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Plasma insulin-like growth factor I levels are higher in depressive and anxiety disorders, but lower in antidepressant medication users

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ABSTRACT

It has been postulated that many peripheral and (neuro)biological systems are involved in psychiatric disorders such as depression. Some studies found associations of depression and antidepressant treatment with insulin-like growth factor 1 (IGF-I) – a pleiotropic hormone affecting neuronal growth, survival and plasticity – but evidence is mixed. We therefore studied whether depressive and anxiety disorders were associated with plasma IGF-I, and explored the role of antidepressant medication in this association in a large observational study.

The sample consisted of 2714 participants enrolled in The Netherlands Study of Depression and Anxiety, classified as healthy controls (n = 602), antidepressant users (76 remitted and 571 with current depressive and/or anxiety disorder(s), n = 647), persons having remitted depressive and/or anxiety disorder(s) without antidepressant use (n = 502), and persons having current depressive and/or anxiety disorder(s) without antidepressant use (n = 963). Associations with IGF-I concentrations were studied and adjusted for socio-demographic, health, and lifestyle variables.

Relative to healthy controls, antidepressant-free individuals with current disorders had significantly higher IGF-I levels (Cohen's d = 0.08, p = 0.006), whereas antidepressant-free individuals with remitted disorders had a trend towards higher IGF-I levels (d = 0.06, p = 0.09). Associations were evident for depressive and for anxiety disorders. In contrast, antidepressant users had significantly lower IGF-I levels compared to healthy controls (d = −0.08, p = 0.028).

Our findings suggests that antidepressant medication use modifies the association between depressive/anxiety disorders and plasma IGF-I. These results corroborate with findings of some previous small-scale case-control and intervention studies. The higher IGF-I levels related to depression and anxiety might point to a compensatory mechanism to counterbalance the impaired neurogenesis, although future studies are needed to support this hypothesis.

1. Introduction

Insulin-like growth factor 1 (IGF-I), a hormone that is mainly produced by the liver upon stimulation by growth hormone, has pivotal roles in somatic growth and metabolism. IGF-I is produced throughout life, with the highest circulating levels during adolescence and a subsequent progressive decline over time. Apart from its anabolic peripheral roles, IGF-I has profound central actions and is an acknowledged neurotrophic factor and stimulates neuronal growth, survival and plasticity throughout the lifespan (Aberg et al., 2000; Torres-Aleman, 2000). IGF-I and its receptors are widely expressed in the brain (Fernandez and Torres-Aleman, 2012) and studies indicate that peripheral IGF-I can be transported across the blood-brain barrier (Armstrong et al., 2000; Pan and Kastin, 2000).

Accumulating evidence suggests that neuroplasticity and neurogenesis is disrupted in major depressive disorder (MDD) (Pittenger and Duman, 2008). MDD is a prevalent (lifetime prevalence: 17%), burdensome psychiatric disorder with a complex pathophysiology with central as well as peripheral dysregulations (Kessler and Wang, 2008). It has been postulated that reduced adult hippocampal neurogenesis may be an underlying mechanism in the etiology of MDD, and that efficacy of antidepressants depends on the upregulation of hippocampal neurogenesis (Eisch and Petrik, 2012). Several neurotrophic factors and growth factors involved in neuronal growth, differentiation, maturation and survival have been linked to MDD (Duman, 2004). Of these, brain-derived neurotrophic factor (BDNF) is the most extensively investigated marker

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in relation to MDD, but IGF-I has also attracted research attention. In adult mice that overexpress IGF-I, rates of hippocampal neurogenesis were increased (O'Kusky et al., 2000). Also, peripheral injections of IGF-I induced neurogenesis on hippocampal progenitors in adult rats (Aberg et al., 2000). Furthermore, the formation of new neurons in the adult hippocampus is thought to be involved in learning and memory, and there is meta-analytic evidence that better cognitive function (e.g. mental process speed, spatial memory, and information processing speed) is related to higher IGF-I levels in healthy elderly (Arwert et al., 2005). Impairments of cognitive functions are frequently reported in persons with MDD (Trivedi and Greer, 2014). Furthermore, studies report associations of IGF-I with pro-inflammatory cytokines (O'Connor et al., 2008) and increased hypothalamic-pituitary-adrenal (HPA)-axis activity (Weber-Hamann et al., 2009), which both have been implicated in the pathogenesis of MDD (Miller et al., 2009; Stetler and Miller, 2011). Taken together, IGF-I could potentially be considered as a marker contributing to the pathophysiology of MDD (Szczesny et al., 2013).

Several studies provide evidence for an association of IGF-I with depression. Experimental studies in rats and mice generally show that increasing IGF-I, either centrally (Hoshaw et al., 2005; Malberg et al., 2007) and peripherally (Duman et al., 2009), results in increased mobility in forced swim tests (Duman et al., 2009, Hoshaw et al., 2005) and tail suspension tests (Malberg et al., 2007). Increased mobility might be indicative of reduced depressive behavior, however, these animal models have been criticized as they measure behavior in acute stress situations rather than depression (Molendijk and de Kloet, 2015). Studies on the association between IGF-I and depression in humans showed very mixed results. Both growth hormone deficiency and acromegaly – two conditions characterized by disturbed growth hormone and IGF-I levels – are associated with poorer mental health (Rosen et al., 1994; Sievers et al., 2009). In line with the hypothesized role of IGF-I in neuronal growth, survival and plasticity, a previous study found that low IGF-I levels were related to depression onset in women (Sievers et al., 2014). For the male participants, however, high IGF-I levels were associated with the onset of depression (Sievers et al., 2014). Another study found distinct associations with IGF-I and depressive symptoms for older males versus females (van Varsseveld et al., 2015). Other studies found higher serum IGF-I levels in depressed patients compared to controls (Deuschle et al., 1997; Franz et al., 1999; Kopczak et al., 2015), whereas some found no cross-sectional association between IGF-I and depression (Lin et al., 2014; Sievers et al., 2014), or in women only (Emeny et al., 2014). These higher IGF-I levels in depression could potentially point to a compensatory mechanism to counterbalance the impaired neurogenesis (Kopczak et al., 2015). In addition, most studies in humans did not investigate the influence of antidepressant medication, or had conflicting findings, with studies showing either decreased levels of serum IGF-I (Deuschle et al., 1997; Kopczak et al., 2015; Weber-Hamann et al., 2009) or increased levels of cerebrospinal fluid IGF-I (Schilling et al., 2011) after antidepressant medication use. Moreover, previous studies are either limited by the small sample sizes [<100 participants, (Deuschle et al., 1997; Franz et al., 1999; Lin et al., 2014); <100 patients (Kopczak et al., 2015)], or use of self-reported instruments rather than clinical interviews to assess the presence of psychiatric disorders (Emeny et al., 2014; Sievers et al., 2014; van Varsseveld et al., 2015). Finally, the association between IGF-I and anxiety disorders in humans has not been investigated, but given the high comorbidity between depressive and anxiety disorders and partial overlap in symptoms (Lamers et al., 2011), it is important to study this as well. Because of the limitations and conflicting findings of previous studies in humans, the objective of this study is to investigate the relationship between depressive and anxiety disorders with plasma IGF-I levels in a large well-characterized psychiatric cohort study (n = 2714, with 1534 persons having a current depressive and/or anxiety disorder). Our second objective was to investigate the role of antidepressant medication in this relationship.

