Neuroendocrinology

Research Article

Neuroendocrinology
DOI: 10.1159/000526418

Received: April 4, 2022
Accepted: July 21, 2022
Published online: August 9, 2022

Use of High-Dose Androgens Is Associated with Reduced Brain-Derived Neurotrophic Factor in Male Weightlifters

Astrid Bjørnebekk[a] Morgan Scarth[a] Sudan Prasad Neupane[b] Lars T. Westlye[c, d] Ingunn R. Hullstein[e] Per Medbøe Thorsby[f] Bente Halvorsen[g, h]

[a]Section for Clinical Addiction Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; [b]National Centre for Suicide Research and Prevention, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [c]Department of Psychology, University of Oslo, Oslo, Norway; [d]Division of Mental Health and Addiction, Norwegian Centre for Mental Disorders Research (NORMENT), Oslo University Hospital, Oslo, Norway; [e]Norwegian Doping Control Laboratory, Oslo University Hospital, Oslo, Norway; [f]Department of Medical Biochemistry and Biochemical Endocrinology and Metabolism Research Group, Hormone Laboratory, Oslo University Hospital, Aker, Oslo, Norway; [g]Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway; [h]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Keywords
Neurotropic factors · Heavy resistance training · Brain-derived neurotropic factor (BDNF) · Sex hormones · Anabolic androgenic steroids

Abstract

Introduction: Use of high-dose androgens causes drastic changes in hormonal milieu and is associated with adverse medical, psychological, and cognitive effects. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family of growth factors plays a critical role in neuroplasticity, with implications for cognitive function and mental health. The impact of long-term, high-dose androgen use on BDNF in a natural setting has not been investigated. This study examined the association between long-term androgen exposure and BDNF levels, and the links between BDNF, heavy resistance exercise, hormones, androgens, and mental health. ***Methods:*** We measured serum levels of BDNF and sex steroid hormones in male weightlifters ($N = 141$) with a history of current ($n = 59$), past ($n = 29$), or no ($n = 52$) androgen use. All participants completed questionnaires assessing maximum strength and measures of anxiety and depression. Group differences in BDNF were tested using general linear models adjusting for age and associations between BDNF and strength, anxiety, and depression using Pearson's or Kendall's correlations. ***Results:*** Both current (mean: 44.1 ng/mL [SD: 12.7]) and past (39.5 ng/mL [SD: 13.9]) androgen users showed lower serum BDNF levels compared to nonusing controls (51.5 [SD: 15.3], $p < 0.001$, $\eta p^2 = 0.10$). BDNF levels were negatively related to maximal strength, and with hormonal status in past androgen users, but no significant associations were found with measures of depression and anxiety. ***Conclusion:*** Lower circulating BDNF concentrations in current and past androgen users suggest that high-dose androgen exposure triggers persistent changes in BDNF expression. Further studies are needed to verify the relationship and its potential clinical implications.

Introduction

It is well established that steroid hormones influence brain development and plasticity [1, 2], and interactions have been shown between steroids and neurotrophins

Karger@karger.com
www.karger.com/nen

Correspondence to:
Astrid Bjørnebekk, askrbj@ous-hf.no

[3], a family of growth-associated proteins. Neurotrophins have a critical role in CNS development and for neuronal survival and synaptic plasticity in adulthood. Due to its prominent role in neuroplasticity and mental health [4, 5], the brain-derived neurotrophic factor (BDNF) has attracted great interest, and emerging findings have implicated a prominent interplay between the BDNF, tropomyosin receptor kinase B (TrkB) receptor, and sex hormones [3].

Androgens are a family of hormones that include the male sex hormone testosterone and its synthetic derivatives. Often these hormones are called anabolic-androgenic steroids. However, since all androgens have both androgenic as well as anabolic effects, we will hereafter only use the more accurate term androgens [6]. While androgens are used for medical purposes, their prominent muscle-building properties led to widespread misuse among professional athletes in power sports and bodybuilders from the 1950s. In the 1980s, androgen use spread to the general population, and today most users are not elite athletes but males who want to increase their muscle mass [7]. The prevalence of such clandestine behavior is difficult to estimate, but reports suggest lifetime prevalence of around 3% in the general population [8] and much higher in certain subpopulations such as athletes (13.4%), recreational sportspeople (18.4%), and substance use patients (28%) [9].

While constituting a heterogeneous group, androgen users typically alternate between heavy use and abstinence periods lasting for several weeks or months. Doses taken are typically 10–100 times greater than what is produced by the testis [10], and exogenous androgens suppress the hypothalamic-pituitary-gonadal (HPG) axis due to negative feedback mechanism [11]. Prolonged suppression of HPG may therefore diminish endogenous testosterone production and cause hypogonadism upon abstinence. The resulting outcomes include low mood, fatigue, anxiety, decreased libido, and erectile dysfunction [12], sometimes leading to depression and suicide [13].

The interplay between sex hormones and neurotrophins and the hormonal disruptions caused by supraphysiological doses of androgens suggest that androgen use might influence BDNF levels. This is supported by animal studies where high-dose androgen treatment downregulates BDNF mRNA levels in several brain regions [14, 15]. Moreover, physical exercise increases systemic as well as CNS BDNF levels [16–19], although the findings for resistance training are less consistent than for endurance training [17, 20, 21]. Also, findings indicating that BDNF increase was more typical in males following exercise than in females [19] suggest relevant sex differences. It is theorized that physical activity-induced increase in BDNF might contribute to enhanced cognition [22, 23] and reduced depression, although direct evidence for the latter is limited [24]. Notably, for practical reasons, in human studies, circulating BDNF levels are mostly measured through blood platelets [25], which potentially, but not necessarily, reflect brain levels [5].

Despite evidence of interplay between sex steroid hormones and BDNF, little is known about the influence of long-term high-dose androgen use on BDNF levels. To this end, we aimed to compare serum BDNF levels between current and past androgen users and a group of weightlifting controls (WLC). Furthermore, we tested for associations between BDNF and levels of sex hormones, symptoms of depression and anxiety, and muscle strength.

