitamin D supplementation with depression but reported no interactions between the measures [64, 65]. In summary, our hypothesis of an interaction between vitamin D and BDNF with obesity was not confirmed.

We revealed an inverse association of vitamin D with depressive symptoms. Thus, our results are consistent with our hypothesis and confirm previous findings [31–33, 66]. Vitamin D is known to be involved in brain functions and passes the blood-brain barrier, and vitamin D receptors are copious distributed in the brain [67]. We saw that a 1 ng/mL increase in vitamin D was related to 6.1% higher odds of being neither depressed nor obese versus being depressed and obese ($p < 0.001$). This might not have clinical relevance at first sight, but Jorde et al. [68] showed in a randomized double blind clinical trial effects in supplementation of vitamin D compared to placebo in obese and overweight depressed patients over a year in decreasing depression scores. Several mechanisms are known to cause this inverse association. Firstly, vitamin D is involved in neuroplasticity [35, 36]. Secondly, depressive disorders are linked to factors that directly influence vitamin D. Persons suffering from depressive disorders often have reduced sun exposure, less engagement in physical activity, and a poorer diet [66]. Thirdly, depressive individuals show a deregulated function of the hypothalamic-pituitary-adrenal axis and sympathoadrenal hyperactivity, combined with elevated levels of inflammatory mediators [69]. Vitamin D has been found to play a role in chronic inflammation [70] and to reduce inflammatory mediators [66]. However, further studies are required to ensure understanding these mechanisms and to determine causation.

In accordance to our hypothesis we found an inverse association of vitamin D and WHR for vitamin D concentrations starting at about 25 ng/mL. Below this threshold the WHR remained constant. These results confirmed previous findings [41–43]. Most obese individuals in our study were postmenopausal women. During menopause a decline in estrogens affects numerous metabolic processes such as changes in body composition [71]. LeBlanc et al. [72] suggested that low vitamin D may be a predisposition for fat accumulation as higher vitamin D levels have been found to be associated with a lower gain in weight.

The main strength of our study is its population-based approach, including the large number of subjects. Data were acquired in a standardized setting. Further, in contrast to previous studies, we were able to adjust for a broad range of confounding factors. On the other hand, its cross-sectional design was a limitation since it does not allow determination of causation in the investigated associations. Additionally, the proportion of subjects who were moderately severely or severely depressed (PHQ-9 score ≥15) was very small (i.e., 1.6%), and thus, we cannot exclude that associations between BDNF and PHQ-9 are present in severely ill patients. Aside from this, there is no information on other psychiatric disorders, e.g., anxiety disorders, obsessive compulsive disorder or psychotic symptoms, and only little information on sleep disorders, which often accompany depressive symptoms. Moreover, all analyses are based on single-occasion measurements, which were taken throughout the year. However season of blood sampling was taken into account in the statistical analyses.

To the best of our knowledge this is one of the first studies to investigate associations of BDNF and vitamin

D with depression and obesity and their interaction in a large population-based sample. The observed *U*-shaped association between BDNF and WHR as well as the marginally significant interaction of BDNF and vitamin D on depression may indicate a potential combined effect of these 2 players in brain development on depression. At the population level, our results support the relevant roles of vitamin D and BDNF in health-related outcomes. Further research focusing on vitamin D and BDNF is necessary to substantiate these results.

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Disclosure Statement

There are no conflicts of interests.

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