2. Materials and methods

Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study on predictors, course and consequences of depressive and anxiety disorders (Penninx et al., 2008). The NESDA sample consists of 2981 participants aged 18–65 years, comprising persons with no depressive or anxiety disorder, persons who have had a disorder in the past, and persons with a current depressive and/or anxiety disorder. To represent the various stages of the depression and anxiety psychopathology, individuals were recruited from the general population (n = 564), primary care (n = 1610), and specialized mental health care (n = 807). Exclusion criteria were (1) a primary clinical diagnosis of a psychiatric disorder not under study in NESDA (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder), and (2) not being fluent in Dutch. Between September 2004 and February 2007, all participants completed the 4-h baseline assessment at one of the research centers, which included face-to-face interviews, written questionnaires, and biological measurements. The research protocol was approved by the Ethical Committee of the participating centers, and all participants provided written informed consent. The present cross-sectional study was based on the baseline assessment.

2.1. Depression and anxiety

During the baseline interview, the presence of depressive disorder (major depressive disorder, dysthymia) and anxiety disorder (generalized anxiety disorder, social phobia, panic disorder, agoraphobia) was ascertained using the Composite Interview Diagnostic Instrument (CIDI) version 2.1 according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. The CIDI was administered by specially trained research staff and is a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994). We distinguished healthy controls (no lifetime psychiatric diagnosis, no antidepressant use), individuals with remitted (lifetime but not in the past 6 months) disorders, and individuals with current (in the past 6 months) disorders. In addition, as a secondary psychopathological measure, the severity of depression and anxiety was measured in all participants using the 30-item self-reported Inventory of depressive symptomatology (Rush et al., 1996) and the 21-item self-reported Beck Anxiety Inventory (Beck et al., 1988), respectively.

Furthermore, participants were asked to bring their medication containers to the visit. Antidepressant (AD) medication taken on a regular basis (at least 50% of the time in the past month) was classified using the World Health Organization Anatomical Therapeutic Chemical classification system codes as tricyclic antidepressants (TCA; N06AA), selective serotonin reuptake inhibitors (SSRI; N06AB), and other antidepressants (N06AX, N06AF, N06AG) (World Health Organization Collaboration Centre for Drug Statistics Methodology, 2007). To be able to study a potential dose-response relationship, derived daily doses were calculated by dividing the participant's mean daily dose by the defined daily dose (DDD) of the World Health Organization. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Derived daily doses exceeding 10 times the DDD, or less than 0.1 times the DDD were set on missing as these were considered very unlikely.

2.2. Insulin-like growth factor-I

Fasting EDTA plasma samples were collected between 8:00 and 9:30 am during the baseline visit at one of the research centers, and kept frozen at −80 °C until IGF-I assaying. IGF-I (nmol/l) was assayed centrally by chemiluminescence immunoassay on the Liaison autoanalyzer (DiaSorin, S.p.A., Italy). The intra-assay and inter-assay coefficient of variation were 8.3% and 11.1%, respectively.

Almost all IGF-I is bound to IGF-I binding proteins that regulate the biological availability of IGF-I (Frystyk, 2004). As a secondary outcome, we therefore calculated IGF-I/IGFBP3 molar ratio's for a subsample of NESDA participants as a relative measure of free IGF-I levels. Insulin-like growth factor binding protein-3 (IGFBP3) levels was measured in ng/ml as part of a panel of 243 analytes (Myriad RBM DiscoveryMAP 250+) with multiplexed microbead immunoassays in a flow cytometric system (Bot et al., 2015). This was done in a subset of 1837 NESDA participants who participated in both baseline and 2-year follow-up assessments, and for whom sufficient serum was available (∼1 ml). IGFBP3 was divided by the molecular mass of 28.5 Da to obtain values in nmol/ml (Rozing et al., 2009).

2.3. Covariates

Potential confounders were selected a priori based on the literature and included the following variables: sex, age, research center (Amsterdam, Leiden, Groningen), self-reported north-European ancestry, education level (years), number of somatic diseases, smoking status (never, previous, current), alcohol intake (average number of drinks per week), body mass index (BMI), physical activity, and sex hormone use. Weight and height were measured by trained staff to calculate BMI (kg/m^2). Physical activity was assessed with the International Physical Activity Questionnaire (IPAQ), and expressed in 1000 metabolic equivalent (MET) minutes per week (Craig et al., 2003). The number of somatic diseases under treatment were based on self-report data, and included heart disease, diabetes, cancer, chronic lung disease, stroke, osteoarthritis or rheumatic disease, intestinal problems, ulcers, liver disease, epilepsy, and thyroid disease. Use of sex hormone intake was defined as hormone replacement therapy (ATC codes G03C, G03D, G03F) or use of oral contraceptives (self-reported or ATC code G03A).