Material and Methods

Participants

The present study consisted of 141 adult male weightlifters, including current (n = 59) and past (n = 30) androgen users and weightlifting controls (WLC, n = 52). Data were derived from a longitudinal study of the brain, medical and mental health consequences of long-term androgen use [26] at Oslo University Hospital. Inclusion criteria for androgen users were previous or current androgen use corresponding to at least 1 year of cumulative androgen use (summarizing on-cycle periods). Current androgen use was defined as having used androgens within the past 6 months, whereas past use was defined as androgen use terminated more than 6 months ago. Inclusion criteria for WLC were adult males engaged in heavy resistance training that never used androgens or equivalent doping substances. We strived to match WLC against androgen users' commitment to heavy strength training and targeted men who had managed to bench press 120 kg (~265 pounds) for at least one repetition, where 100 kg (220 pounds) was the minimum criteria for inclusion. Demographic and clinical characteristics of the sample are shown in Table 1. Exclusion criteria included self-reported history of severe head injury with loss of consciousness for >1 min, a vascular or neurological disorder affecting the brain (e.g., history of diagnosed stroke, brain tumor, Parkinson's disease, or epilepsy), or IQ <80. In addition, WLC reporting the use of testosterone replacement therapy were excluded (2 cases). Participants were recruited through social media, online forums targeting people interested in heavy weight training, bodybuilding, and forums addressing androgen use. In addition, posters and flyers were distributed in select gyms in Oslo and surrounding areas.

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and the study was approved by the Regional Committees for Medical and Health Research Ethics South-East Norway (REC; 2013/601 and 2018/736). The participants were compensated (for the travelling to the hospital) with 500 Norwegian kroner (approximately USD 60 or Euro 50).

Questionnaires

After obtaining written informed consents, the participants were requested to complete a set of structured questionnaires using a web solution offered by the Services for Sensitive Data provided by the University of Oslo. The questionnaires assessed relevant background and health information, characteristics of training history, including personal lift records in classic powerlifting exercises, and other sports achievements (maximum strength). Androgen users were also asked about the nature of their androgen use, the extent of current or previous androgen use, doses applied, and age of initiation.

Depression and anxiety symptoms were measured using the Hopkins Symptom Checklist-25 [27]. It consists of a 10-item subscale for anxiety and a 15-item subscale for depression, where each item is scored on a Likert scale from 1 (not at all) to 4 (extremely). A mean total score of 1.75 or above is a widely used cut-off for significant psychological distress [28].

Doping Analysis

Urine samples were collected and analyzed for external use of androgens using gas and liquid chromatography coupled to mass spectrometry at the WADA-accredited Norwegian Doping Laboratory at Oslo University Hospital [29]. The criteria used to determine external androgen use were (1) urine samples positive for synthetic testosterone compounds (2) a testosterone to epitestosterone ratio (T/E) >15 equivalent to previous work [26, 29, 30].

Blood Sampling and Laboratory Analysis

Blood was drawn from the antecubital vein in anticoagulant-free tubes and kept at room temperature for 1 h and centrifuged at 3,500 *g* for 15 min at 4°C. The serum layer was aliquoted and frozen at −80°C for further analyses. Blood was drawn between 9:00 and 11:30 a.m.

BDNF

Serum BDNF levels were analyzed by using U-plex Metabolic Group 1 Multiplex Assay from Meso Scale Discovery (Meso Scale Diagnostics; LLC, Rockville, MD, USA) using a QuickPlex SQ120. This is a MULTI-ARRAY technology, a combination of electrochemiluminescence detection and patterned arrays, and the samples were assessed according to instructions from the manufacturer. Intra-assay and inter-assay variations were 3.4 and 14.2%, respectively.

Hormones

All hormone analyses were performed at the Hormone Laboratory, Oslo University Hospital, Oslo, Norway, and they were all accredited according to ISO 17025. Follicle-stimulating hormone (FSH) (LOQ 0.1 IU/L, CV% 7), luteinizing hormone (LH) (LOQ 0.1 IU/L, CV% 3.8), sex hormone-binding globulin (SHBG) (LOQ 2 nmol/L, CV% 7) were analyzed by noncompetitive immunoluminometric assays (Siemens Healthineers), estradiol (E2) (LOQ 0.06 nmol/L, CV% 9) by competitive chemoluminescence (Diaorin Inc.), and testosterone (T) (LOQ 0.1 nmol/L, CV% 8) by LCMS (Hormone Laboratory, Oslo University Hospital, Norway). Normal range for FSH, LH, E2, T, and SHBG in adult males were 0.70–11 IU/L, 0.80–7.6 IU/L, 50–200 pmol/L, 7.2–24 nmol/L, and 8–60 nmol/L, respectively. Values below the minimum detection level (DL) for FSH, LH, and E2 were replaced with DL/√2 suggested as a minimally biased method to overcome the left censoring bias in serum steroid measurements [31]. The number of cases below the DL for FSH was 37 (29%), mainly comprising current androgen users 36 (67%), and 1 past androgen user (4%). Similarly, 43 cases were below the DL for LH where 42 of those were current androgen users (78%), and 1 past user (4%). For E2, 29 cases fall below the DL including 12 WLC (24%), 11 current (22%), and 5 past androgen users (21%).

Moreover, given the negative feedback loops involved in sex hormone regulation – the combined status of different hormones together might provide useful information about the hormonal condition (e.g., testosterone deficiency), than a single hormone in itself. Thus, to extract relevant information from the hormone data, a principal component analysis (PCA) was performed, where inter-related patterns are likely to provide interlinked grouping of the hormones. PCA has recently been shown to provide endocrine profiles that with high accuracy distinguished patients with pediatric congenital adrenal hyperplasia according to treatment efficacy and to elucidate biochemical differences between classical and nonclassical congenital adrenal hyperplasia [32].

Statistics

Three-group comparisons of demographic data, psychological distress, hormones, and other relevant blood biomarkers were performed using analysis of variance, with Bonferroni significant difference tests for pairwise group comparisons. χ^2 or Fisher's exact tests were used for categorical data.

PCA with Direct Oblimin rotation and Kaiser normalization were conducted to investigate composite variables of the main hormones. The factorability of the hormone data was inspected by Bartlett's Test of Sphericity, which evaluates the presence of correlations among the included variables and the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy, which evaluates the degree to which the data are suited for factor analysis.

General linear models were used when covariates were included in the model. For instance, models assessing group differences in BDNF levels included age, as BDNF levels might level off with higher age [33]. Bonferroni post hoc tests were used to test for group differences between the three groups. Also, sensitivity general linear model analyses were conducted to statistically control for the effect of weekly alcohol intake, body mass index (BMI), and current use of psychiatric, sleep, or cardiovascular medication on BDNF levels, by including these measures as additional covariates in the models. The relations among psychological distress, hormones, maximum strength, and BDNF levels were investigated with Pearson's or Kendall's tau-b correlations upon violation of normality and/or linearity, across and within the three groups. To adjust for the age contribution to BDNF levels in correlation analyses, standardized residuals from a simple regression were computed, and the z-transformed age-adjusted variable was used in further analyses.