2.4. Statistical analyses

We excluded persons for whom no blood was sampled in NESDA (n = 113), persons whose IGF-I levels could not be determined by the lab (n = 145), individuals on growth hormone medication (ATC code H01AC; n = 3), and AD users with no lifetime depressive/anxiety disorder (n = 6), which resulted in 2714 participants to be included in the analyses. Descriptive statistics were shown for four strata based on the presence of psychiatric disorders and AD medication use (healthy control group, remitted disorder without AD use, current disorder without AD use, and AD users). We simultaneously assessed the association of psychiatric disorders (current/remitted/never) and AD use (yes/no) with plasma IGF-I as dependent variable in linear regression analyses. Psychiatric disorders were entered as two dummy variables representing current and remitted disorders, with the healthy controls serving as reference group. Analyses were adjusted for sociodemographic variables (adjustment A) and additionally for health and lifestyle related variables (adjustment B; fully adjusted model). The sociodemographic variables consisted of sex, age (both linear and quadratic terms), research center, ancestry, and education level; the health and lifestyle variables consisted of somatic diseases, smoking, alcohol intake, body mass index, physical activity, and sex hormone use. To check whether results should be stratified for men and women, we tested whether the association between mental health status and IGF-I was modified by sex by including interactions terms and testing their significance. Similarly, we tested for potential effect modification by sex in the association between AD use and IGF-I. No significant effect modification by sex was found for the association between mental disorders and IGF-I (p = 0.70 and p = 0.20 for current disorder*sex and remitted disorder*sex in the fully adjusted model, respectively), nor for the association of AD use for IGF-I (p = 0.92 for sex*AD use). Therefore, analyses were performed for men and women combined. We used ANCOVA's to obtain covariate-adjusted estimated means of IGF-I for the disorder status and antidepressant groups. We calculated Cohen's d effects sizes for each of the groups, relative to controls (Cohen, 1988).

In order to test specificity of the results for depression versus anxiety, the hierarchical linear regression analyses were repeated for the following depression and anxiety related independent variables: current and remitted depressive disorders, current and remitted anxiety disorders, depressive symptoms, and anxiety symptoms. Furthermore, we studied the specificity of the results for the AD medication classes (TCA, SSRI, and other AD) and their doses in linear regression models. As a secondary analysis, for the subset of NESDA participants with IGFBP3 levels available, we repeated the hierarchical linear regression analyses for disorder status with IGF-I/IGFBP3 molar ratio's to study the association of psychopathology with free IGF-1 levels. All statistical analyses were conducted in SPSS version 20 (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered statistical significant.

3. Results

Table 1 describes the sample characteristics stratified by the presence of psychiatric disorder(s) and AD use. There were 602 healthy controls, 502 persons with a remitted disorder without AD use, 963 persons with a current disorder without AD use, and 647 AD users. The large majority of AD users had a current disorder (n = 571; 88%), with just 76 AD users (12%) having a remitted disorder. Overall, sixty-six percent was women and the mean age was 41.7 years (SD 13.1). Over a third of the sample was a current smoker (38.4%). The mean BMI was 25.5 (SD 4.9) kg/m^2. Healthy controls tended to be more often males, had followed more years of education, and were less often smokers and had lower BMI compared to the other three groups (Table 1). The mean plasma IGF-I was 25.9 (SD 8.4) nmol/l. IGF-I levels were significantly lower with increasing age (Spearman's rho −0.53, $p < 0.001$). The age (linear and quadratic) adjusted mean IGF-I values were 25.8 nmol/l for controls, 26.2 nmol/l for remitted disorder individuals, 26.5 nmol/l for current disorder individuals, and 24.9 nmol/l for AD users (Table 1).

3.1. Depression and anxiety characteristics and IGF-I

Table 2 shows the association of psychiatric disorders and AD medication use with IGF-I, after adjustment for potential confounders. In the fully adjusted model, persons with current depressive and/or anxiety disorders had higher IGF-I values (B = 0.90 95%CI = 0.24 to 1.55, p = 0.007) compared to healthy controls, whereas antidepressant medication use was associated with lower IGF-I values (B = −1.71 95%CI = −2.32 to −1.09, $p < 0.001$) compared to no use. A trend towards higher IGF-I values was observed for those with remitted disorders (fully adjusted model: B = 0.72 95%CI = −0.002 to 1.46, p = 0.056) compared to controls. When studying the two types of disorders separately, both current depressive disorders and current anxiety disorders were associated with higher IGF-I levels (Table 2, model 2 and 3). Similarly, depres-

Table 1
Sample characteristics of participants of NESDA with insulin like growth factor-I levels stratified by depressive/anxiety disorder status and antidepressant use (n = 2714).

	Healthy controls	Remitted depressive/anxiety disorder, no AD	Current depressive/anxiety disorder, no AD	AD user	p
n	602	502	963	647	–
Women, n (%)	370 (61.5%)	348 (69.3%)	654 (67.9%)	429 (66.3%)	0.023
Age in years, mean (sd)	41.0 (14.6)	44.2 (13.1)	40.3 (12.8)	42.6 (11.5)	<0.001
Area, n (%)					
Amsterdam	256 (42.5%)	223 (44.4%)	454 (47.1%)	258 (39.9%)	0.003
Leiden	150 (24.9%)	115 (22.9%)	246 (25.5%)	204 (31.5%)	
Groningen	196 (32.6%)	164 (32.7%)	263 (27.3%)	185 (28.6%)	
North European ancestry, n (%)	578 (96.0%)	488 (97.2%)	894 (92.8%)	609 (94.1%)	0.002
Education in years, mean (sd)	12.9 (3.2)	12.7 (3.2)	11.9 (3.3)	11.8 (3.3)	<0.001
Number of chronic diseases, mean (sd)	0.5 (0.8)	0.6 (0.8)	0.6 (0.9)	0.7 (0.9)	<0.001[a]
Smoking status, n (%)					<0.001
Never smoker	220 (36.5%)	134 (26.7%)	247 (25.6%)	161 (24.9%)	
Former smoker	220 (36.5%)	194 (38.6%)	309 (32.1%)	188 (29.1%)	
Current smoker	162 (26.9%)	174 (34.7%)	407 (42.3%)	298 (46.1%)	
Body mass index in kg/m^2, mean (sd)	25.0 (4.6)	25.5 (4.3)	26.2 (5.5)	25.5 (4.9)	<0.001
Sex hormone use, n (%)	120 (19.9%)	82 (16.3%)	192 (19.9%)	117 (18.1%)	0.316
Physical activity in 1000 MET minutes/week, median (IQR)	3.1 (1.6–5.0)	3.1 (1.7–5.2)	2.8 (1.4–5.2)	2.4 (1.1–4.7)	<0.001[a]
Alcohol intake, n (%)					<0.001
Low (<1 drink/week)	139 (23.1%)	124 (24.7%)	303 (31.5%)	283 (43.7%)	
Moderate (men 1–21 drinks/week, women 1–14 drinks/week)	395 (65.6%)	319 (63.5%)	546 (56.7%)	293 (45.3%)	
High (men > 21 drinks/week, women > 14 drinks/week)	68 (11.3%)	59 (11.8%)	114 (11.8%)	71 (11.0%)	
Current depressive disorder, n (%)	–	–	606 (77.6%)	440 (72.8%)	
Current anxiety disorder, n (%)	–	–	725 (91.5%)	445 (82.6%)	
Lifetime depressive disorder, n (%)	–	407 (81.1%)	781 (81.1%)	604 (93.4%)	
Lifetime anxiety disorder, n (%)	–	266 (53.0%)	792 (82.2%)	539 (83.3%)	
Depression severity IDS score, median (IQR)	6 (3–12)	12 (7–19)	27 (18–35)	30 (19–40)	<0.001[a]
Anxiety severity BAI score, median (IQR)	2 (1–6)	5 (2–10)	14 (8–21)	17 (9–25)	<0.001[a]
Current antidepressant use, n (%)					
Tricyclic antidepressants	0	0	0	62 (9.6%)	
Selective serotonin reuptake inhibitors	0	0	0	451 (69.7%)	
Other antidepressants	0	0	0	152 (23.5%)	
IGF-I in nmol/liter, mean (sd)[b]	25.8 (6.9)	26.2 (6.9)	26.5 (6.8)	24.9 (6.9)	<0.001