Results

Demographics

Table 1 summarizes key clinical and demographic characteristics. No significant differences in age were seen between WLC and androgen users ($p = 0.374$), but the current users were significantly older than the past users. Current users had less education compared to

Table 1. Demography of the study participants

	WLC (n = 52) mean (SD)	AAS current (n = 60) mean (SD)	AAS past (n = 29) mean (SD)	Main effect of group		
				F	p value	ηp^2
Age	37.5 (8.6)	40.8 (11.3)	34.6 (8.5)	4.249	0.016[a]	0.06
Education, years	16.5 (2.9)	14.2 (2.9)	15.2 (2.2)	8.458	<0.001[b]	0.12
Alcohol, units/week	3.6 (3.8)	3.4 (3.1)	3.2 (3.2)	0.068	0.934	0.00
Weight, kg	93.0 (8.4)	102.1 (15.5)	97.9 (15.3)	5.805	0.004[b]	0.09
Height, cm	182.6 (5.9)	181.9 (5.8)	182.1 (6.7)	0.134	0.875	0.00
BMI, kg/m^2	27.9 (2.7)	30.8 (4.4)	29.5 (4.1)	7.126	0.001[b]	0.11
Strength training, min/week	322.0 (159.1)	395.9 (224.4)	252.9 (164.5)	4.91	0.009[a]	0.08
Endurance training, min/week	114.3 (151.8)	93.5 (158.5)	95.4 (107.9)	0.267	0.766	0.00
Squats max, kg	179.4 (34.0)	227.6 (56.2)	208.3 (48.5)	11.104	<0.001[b]	0.17
Bench max, kg	141.1 (17.9)	181.8 (36.4)	163.3 (30.4)	22.783	<0.001[c]	0.28
Ground lift max, kg	200.5 (39.2)	248.5 (57.2)	241.0 (45.5)	11.239	<0.001[b, d]	0.18
HSCL total	1.22 (0.3)	1.40 (0.4)	1.38 (0.4)	2.828	0.064	0.06
HSCL anxiety	1.14 (0.4)	1.36 (0.4)	1.31 (0.4)	3.678	0.029[b]	0.07
HSCL depression	1.27 (0.4)	1.43 (0.4)	1.43 (0.4)	1.933	0.151	0.04
	%	%	%	X2	p	
Smoker	0.0	9.4	12.0	5.97	0.03	
Student	8	11.3	28.0	4.91	0.08	
Working	93.5	94.3	84.0	7.90	0.10	
Norwegian origin	97.80	96.20	92.00	1.44	0.49	
Psychopharmaceutics (current)	4.30	18.90	8.00	5.11	0.07	
Sleep medication (current)	2.20	24.50	8.00	20.33	0.00	
Cardiovascular medications (current)	2.20	17.00	4.00	11.25	0.02	
Training classification (lifetime)						
Bodybuilding/fitness	32.60	71.70	60.00	15.53	0.00	
Weightlifting	28.30	30.20	28.00	0.61	0.97	
Combat sports	32.60	34.00	36.00	0.84	0.96	
Recreational exercise	30.40	9.40	32.00	8.30	0.16	

Of note, there are some missing cases for background measures (besides age), where mean values or percentages are based on 46 nonexposed, 53 current, and 25 past users of androgens. Psychopharmaceutic includes current use of anxiolytics, antidepressants, attention deficits hyperactivity disorder medication, or opiate maintenance treatment, while sleep medication is presented separately. For training classification, the most frequently mentioned sports ever engaged in are reported. Note that multiple responses were allowed. Fisher's exact test was applied when responses for a category were less than 5. HSCL, Hopkins symptom checklist. [a] Current androgen use significantly different from past androgen use. [b] Current androgen use significantly different from WLC. [c] All groups significantly different from one another. [d] Past androgen use significantly different from WLC.

WLC and were heavier and stronger than WLC for all measures and past users on some strength measures. Anxiety scores were higher for current users compared to WLC. The majority of WLC (96.2%), current (83.1%), and past users (93.3%) reported no current use of prescribed psychotropic medication, although significant group differences were found, with current users being the highest consumers. Significant group differences were also seen for sleep and blood pressure medications, with highest use reported by current users. There were few group differences in the lifetime engagement of sport activities, except for bodybuilding/fitness that was more typical of the androgen users.

Characteristics of Androgen Use

On average, androgen use was initiated at 22.7 years (SD = 8.1, range 15–55) and had been used for 11.5 years (SD = 8.4, range 1–35), and the mean weekly applied androgens dose was 1,114 mg (SD = 735, range 125–4,500). Current and past androgen users did not differ in age of androgen debut, or the doses used; however, current users had used androgens for 13.1 years (SD = 9.1, range

Table 2. Hormone levels in weightlifting controls, current, and past androgen users

Hormone	WLC (n = 51) mean (SD)	Current androgen use (n = 54) mean (SD)	Past androgen use (n = 25) mean (SD)	Main effect of group		
				F	p value	ηp^2
Follicle-stimulating hormone, IU/L	5.0 (3.0)	0.9 (1.7)	4.4 (2.7)	40.68	<0.001[a, b]	0.39
Luteinizing hormone, IU/L	4.7 (1.8)	0.7 (1.4)	3.7 (1.5)	89.50	<0.001[a, b, c, d]	0.59
Estradiol, nmol/L	79.6 (31.4)	207.9 (225.5)	78.8 (24.5)	12.01	<0.001[a, b]	0.16
Testosterone, nmol/L	19.4 (7.0)	39.5 (37.4)	12.9 (5.5)	12.81	<0.001[a, b]	0.18
Sex hormone-binding globulin, nmol/L	42.0 (19.5)	21.7 (17.7)	31.7 (13.1)	17.00	<0.001[a]	0.21
PCA factor 1	0.7 (0.8)	−0.8 (0.7)	0.2 (0.6)	58.94	<0.001[a, b, c, d]	0.50
PCA factor 2	−0.3 (0.3)	0.6 (1.4)	−0.5 (0.2)	16.01	<0.001[a, b]	0.21

FTI, free testosterone index; SHBG, sex hormone-binding globulin; PCAfac1, principal component analysis factor 1; PCAfac2, principal component analysis factor 2; WLC, weightlifting controls. The Bonferroni post hoc test. [a] Current androgen use significantly different from WLC. [b] Current androgen use significantly different from past androgen use. [c] All groups significantly different from one another.