AD = antidepressant use. NESDA = Netherlands Study of Depression and Anxiety. SD = standard deviation. IQR = Interquartile range, p = overall p value.
[a] Kruskall–Wallis test.
[b] Estimated marginal means from ANOVA, adjusted for age and age^2. SD was calculated by multiplying the standard error by the square root of n.

sive and anxiety symptom scores were positively related to IGF-I in the fully adjusted model (Table 2, model 4 and 5). Antidepressant medication use was consistently related to lower IGF-I levels throughout the different models (Table 2).

To study the joint influence of psychiatric disorders and antidepressant medications, Fig. 1 shows the adjusted IGF-I values for the psychiatric disorder and AD use classification as used in Table 1. Compared to controls, those with current disorders who used no antidepressant medication had significantly higher IGF-I values (Cohen's d = 0.08; p = 0.006), whereas AD medication users had significantly lower IGF-I values (Cohen's d = −0.08, p = 0.028). Persons with remitted disorders had a non-significant higher IGF-I values relative to controls (Cohen's d = 0.06, p = 0.09). IGF-I levels of the 76 AD users with remitted disorders (adjusted mean 23.7 nmol/l) did neither differ from controls (adjusted mean 24.3, p = 0.42) nor from the 571 AD users with current disorders (adjusted mean 23.4, p = 0.77; data not shown).

3.2. Specific antidepressant medication and daily derived dose

To explore the association between AD medication and IGF-I, we investigated whether specific AD medications were related to IGF-I. Only specific ADs that were used by at least 20 participants were considered, and persons using multiple AD medications were excluded (n = 23). With respect to the antidepressant medication classes, SSRI and other antidepressant use were significantly related to lower IGF-I values (B = −1.95 95%CI = −2.65 to −1.25, p < 0.001, and B = −1.26 95%CI = −2.40 to −0.12, p = 0.03, respectively), and a trend was observed for TCA use (B = −1.46, 95%CI = −3.18 to 0.27, p = 0.098) compared to non-antidepressant use (Table 3, model 1). With respect to the specific AD classes, use of fluoxetine (52 users), citalopram (96 users) paroxetine (195 users), sertraline (40 users) en fluvoxamine (38 users), venlafaxine (95 users) was significantly related to lower IGF-I levels in the fully adjusted model. Use of clomipramine (26 users), amitriptyline (21 users), mirtazapine (33 users) was not significantly related to IGF-I (Table 3). To further investigate the association of antidepressant medication with IGF-I, we studied the relationship between the derived daily dose of the antidepressant medication and IGF-I in the subgroup of antidepressant medication users. In the SSRI users, a significant inverse association between the derived daily dose of the SSRI and IGF-I was found after adjustment for sex, age and age^2, suggesting that IGF-I levels decreases with higher doses of SSRI (Appendix of Supplementary material). No significant association with IGF-I was found for the doses of other antidepressant medication classes (regression coefficients of the derived daily doses ranging from −3.99 to 1.16).

3.3. IGF-I/IGFBP3 molar ratio's

IGF-I/IGFBP3 molar ratio's were available for 1638 participants. In the fully adjusted model, antidepressant medication use was related to lower IGF-I/IGFBP3 molar ratio's (B = −0.017, 95%CI = −0.026 to −0.008, p < 0.001), whereas persons with remitted disorders had higher IGF-I/IGFBP3 levels relative to controls (B = 0.013, 95%CI = 0.002 to 0.023, p = 0.017). Persons with current

Table 2
Association of depression and anxiety variables and antidepressant medication use with insulin-like growth factor-I (n = 2714).

	Predictor	n	Adjustment A				Adjustment B			
			B	95%CI low	95%CI high	p	B	95%CI low	95%CI high	p
1	Depressive/anxiety disorders and AD									
	Healthy control	602	ref				ref			
	Remitted disorder[a]	578	0.61	−0.14	1.36	0.110	0.72	−0.019	1.46	0.056
	Current disorder[a]	1534	0.75	0.09	1.41	0.027	0.90	0.24	1.55	0.007
	No AD use	2067	ref				ref			
	AD use	647	−1.86	−2.48	−1.24	<0.001	−1.71	−2.32	−1.09	<0.001
2	Depressive disorders and AD									
	Healthy control	602	ref				ref			
	Remitted depressive disorder	746	0.52	−0.19	1.24	0.151	0.61	−0.10	1.32	0.092
	Current depressive disorder	1046	0.85	0.13	1.56	0.020	1.07	0.36	1.78	0.003
	No AD use	1790	ref				ref			
	AD use	604	−1.81	−2.46	−1.16	<0.001	−1.68	−2.32	−1.03	<0.001
3	Anxiety disorders and AD									
	Healthy control	602	ref				ref			
	Remitted anxiety disorder	427	0.81	−0.01	1.63	0.051	0.88	0.08	1.69	0.032
	Current anxiety disorder	1170	0.81	0.12	1.51	0.022	0.92	0.23	1.61	0.009
	No AD use	1660	ref				ref			
	AD use	539	−2.06	−2.74	−1.38	<0.001	−1.84	−2.52	−1.17	<0.001
4	Depression severity and AD									
	Depression severity IDS score	2678	0.01	−0.01	0.03	0.226	0.02	0.003	0.04	0.023
	No AD use	2044	ref				ref			
	AD use	634	−1.82	−2.44	−1.20	<0.001	−1.73	−2.35	−1.12	<0.001
5	Anxiety severity and AD									
	Anxiety severity BAI score	2682	0.02	−0.01	0.04	0.227	0.03	0.004	0.06	0.021
	No AD use	2046	ref				ref			
	AD use	636	−1.81	−2.42	−1.20	<0.001	−1.71	−2.32	−1.11	<0.001