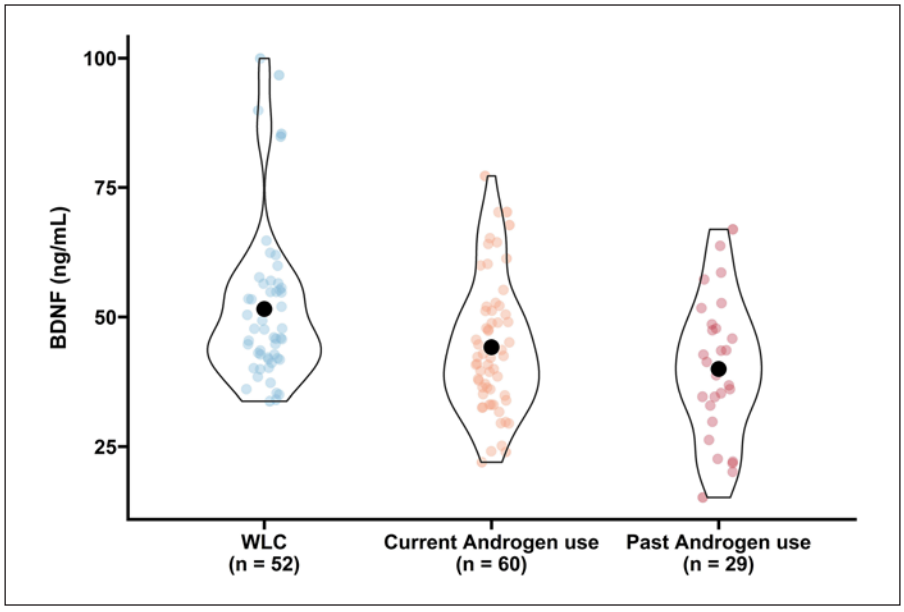

Fig. 1. Serum levels of brain-derived neurotrophic factor (BDNF, ng/mL) in weightlifting controls, current, and past androgen users. BDNF, brain-derived neurotrophic factor; WLC, weightlifting controls.

1–35), which was significantly longer (t = 3.3, p = 0.002) compared to past users (mean 7.7 years, SD = 5.1, range 1–20). Among current users, 77% reported using androgens at the time when blood was sampled. Previous users had on average stopped using androgens 3.2 years ago (SD = 2.7, range 1–8).

None of the WLC tested positive for synthetic androgens or had T/E ratio above threshold. Positive doping tests were seen in 73.3% (n = 44) of current users (6 missing) and in 0% (n = 25) of previous users (4 missing). The mean T/E ratio for the groups was 1.1 (SD = 1.0, range 0.1–4.8) for WLC (n = 47), 40.5 (SD = 39.4, range 0.1–127.5) for current users (n = 53), and 1.7 (SD = 1.8, range 0.0–8.8) for previous users, where previous users and WLC were significantly different from current users (df = 125, F = 35.4, p < 0.001, ηp^2 = 0.37).

PCA of Main Hormones

Inspection of the correlation matrix revealed several coefficients $r \geq 0.30$. The KMO value was 0.69, exceeding the recommended value of 0.60, and Bartlett's Test of Sphericity was significant (p < 0.001), suggesting that factor analysis is appropriate [34]. PCA revealed two components with eigenvalue >1, explaining 77.3% of the total

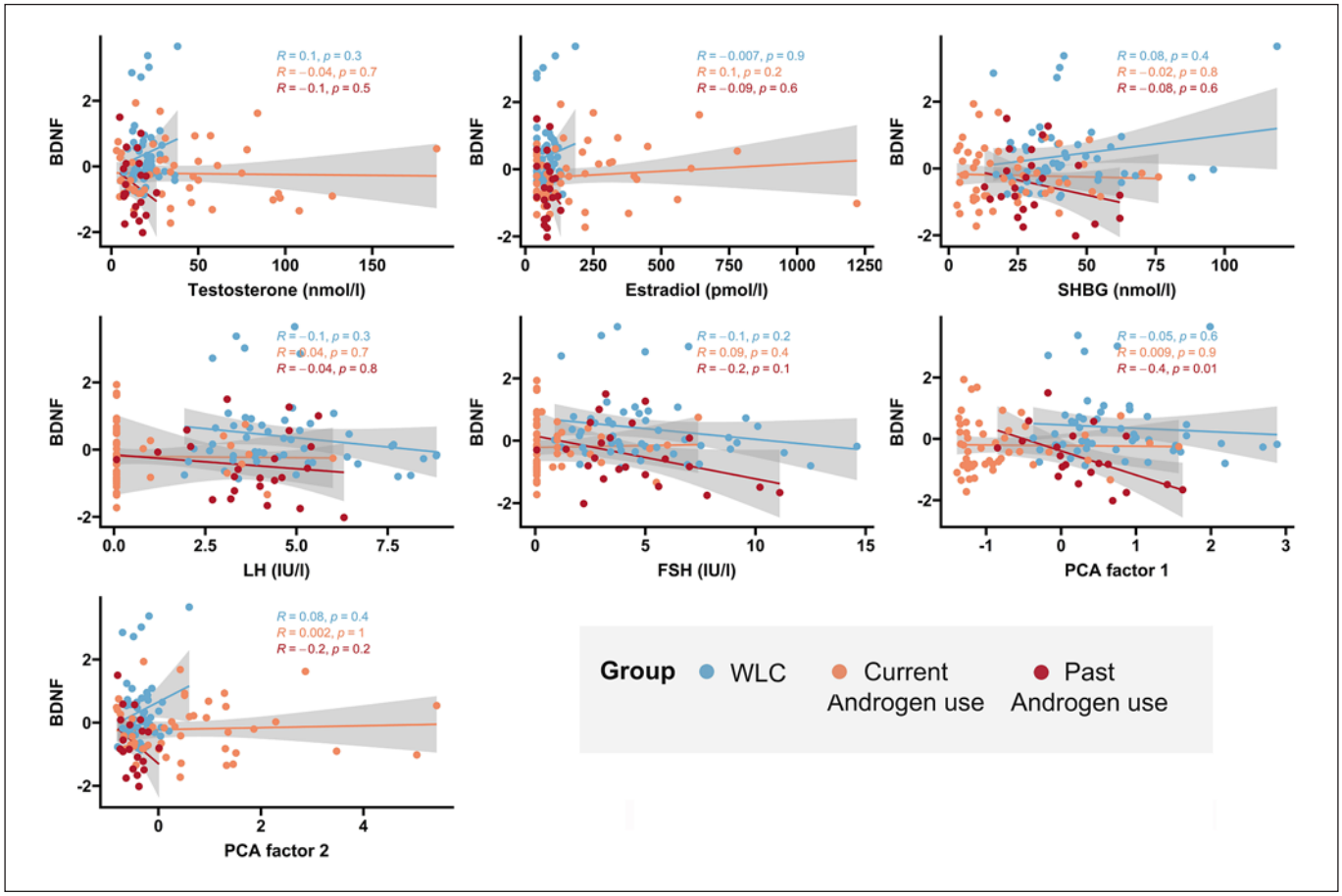

Fig. 2. Associations between serum brain-derived neurotrophic factor (BDNF, ng/mL) and sex hormones. Visualization of the relationship between serum BDNF levels and hormones in weightlifting control (blue), current (orange), and previous users of androgens (red). Note that for some hormones, there are a substantial proportion of tests at the lower end and also below detectable levels that being replaced, leading to a left-shewed distribution of data toward low values. BDNF, brain-derived neurotrophic factor; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PCA factor 1, principal component analysis factor 1; PCA factor 2, principal component analysis factor 2; WLC, weightlifting controls.

variance of the included hormone data. Based on inspections of the scree plot in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526418), this two-factor solution was chosen. The first factor had high loading for LH, FSH, and SHBG, with loading ranging from 0.77 to 0.88. The second factor had high loading for testosterone and E2 with similar strong loadings on both components (0.92). See online supplementary Table S1 for details.

Blood Biomarkers

Group Differences in Sex Hormone Levels

As expected, significant group differences in hormone levels between the three groups were found, with current users diverging from WLC on all hormones and from past users on all besides SHBG. All groups were significantly different from one another on LH and the PCA factor 2 comprising the gonadotropins and SHBG, see Table 2 for details.

Associations between Androgen Use and BDNF

Figure 1 shows BDNF distributions for all three groups. The main GLM univariate analyses revealed significant group differences in BDNF levels ($F(3, 135) = 7.90$, $p = 0.001$, $\eta p^2 = 0.11$). Post hoc tests revealed that current users (mean = 44.1 ng/mL [SD = 12.7]) and previous users (38.5 ng/mL [13.9]) had significantly lower BDNF levels compared to WLC (51.5 ng/mL [15.3]), but no differenc-

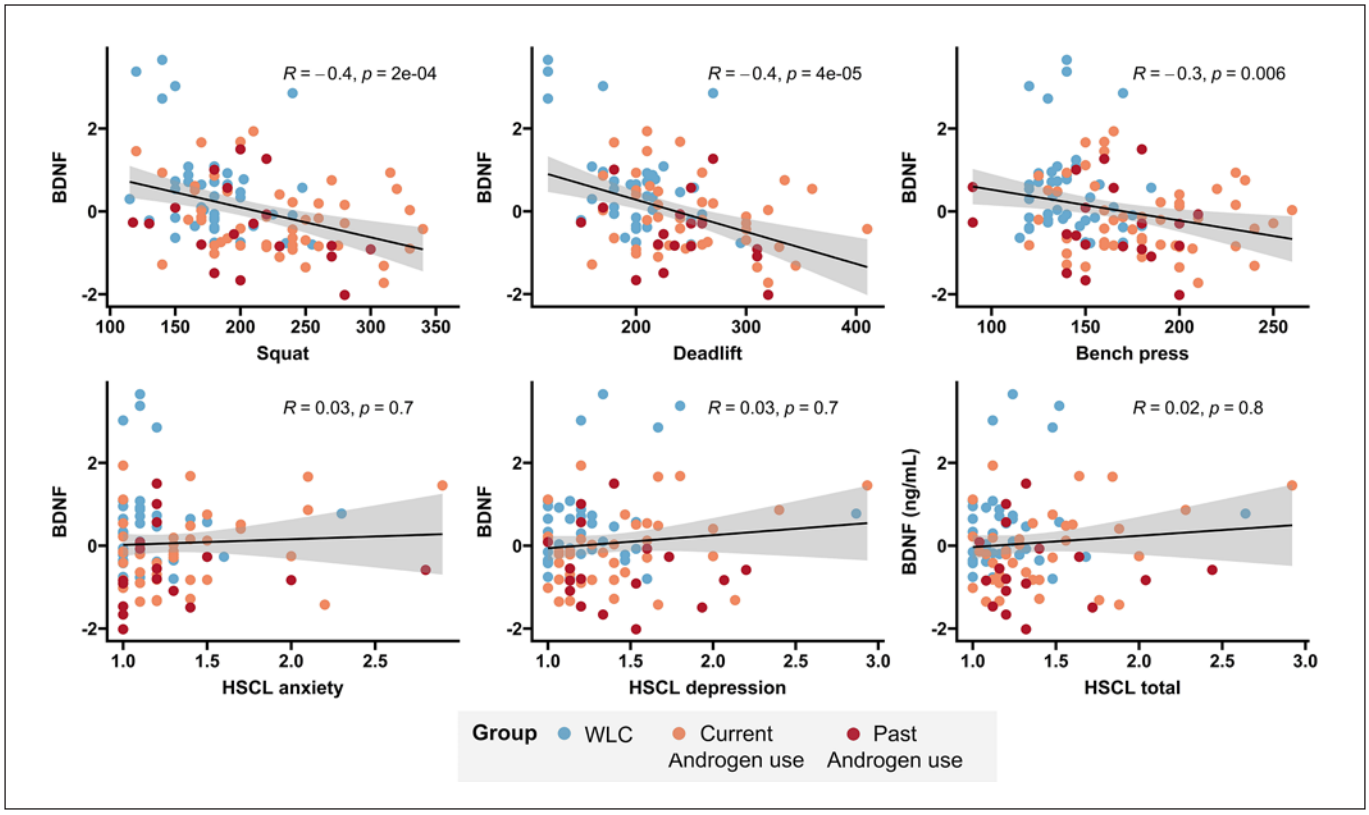

Fig. 3. Associations between serum brain-derived neurotrophic factor (BDNF, ng/mL), maximum strength, and psychological distress. Correlations between serum BDNF levels and maximum lift records on the base powerlifting exercises (upper row), and symptoms of anxiety and depression (lower row), across groups. HSCL, Hopkins symptom checklist; WLC, weightlifting control subjects.

es between current and past users. Age had minor influence on the model ($\eta p^2 = 0.01$) but was still adjusted for in further correlations. Online supplementary Table S2 shows the results after correcting for use of alcohol, BMI, and current use of medications for sleep disturbances, cardiovascular conditions, and mental illness. Adjusting for these potential confounders had minimal influence on the findings and rather increased the explained variance attributable to group belonging to 16% (online suppl. Table S2).