AD = antidepressant medication use.
Adjustment A is additionally adjusted for: age, age^2, sex, area, north European ancestry, education level.
Adjustment B is additionally adjusted for: age, age^2, sex, area, north European ancestry, education level, number of chronic diseases, smoking status, body mass index, physical activity, alcohol intake, sex hormone use.
[a] Disorder refers to depressive disorder (MDD or dysthymia) and/or anxiety disorder (social phobia, agoraphobia, panic disorder, GAD).

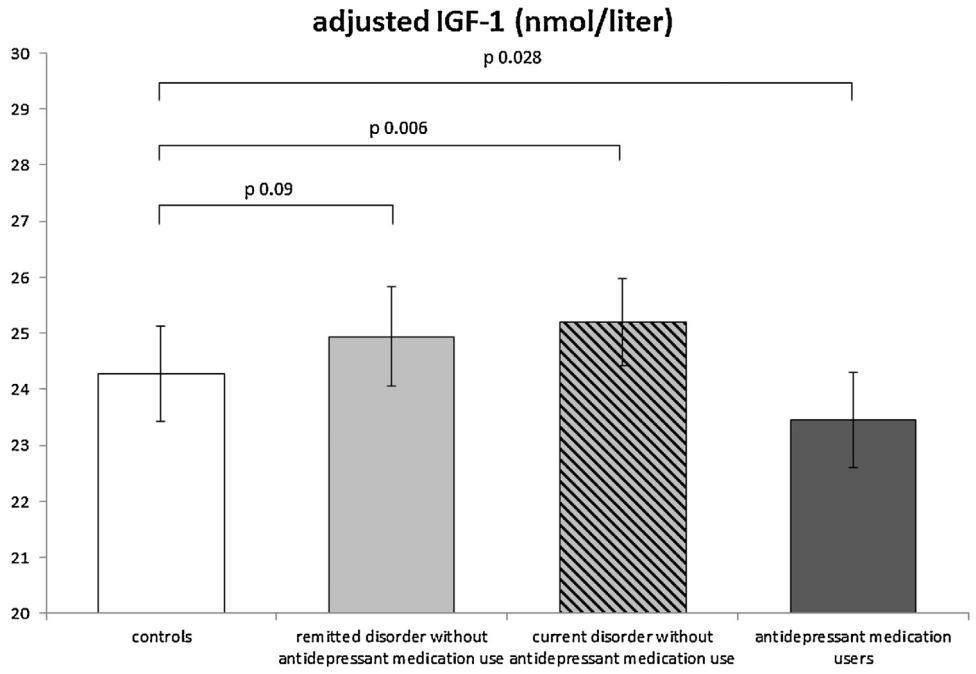

Fig. 1. Adjusted IGF-I levels stratified by disorder status and antidepressant medication use.

disorders did not differ from controls in IGF-I/IGFBP3 ratio levels (B = 0.005, 95%CI = −0.004 to 0.015, p = 0.25).

4. Discussion

In this observational cross-sectional study, we observed weak but distinct associations between plasma IGF-I levels and presence of depressive and/or anxiety disorders with and without AD medication use. AD-medication free individuals with current depressive or anxiety disorders – either analyzed apart or grouped together – had higher plasma IGF-I levels compared with controls. In contrast, depressed/anxious persons that used AD medication had lower plasma IGF-I levels relative to controls. This relationship appeared to be present for most AD classes and several of the specific AD

Table 3
Association of specific antidepressant medications with insulin-like growth factor-I (n = 2691).

	Predictor	n	Adjustment A				Adjustment B				Adjustment C			
			B	95%CI low	95%CI high	p	B	95%CI low	95%CI high	p	B	95%CI low	95%CI high	p
1	AD classes													
	No AD use	2067	ref				ref				ref			
	SSRI use	433	−1.93	−2.60	−1.25	<0.001	−1.70	−2.38	−1.03	<0.001	−1.95	−2.65	−1.25	<0.001
	TCA use	55	−1.51	−3.25	0.22	0.088	−1.23	−2.95	0.49	0.160	−1.46	−3.18	0.27	0.098
	Other AD use	136	−1.05	−2.17	0.08	0.069	−1.01	−2.12	0.11	0.077	−1.26	−2.40	−0.12	0.030
2	Specific AD													
	No AD use	2067	ref				ref				ref			
	Clomipramine	26	−1.17	−3.68	1.33	0.358	−1.02	−3.50	1.46	0.419	−1.21	−3.69	1.27	0.337
	Amitriptyline	21	−1.40	−4.19	1.39	0.324	−1.18	−3.93	1.57	0.400	−1.42	−4.18	1.34	0.313
	Fluoxetine	52	−3.23	−5.01	−1.45	<0.001	−2.63	−4.39	−0.87	0.003	−2.86	−4.63	−1.09	0.002
	Citalopram	96	−1.67	−2.99	−0.34	0.014	−1.58	−2.88	−0.27	0.018	−1.83	−3.16	−0.51	0.007
	Paroxetine	195	−1.63	−2.59	−0.68	0.001	−1.45	−2.39	−0.50	0.003	−1.69	−2.65	−0.72	0.001
	Sertraline	40	−2.37	−4.40	−0.34	0.022	−2.06	−4.06	−0.06	0.044	−2.30	−4.31	−0.29	0.025
	Fluvoxamine	38	−2.26	−4.34	−0.18	0.033	−2.14	−4.20	−0.08	0.041	−2.38	−4.44	−0.31	0.024
	Mirtazapine	33	−0.51	−2.74	1.72	0.652	−0.40	−2.60	1.80	0.724	−0.63	−2.85	1.58	0.575
	Venlafaxine	95	−1.20	−2.53	0.13	0.078	−1.23	−2.55	0.08	0.066	−1.49	−2.83	−0.16	0.029
	All other AD	28	−1.45	−3.86	0.96	0.237	−0.96	−3.35	1.43	0.430	−1.19	−3.59	1.20	0.328