Relationship of Serum BDNF and Hormone Levels

Figure 2 shows correlations between BDNF and sex hormones for each subgroup. In past users, BDNF was negatively correlated with the PCA factor 1 with medium effect size ($\tau = -0.4$, $p < 0.01$). No other significant associations between BDNF and hormone levels were found.

Association between BDNF, Heavy Resistance Exercise, and Mental Health

Figure 3 shows the associations between psychological distress, lift records on the base powerlifting exercises, and BDNF levels across groups. All lift records were negatively associated with BDNF levels, indicating that higher reported maximum strength was associated with lower BDNF. These associations could not be explained by androgen use, as the strongest correlation was seen in WLCs with no history of androgen use (online suppl. Fig. S2). No significant associations were observed for psychological distress as measured by the Hopkins Symptom Checklist-25 and BDNF levels across or within groups.

Discussion

Accumulating evidence suggests that long-term steroid use may have harmful consequences for the brain, cognition [26, 30, 35–37], and mental health [38]. These

effects are thought to be mediated through reduced neurotrophic support to specific brain regions. In a sample of androgen-exposed and nonexposed weightlifters, we examined the relationship between long-term high-dose androgen-exposure and serum BDNF levels and tested whether BDNF levels were related to sex hormones, symptoms of depression and anxiety, and maximal strength. We found that past or current long-term high-dose androgen users showed lower serum BDNF compared to WLC. BDNF levels were not significantly related to anxiety or depression; however, an unexpected negative correlation was seen between maximum strength and BDNF levels.

Use of High-Dose Androgens Associated with Markedly Lower Serum BDNF

The markedly reduced levels of BDNF in current and past androgen users are in line with emerging evidence that suggests a link between sex-hormones [3, 39], androgen use [14, 15, 40], and BDNF. In animal models, androgen treatment is found to reduce hippocampal [41], prefrontal cortex [14, 15], and striatal [15] BDNF. Furthermore, 1 year of gender-affirming hormone therapy in transwomen (male-to-female) resulted in a significant drop in BDNF serum levels [40] which supports the exogenous sex hormone control of BDNF also found in our study. The observed BDNF findings could not be explained by BMI, alcohol, or current use of heart medications or pharmacotherapy for mental illnesses or sleep disorders. Instead, the explained variance by current or past use of androgens increased when adding these covariates, which strengthens the interpretation that the observed group differences are caused by current or past use of androgens. In addition, the objective verification of the drug androgen history with antidoping drug screening, showing a strikingly good fit, is consistent with a recent report [42] and supports the interpretation of the findings.

Hormonal Disruptions and BDNF

Our hormone findings are similar to what is seen in other studies [11, 43] and in accordance with what we know about how different phases of androgen administration and withdrawal affect the hormonal environment. In current users, significantly lower levels of LH, FSH, and SHBG were seen, whereas serum testosterone level and E2 were markedly elevated [11, 43]. In past users, LH levels and PCA factor 1 were significantly different from WLC. Also, although no statistically significant group differences were seen between WLC and past users for other hormones, a high proportion of past users (33.3%) had testosterone levels below the reference limit for healthy adult males (9.0 nmol/L), although only two (*n*%) when a stricter criterion (6.6 nmol/L) was applied. The findings suggest that although few have markedly low testosterone levels, many users have testosterone levels in the lower range years after cessation, as previously reported [11, 12]. The testosterone levels of past and current users likely partly reflect the SHBG levels, and the impact of androgen abuse on SHBG, given it being the main carrier of circulating testosterone [44]. Moreover, the lower LH levels seen in past users support long-term impact of androgen use on pituitary functioning. BDNF is expressed in the pituitary [45], indicating that BDNF plays a role in endocrine function. Emerging evidence suggests that hormonal status might influence the expression of BDNF and/or trkB expression (reviewed in [46]). Findings from the Baltimore Longitudinal Study of Aging support a linkage between circulating hormones and BDNF levels. Among middle-aged and elderly men, BDNF levels correlated positively with bioavailable testosterone and negatively with SHBG levels [47]. Although the group differences in BDNF levels between WLC and current and past androgen users in our study suggest hormonal influence on BDNF regulation, the associations are likely complex, and we found no direct support for a linkage between any single hormone measure and BDNF levels.

Two endocrine profiles emerged from the PCA, one factor comprising hormones that are markedly reduced by androgen intake, none of which seems to fully recover upon quitting, and the second factor consisting of hormones where levels are elevated by use. The PCA factors could be useful to understand complex associations, as the endocrine profiles probably provide greater insight about the endocrine disturbances than indicated by a single hormone measure. The negative correlation between BDNF and the first PCA factor among past users may suggest that a slow recovery of the HPG axis, and resulting lower gonadotrophin levels after androgen use potentially could affect the BDNF. Gonadotrophins and SHBG are suppressed even with low doses of androgen exposure, whereas the testosterone and E2 level show higher variation depending on the compounds being used [48]. Also, the action of androgens is mediated via the androgen receptors (AR) [49] and subsequent binding to DNA to regulate target gene transcription [49]. There is evidence that testosterone might regulate trkB and BDNF mRNA expression in motor neurons [50, 51] and brain tissue [14, 15]. Suggested pathways for androgen-mediated regulation of BNDF involve an androgen-mediated

regulation of the calcium-dependent signaling pathway for BDNF [52]. They could also be estrogenic in nature, through testosterones' conversion to dihydrotestosterone or estrogenic metabolites [53]. Estrogenic regulation of BDNF has been reported in several brain regions [54–56], and there is evidence of an estrogen response element on the gene encoding BDNF, providing a direct mechanism for steroid hormone control of BDNF expression [57].

BDNF Negatively Related to Maximum Strength but Not Depression

The neurotrophic hypothesis of depression posits that BDNF reductions in brain limbic areas in response to chronic stress may be responsible for the depressed mood [58]. Other associated disorders including schizophrenia, eating disorders, neurodevelopmental disorders, and substance use disorder also show significant disturbance in the neurotrophic support [4, 5]. Lower BDNF levels in androgen users, and the higher prevalence of mental health problems seen in androgen users fits well with this hypothesis. However, we found no support for a direct link between serum BDNF and depression or anxiety in our sample. Instead, a negative correlation was observed between maximum strength gains and BDNF levels. This could not be explained by use of androgens, as the association was even more prominent in the WLC group. Physical activity has repeatedly been shown to be a powerful modifier of the brain and circulating BDNF, and a wealth of data demonstrates that endurance training results in increased serum and plasma BDNF levels [17, 59, 60]. However, strongest evidence points to a "transient" increase in serum or plasma BDNF following an acute aerobic exercise [17], and that the BDNF response to training could be modulated by intensity and physical fitness level [61].