Analyses for specific antidepressant medications were performed when at least 20 participants were using that particular drug, smaller classes were merged into all other AD.
1 Antidepressant medication classes were entered together in the model, reference group was no antidepressant medication use (n = 2067).
2 Specific antidepressant medications were entered together in the model, reference group was no antidepressant medication use (n = 2067).
Participants who used more than one of the specified antidepressant medication classes (n = 24) were excluded from the analyses.
Adjustment A is adjusted for: age, age^2, sex, area, north European ancestry, education level.
Adjustment B is adjusted for: age, age^2, sex, area, north European ancestry, education level, number of chronic diseases, smoking status, body mass index, physical activity, alcohol intake, sex hormone use.
Adjustment C is adjusted for: age, age^2, sex, area, north European ancestry, education level, number of chronic diseases, smoking status, body mass index, physical activity, alcohol intake, sex hormone use, current depressive and anxiety disorders, remitted depressive and anxiety disorders.

medications. The effect sizes calculated for these associations are small.

Our results are in line with several previous studies showing that MDD patients free of AD medication had higher serum IGF-I levels compared to healthy controls (Deuschle et al., 1997; Franz et al., 1999; Kopczak et al., 2015). In contrast to some earlier studies (Emeny et al., 2014; Sievers et al., 2014; van Varsseveld et al., 2015), no effect modification by sex was present in our study. Our findings are divergent from Sievers et al. (Sievers et al., 2014) who observed no significant cross-sectional relationship between depressive disorders and IGF-I. However, the potential modifying role of AD medication was not studied in the latter study, and may have masked opposing associations.

The lower IGF-I levels in AD users relative to controls for a rather broad range of AD types is partially in agreement with previous studies (Deuschle et al., 1997; Weber-Hamann et al., 2009). Both Deuschle et al. (1997) and Weber-Hamann et al. (2009) found a decline in IGF-I levels in depressed patients responding to AD treatment, but not in non-responders. In these studies, various antidepressant were used, suggesting that the decline in IGF-I was irrespective of the type of AD. In contrast, Kopczak et al. (2015) found that AD non-responders had higher initial IGF-I levels compared AD responders, and another study assessing IGF-I in cerebrospinal fluid found increases in IGF-I after AD use (Schilling et al., 2011). The latter observation may point to differences in IGF-I actions in the peripheral versus central systems.

Literature of animal studies, however, appears to be less consistent with our observations and the previous reports in humans. Experimental studies in rats and mice generally show that increasing IGF-I levels – either centrally and peripherally – result in reduced immobility (Duman et al., 2009; Hoshaw et al., 2005; Malberg et al., 2007) and behavior indicative of lower anxiety (Malberg et al., 2007). However, the validity of these animal models as indicators of depression and anxiety is questionable (Molendijk and de Kloet, 2015). Given the neurotrophic properties that have been ascribed to IGF-I, one would expect to find lower IGF-I levels in depressed persons and a normalization (i.e. increase) of IGF-I after successful antidepressant treatment in human studies as well. For another neurotrophin, BDNF, this was indeed the case: meta-analyses found that serum BDNF was lower in persons with MDD compared to healthy controls, whereas antidepressant treatment was related to an increase in BDNF (Molendijk et al., 2014; Sen et al., 2008). This suggests that rather different mechanisms are at hand for BDNF and IGF-I. In contrast to the neurotrophin hypothesis of depression which has been postulated for BDNF (Duman et al., 1997), it could be that IGF-I levels were boosted in depression and anxiety as a response mechanism to counteract the impaired neurogenesis (Kopczak et al., 2015), although data supporting this hypothesis are lacking.

Although the association between AD and lower IGF-I was partially in line with some other studies (Deuschle et al., 1997; Weber-Hamann et al., 2009), its explanation is not that straightforward. AD use may directly lower peripheral IGF-I levels, or indirectly by lowering growth hormone (GH) secretion, which is the main stimulator of IGF-I release. In general, studies observe a blunted GH response after stimulation (e.g. exercise) in depressed patients compared controls (Auer et al., 2012). However, the effects of AD treatment on GH appears to be very mixed: treatment with the antidepressant fluoxetine reduced GH compared to placebo treatment in depressed persons (O'Flynn et al., 1992), but the antidepressant desipramine was related to a blunted GH response in premenopausal females, but not in males (Meesters et al., 1985), and to GH increase in a small-scaled pilot study (Wilkins et al., 1989). Another explanation for the apparently modifying role of AD might come from the Alzheimer's disease literature (Aleman and Torres-Aleman, 2009). In Alzheimer's disease, both higher and lower IGF-I levels have been reported (Aleman and Torres-Aleman, 2009). This discrepancy has been hypothesized to arise from an increase in IGF-I in the early stages of Alzheimer's disease, followed by a decrease in IGF-I in later stages of Alzheimer's disease. The same may apply to our depressed/anxiety cases: milder psychopathology symptoms may be linked to increases in IGF-I, but persons with a more advanced MDD stage – which are more likely

to receive antidepressant treatment – could be more prone to lower IGF-I levels.

Another interesting observation is that persons who had a depression/anxiety disorder in the past had IGF-I levels in between controls and current non-medicated cases. As individuals with remitted psychiatric disorders often display residual symptoms, this is suggestive of a dose-response relationship.