Efforts have been made to establish whether resistance training also impacts BDNF levels, but the findings are less clear [17, 20, 21]. Many of these studies are of elderly individuals examining the effects of resistance training interventions on neuroplasticity and age-related cognitive decline [62, 63]. Few have studied the impact of heavy resistance training, and the strength status and the interventions applied in previous studies are not comparable with the strength status or training practices of the participants in the current study. Many compete on national and international level in weightlifting and bodybuilding, and the inclusion of WLC who have managed to bench press 100 kg makes this study clearly different from other studies. Hence, whereas resistance training in untrained elderly males might boost serum BDNF [64], our findings suggest that the opposite might be the case in more extreme forms of heavy resistance training and achieved strength. Of note, the observed BDNF-strength association reflects the participants' maximum achieved strength ever, whereas acute effects are not recorded. It is possible that both our findings linking androgen use and maximum strength to BDNF levels could involve HPG axis alterations. It has been shown that intensive exercise training time attenuates the responsiveness of the pituitary to release hormones and may cause hypogonadism [12]. In elite trained weightlifters, stressful strength training periods are shown to decrease selected serum hormones including testosterone, which again correlate with weightlifting performance [65]. More experimental and longitudinal studies are needed to understand the impact of androgen use and strength training on peripheral and brain BDNF signaling, and the potential clinical significance of the lower BDNF levels seen in current and past androgen users.

The current results should be interpreted considering some limitations. First, while the WLC group was carefully chosen as a control group that matches the androgen users on many aspects, we cannot rule out that use of androgens is associated with lifestyle or other factors with a potential influence on BDNF. Although our findings remained significant after the inclusion of covariates related to physical and mental health, it is possible that other physical consequences of androgen use might explain the observed relations. We do not know whether our sample is representative of the population of current and past androgen users. In particular, as one major aim of our research was to understand long-term effects of use, we recruited men with at least 1 year of cumulative androgen exposure. The average use of 11.5 years emphasizes that this sample consists of established users, and users with shorter history of androgen use might have less severe hormonal disturbances and medical consequences that potentially could be linked with the findings. There are also other methodological considerations that might influence the BDNF findings such as time of testing, fasting state, and smoking. While blood was sampled in the morning, we have less control of those other variables. Moreover, to which degree the observed serum levels reflect BDNF levels in the brain in this specific population is uncertain. The majority (90%) of BDNF found in blood is contained in platelets [66]. While serum BDNF levels are regarded to resemble BDNF concentrations in the brain [59], it has become clear that circulating BDNF is not derived from brain blood platelets but is released upon platelet activation [25]. Still, there seem to be many

shared components in the molecular pathways that regulate vesicular release in the brain and in platelets [67], and it is possible that the release from platelets could reflect BDNF release in the brain [5]. Also, the cardiovascular effects of androgen misuse, including a potential increase in blood platelets, activity, and aggregation [68] could be related to the BDNF findings. Blood platelets store BDNF mainly in α-granules [69] and release it into the bloodstream during platelet activation [70, 71]. Blood platelets and megakaryocytes contain estrogen and AR, and it has been shown that testosterone regulates AR levels in these cells [72]. Although suggesting a putative pathway between high-dose androgen use and BDNF levels, the direction of the findings does not quite fit including the finding of lower BDNF levels in both current and past users. Further studies are needed to confirm the observed association, understand the underlying mechanisms and their potential clinical implications.

In conclusion, our findings suggests that chronic androgen use decreases circulating BDNF levels in both current and previous users. The findings are worrying, pointing to potential persistent reduced neuroplasticity due to androgen use, which could pose a vulnerability or causal explanation for psychiatric and somatic pathology that sometimes follows androgen use.

Acknowledgments

The authors would like to thank to Lisa Evju Hauger for her help in collecting these data and Ellen Lund Sagen for technical assistance.

Statement of Ethics

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and the study was approved by the Regional Committees for Medical and Health Research Ethics South-East Norway (REC; 2013/601 and 2018/736). Written informed consent was obtained from all participants in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research was funded by the South-Eastern Norway Regional Health Authority (Grant No. 2016049, 2017025, 2018075, and 2020088 [to Astrid Bjørnebekk]) and by internal research grants from the Division on Mental Health and Addiction (to Astrid Bjørnebekk).

Author Contributions

Astrid Bjørnebekk is the project manager and conceived and designed the study. Data collection: Lisa Evju Hauger and Astrid Bjørnebekk. Hormone analysis and expertise guidance: Per Medbøe Thorsby, BDNF analysis: Bente Halvorsen, and expertise guidance: Bente Halvorsen and Sudan Prasad Neupane. Doping analysis and expertise guidance: Ingunn Riise Hullstein. Data management and analysis: Astrid Bjørnebekk, Morgan Scarth, Per Medbøe Thorsby, and Bente Halvorsen. All authors took part in planning of the analysis and interpretation of the findings. Astrid Bjørnebekk wrote the first draft of the manuscript. All authors agree with manuscript results and conclusions, made critical revisions, and approved final version of the manuscript.

Data Availability Statement

A preprint version of this article is available on PsyArXiv [73]. The data that support the findings of this study are not publicly available due to their sensitive nature, where our ethical approval prevents us from sharing data beyond named collaborators. However, upon reasonable request, we will allow necessary insight into the material. Further inquiries can be directed to the corresponding author.

References

1 Perrin JS, Herve PY, Leonard G, Perron M, Pike GB, Pitiot A, et al. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. J Neurosci. 2008 Sep 17;28(38):9519–24.
2 Liao Z, Patel Y, Khairullah A, Parker N, Paus T. Pubertal testosterone and the structure of the cerebral cortex in young men. Cereb Cortex. 2021 May 10;31(6):2812–21.
3 Begliuomini S, Casarosa E, Pluchino N, Lenzi E, Centofanti M, Freschi L, et al. Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. Hum Reprod. 2007 Apr;22(4):995–1002.
4 Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev. 2012 Apr;64(2):238–58.
5 Castren E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021 Jul 15;90(2):128–36.
6 Handelsman DJ. Commentary: androgens and "anabolic steroids" – the one-headed janus. Endocrinology. 2011 May;152(5):1752–4.