Strengths of this study include the large number of participants, use of depression and anxiety diagnosis, extensive documentation of various antidepressant medications, and adjustment for a wide range of potential confounding factors. However, several limitations need to be acknowledged. First, this is a cross-sectional, observational study and therefore, no conclusions regarding causality can be drawn. In particular, it is unclear whether AD medication use causes a decrease in plasma IGF-I, or whether our observations are explained by residual confounding or confounding by indication as use of AD medication might be related to a more advanced disorder stage. Second, no information on diet was collected at baseline. Diet and weight loss can affect peripheral IGF-I levels (Giovannucci et al., 2003; Mason et al., 2013), and may partially account for some of the differences in IGF-I levels between depressed/anxiety cases and controls. Third, although peripheral IGF-I can cross the blood brain barrier, and has some central actions (Armstrong et al., 2000; Pan and Kastin, 2000), we can only speculate on whether plasma IGF-I differences also reflect differences in brain IGF-I levels, adding further complexity to the discussion of potential mechanisms. Finally, similar to many other studies, we measured total IGF-I levels. IGF-I/IGFBP3 ratio's, indicative of free IGF-I levels, were only measured in a subsample. The associations with AD use and psychopathology were largely similar to the findings of IGF-I. The positive association between current disorders and IGF-I/IGFBP3 ratio's was not significant, but this might be due to the smaller sample size. Previously, moderate to strong correlation between total and free IGF-I were reported (Frystyk, 2004).

The relationship of IGF-I and depression/anxiety appears to be complex. Although IGF-I is considered a neurotrophic factor, our observed associations between plasma IGF-I, depression, anxiety and antidepressant medication do not directly reconcile with the neurotrophic hypothesis of depression. Our findings therefore need to be replicated in other large scale studies, and intervention studies testing the potential impact of antidepressant medication on peripheral IGF-I levels are needed. Furthermore, findings from present observational studies may stimulate the development of more mechanistic and basic studies aimed at characterizing the mechanism underlying the complex association between IGF-I, psychiatric disorders and related psychotropic medications.

In conclusion, this observational cohort study suggests that the association of depression and anxiety and IGF-I may be modified by AD medication, with higher plasma IGF-I levels in AD-free depressed or anxious patients and lower IGF-I levels in AD users, relative to healthy controls. Whether this association is causal needs to be established. Although the overall associations were weak, our data suggests it could be important to differentiate in AD use when studying associations of affective disorders with plasma IGF-I.

Conflict of interest

M.B., Y.M., B.P., and M.D. reported no potential conflicts of interest.

Contributors

B.P. contributed to the design of the NESDA study. B.P. and M.D. contributed to the analytical measures. M.B. analyzed and interpreted the data, and wrote the first draft of the manuscript. Y.M., B.P., and M.D. interpreted the data and provided critical revisions. All authors have approved the final version of the article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.02.028.

References

Aberg, M.A., Aberg, N.D., Hedbacker, H., Oscarsson, J., Eriksson, P.S., 2000. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J. Neurosci. 20, 2896–2903.

Aleman, A., Torres-Aleman, I., 2009. Circulating insulin-like growth factor I and cognitive function: neuromodulation throughout the lifespan. Prog. Neurobiol. 89, 256–265.

Armstrong, C.S., Wuarin, L., Ishii, D.N., 2000. Uptake of circulating insulin-like growth factor-I into the cerebrospinal fluid of normal and diabetic rats and normalization of IGF-II mRNA content in diabetic rat brain. J. Neurosci. Res. 59, 649–660.

Arwert, L.I., Deijen, J.B., Drent, M.L., 2005. The relation between insulin-like growth factor I levels and cognition in healthy elderly: a meta-analysis. Growth Horm. IGF Res. 15, 416–422.

Auer, A., Sievers, C., Schneider, H.J., Stalla, G.K., 2012. The GH/IGF-1-axis in psychopathological functions. TOEJ 6, 62–67.

Beck, A.T., Brown, G., Epstein, N., Steer, R.A., 1988. An inventory for measuring clinical anxiety ? psychometric properties. J. Consult. Clin. Psych. 56, 893–897.

Bot, M., Chan, M.K., Jansen, R., Lamers, F., Vogelzangs, N., Steiner, J., et al., 2015. Serum proteomic profiling of major depressive disorder. Transl. Psychiatry 5, e599.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates, Hillsdale, NJ.

Craig, C.L., Marshall, A.L., Sjostrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., et al., 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports 35, 1381–1395.

Deuschle, M., Blum, W.F., Strasburger, C.J., Schweiger, U., Weber, B., Korner, A., et al., 1997. Insulin-like growth factor-I (IGF-I) plasma concentrations are increased in depressed patients. Psychoneuroendocrinology 22, 493–503.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.

Duman, C.H., Schlesinger, L., Terwilliger, R., Russell, D.S., Newton, S.S., Duman, R.S., 2009. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. Behav. Brain Res. 198, 366–371.
Duman, R.S., 2004. Role of neurotrophic factors in the etiology and treatment of mood disorders. Neuromol. Med. 5, 11–25.
Eisch, A.J., Petrik, D., 2012. Depression and hippocampal neurogenesis: a road to remission? Science 338, 72–75.
Emeny, R.T., Bidlingmaier, M., Lacruz, M.E., Linkohr, B., Peters, A., Reincke, M., et al., 2014. Mind over hormones: sex differences in associations of well-being with IGF-I, IGFBP-3 and physical activity in the KORA-Age study. Exp. Gerontol. 59, 58–64.
Fernandez, A.M., Torres-Aleman, I., 2012. The many faces of insulin-like peptide signalling in the brain. Nat. Rev. Neurosci. 13, 225–239.
Franz, B., Buysse, D.J., Cherry, C.R., Gray, N.S., Grochocinski, V.J., Frank, E., et al., 1999. Insulin-like growth factor 1 and growth hormone binding protein in depression: a preliminary communication. J. Psychiatr. Res. 33, 121–127.
Frystyk, J., 2004. Free insulin-like growth factors—measurements and relationships to growth hormone secretion and glucose homeostasis. Growth Horm. IGF Res. 14, 337–375.
Giovannucci, E., Pollak, M., Liu, Y., Platz, E.A., Majeed, N., Rimm, E.B., et al., 2003. Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer Epidemiol. Biomarkers Prev. 12, 84–89.
Hoshaw, B.A., Malberg, J.E., Lucki, I., 2005. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. Brain Res. 1037, 204–208.
Kessler, R.C., Wang, P.S., 2008. The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu. Rev. Public Health 29, 115–129.
Kopczak, A., Stalla, G.K., Uhr, M., Lucae, S., Hennings, J., Ising, M., et al., 2015. IGF-I in major depression and antidepressant treatment response. Eur. Neuropsychopharmacol. 25, 864–872.
Lamers, F., van Oppen, P., Comijs, H.C., Smit, J.H., Spinhoven, P., van Balkom, A.J.L.M., et al., 2011. Comorbidity patterns of anxiety and depressive disorders in a large Cohort Study: the Netherlands Study of Depression and Anxiety (NESDA). J. Clin. Psychiatry 72, 341–348.
Lin, F., Suhr, J., Diebold, S., Heffner, K.L., 2014. Associations between depressive symptoms and memory deficits vary as a function of insulin-like growth factor (IGF-1) levels in healthy older adults. Psychoneuroendocrinology 42, 118–123.
Malberg, J.E., Platt, B., Rizzo, S.J., Ring, R.H., Lucki, I., Schechter, L.E., et al., 2007. Increasing the levels of insulin-like growth factor-I by an IGF binding protein inhibitor produces anxiolytic and antidepressant-like effects. Neuropsychopharmacology 32, 2360–2368.
Mason, C., Xiao, L., Duggan, C., Imayama, I., Foster-Schubert, K.E., Kong, A., et al., 2013. Effects of dietary weight loss and exercise on insulin-like growth factor-I and insulin-like growth factor-binding protein-3 in postmenopausal women: a randomized controlled trial. Cancer Epidemiol. Biomarkers Prev. 22, 1457–1463.
Meesters, P., Kerkhofs, M., Charles, G., Decoster, C., Vanderelst, M., Mendlewicz, J., 1985. Growth hormone release after desipramine in depressive illness. Eur. Arch. Psychiatry Neurol. Sci. 235, 140–142.
Miller, A.H., Maletic, V.F., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.
Molendijk, M.L., de Kloet, E.R., 2015. Immobility in the forced swim test is adaptive and does not reflect depression. Psychoneuroendocrinology 62, 389–391.
Molendijk, M.L., Spinhoven, P., Polak, M., Bus, B.A., Penninx, B.W., Elzinga, B.M., 2014. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N = 9484). Mol. Psychiatry 19, 791–800.
O'Connor, J.C., McCusker, R.H., Strle, K., Johnson, R.W., Dantzer, R., Kelley, K.W., 2008. Regulation of IGF-I function by proinflammatory cytokines: at the interface of immunology and endocrinology. Cell. Immunol. 252, 91–110.
O'Flynn, K., O'Keane, V., Dinan, T.G., 1992. Effect of fluoxetine on noradrenergic mediated growth hormone release: a double blind controlled study. J. Psychopharmacol. 6, 119.
O'Kusky, J.R., Ye, P., D'Ercole, A.J., 2000. Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development. J. Neurosci. 20, 8435–8442.
Pan, W., Kastin, A.J., 2000. Interactions of IGF-1 with the blood-brain barrier in vivo and in situ. Neuroendocrinology 72, 171–178.
B.W.J.H, Penninx, Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., et al., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int. J. Method Psychiatr. 17, 121–140.
Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33, 88–109.
Rosen, T., Wiren, L.F., Wilhelmsen, L.F., Wiklund, I.F., Bengtsson, B.A., 1994. Decreased psychological well-being in adult patients with growth hormone deficiency. Clin. Endocrinol. (Oxf.) 40, 111–116.
Rozing, M.P., Westendorp, R.G., Frolich, M., de Craen, A.J., Beekman, M., Heijmans, B.T., et al., 2009. Human insulin/IGF-1 and familial longevity at middle age. Aging (Albany, NY) 1, 714–722.
Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The inventory of depressive symptomatology (IDS): psychometric properties. Psychol. Med. 26, 477–486.
Schilling, C., Blum, W.F., Heuser, I., Paslakis, G., Wudy, S.A., Deuschle, M., 2011. Treatment with antidepressants increases insulin-like growth factor-I in cerebrospinal fluid. J. Clin. Psychopharmacol. 31, 390–392.
Sen, S., Duman, R., Sanacora, G., 2008. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol. Psychiatry 64, 527–532.
Sievers, C., Dimopoulou, C., Pfister, H., Lieb, R., Steffin, B., Roemmler, J., et al., 2009. Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. Clin. Endocrinol. (Oxf.) 71, 691–701.
Sievers, C., Auer, M.K., Klotsche, J., Athanasoulia, A.P., Schneider, H.J., Nauck, M., et al., 2014. IGF-I levels and depressive disorders: results from the Study of Health in Pomerania (SHIP). Eur. Neuropsychopharmacol. 24, 890–896.
Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom. Med. 73, 114–126.
Szczesny, E., Slusarczyk, J.F., Glombik, K.F., Budziszewska, B.F., Kubera, M.F., Lason, W.F., et al., 2013. Possible contribution of IGF-1 to depressive disorder. Pharmacol. Rep. 65, 1622–1631.
Torres-Aleman, I., 2000. Serum growth factors and neuroprotective surveillance: focus on IGF-1. Mol. Neurobiol. 21, 153–160.
Trivedi, M.H., Greer, T.L., 2014. Cognitive dysfunction in unipolar depression: implications for treatment. J. Affect. Disord. 152-154, 19–27.
Weber-Hamann, B., Blum, W.F., Kratzsch, J.F., Gilles, M.F., Heuser, I.F., Deuschle, M., 2009. Insulin-like growth factor-I (IGF-I) serum concentrations in depressed patients: relationship to saliva cortisol and changes during antidepressant treatment. Pharmacopsychiatry 42, 23–28.
Wilkins, J.N., Spar, J.E., Carlson, H.E., 1989. Desipramine increases circulating growth hormone in elderly depressed patients: a pilot study. Psychoneuroendocrinology 14, 195–202.
Wittchen, H.U., 1994. Reliability and validity studies of the who composite international diagnostic interview (Cidi)—a critical-review. J. Psychiatr. Res. 28, 57–84.
World Health Organization Collaboration Centre for Drug Statistics Methodology, 2007. Anatomical Therapeutic Chemical (ATC) Classification System. World Health Organization, Oslo, Norway.
van Varsseveld, N.C., van Bunderen, C.C., Sohl, E., Comijs, H.C., Penninx, B.W., Lips, P., et al., 2015. Serum insulin-like growth factor 1 and late-life depression: a population-based study. Psychoneuroendocrinology 54, 31–40.