7 Kanayama G, Pope HG Jr. History and epidemiology of anabolic androgens in athletes and non-athletes. Mol Cell Endocrinol. 2018 Mar 15;464:4–13.
8 Sagoe D, Molde H, Andreassen CS, Torsheim T, Pallesen S. The global epidemiology of anabolic-androgenic steroid use: a meta-analysis and meta-regression analysis. Ann Epidemiol. 2014 May;24(5):383–98.
9 Havnes IA, Jørstad ML, McVeigh J, Van Hout MC, Bjørnebekk A. The anabolic androgenic steroid treatment gap: a national study of substance use disorder treatment. Subst Abuse. 2020;14:1178221820904150.
10 Reyes-Fuentes A, Veldhuis JD. Neuroendocrine physiology of the normal male gonadal axis. Endocrinol Metab Clin North Am. 1993 Mar;22(1):93–124.
11 Rasmussen JJ, Selmer C, Ostergren PB, Pedersen KB, Schou M, Gustafsson F, et al. Former abusers of anabolic androgenic steroids exhibit decreased testosterone levels and hypogonadal symptoms years after cessation: a case-control study. PLoS One. 2016;11(8):e0161208.
12 Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018 May 1; 103(5):1715–44.
13 Thiblin I, Runeson B, Rajs J. Anabolic androgenic steroids and suicide. Ann Clin Psychiatry. 1999 Dec;11(4):223–31.
14 Matrisciano F, Modafferi AM, Togna GI, Barone Y, Pinna G, Nicoletti F, et al. Repeated anabolic androgenic steroid treatment causes antidepressant-reversible alterations of the hypothalamic-pituitary-adrenal axis, BDNF levels and behavior. Neuropharmacology. 2010 Jun;58(7):1078–84.
15 Cattelan Souza L, de Brito MLO, Jesse CR, Boeira SP, de Gomes MG, Goes ATR, et al. Involvement of kynurenine pathway in depressive-like behaviour induced by nandrolone decanoate in mice. Steroids. 2020 Dec; 164:108727.
16 Bjornebekk A, Mathe AA, Brene S. The antidepressant effect of running is associated with increased hippocampal cell proliferation. Int J Neuropsychopharmacol. 2005 Sep;8(3): 357–68.
17 Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity: exercise-induced response of peripheral brain-derived neurotrophic factor – a systematic review of experimental studies in human subjects. Sports Med. 2010 Sep 1;40(9):765–801.
18 Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. Trends Cognit Sci. 2013 Oct;17(10):525–44.
19 Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res. 2015 Jan;60:56–64.
20 Goekint M, De Pauw K, Roelands B, Njemini R, Bautmans I, Mets T, et al. Strength training does not influence serum brain-derived neurotrophic factor. Eur J Appl Physiol. 2010 Sep; 110(2):285–93.
21 Dinoff A, Herrmann N, Swardfager W, Liu CS, Sherman C, Chan S, et al. The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): a meta-analysis. PLoS One. 2016; 11(9):e0163037.
22 Bechara RG, Lyne R, Kelly AM. BDNF-stimulated intracellular signalling mechanisms underlie exercise-induced improvement in spatial memory in the male Wistar rat. Behav Brain Res. 2014 Dec 15;275:297–306.
23 Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science. 2018 Sep 7;361(6406):eaan8821.
24 Kurebayashi Y, Otaki J. Does physical exercise increase brain-derived neurotrophic factor in major depressive disorder? A meta-analysis. Psychiatr Danub. 2018 Jun;30(2): 129–35.
25 Serra-Millas M. Are the changes in the peripheral brain-derived neurotrophic factor levels due to platelet activation? World J Psychiatry. 2016 Mar 22;6(1):84–101.
26 Bjørnebekk A, Kaufmann T, Hauger LE, Klonteig S, Hullstein IR, Westlye LT. Long-term anabolic-androgenic steroid use is associated with deviant brain aging. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 May; 6(5):579–89.
27 Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The hopkins symptom checklist (HSCL): a self-report symptom inventory. Behav Sci. 1974;19(1):1–15.
28 Glaesmer H, Braehler E, Grande G, Hinz A, Petermann F, Romppel M. The German Version of the Hopkins Symptoms Checklist-25 (HSCL-25): factorial structure, psychometric properties, and population-based norms. Compr Psychiatry. 2014 Feb;55(2):396–403.
29 Hullstein IR, Malerod-Fjeld H, Dehnes Y, Hemmersbach P. Black market products confiscated in Norway 2011-2014 compared to analytical findings in urine samples. Drug Test Anal. 2015 Nov–Dec;7(11–12):1025–9.
30 Bjørnebekk A, Walhovd KB, Jørstad ML, Due-Tønnessen P, Hullstein IR, Fjell AM. Structural brain imaging of long-term anabolic-androgenic steroid users and nonusing weightlifters. Biol Psychiatry. 2017 Aug 15; 82(4):294–302.
31 Handelsman DJ, Ly LP. An accurate substitution method to minimize left censoring bias in serum steroid measurements. Endocrinology. 2019 Oct 1;160(10):2395–400.
32 Ljubicic ML, Madsen A, Juul A, Almstrup K, Johannsen TH. The application of principal component analysis on clinical and biochemical parameters exemplified in children with congenital adrenal hyperplasia. Front Endocrinol. 2021;12:652888.
33 Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, et al. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci. 2010 Apr 14;30(15):5368–75.
34 Kaiser HF. An index of factorial simplicity. Psychometrika. 1974 Mar 01;39(1):31–6.
35 Kanayama G, Kean J, Hudson JI, Pope HG Jr. Cognitive deficits in long-term anabolic-androgenic steroid users. Drug Alcohol Depend. 2013 Jun 1;130(1–3):208–14.
36 Bjørnebekk A, Westlye LT, Walhovd KB, Jørstad ML, Sundseth ØØ, Fjell AM. Cognitive performance and structural brain correlates in long-term anabolic-androgenic steroid exposed and nonexposed weightlifters. Neuropsychology. 2019 May;33(4):547–59.
37 Scarth M, Bjørnebekk A. Androgen abuse and the brain. Curr Opin Endocrinol Diabetes Obes. 2021 Dec 1;28(6):604–14.
38 Bertozzi G, Salerno M, Pomara C, Sessa F. Neuropsychiatric and behavioral involvement in AAS abusers. A literature review. Medicina. 2019 Jul 22;55(7):396.
39 Pluchino N, Russo M, Santoro AN, Litta P, Cela V, Genazzani AR. Steroid hormones and BDNF. Neuroscience. 2013 Jun 3;239:271–9.
40 Fuss J, Hellweg R, Van Caenegem E, Briken P, Stalla GK, T'Sjoen G, et al. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). Eur Neuropsychopharmacol. 2015 Jan;25(1):95–9.
41 Onakomaiya MM, Porter DM, Oberlander JG, Henderson LP. Sex and exercise interact to alter the expression of anabolic androgenic steroid-induced anxiety-like behaviors in the mouse. Horm Behav. 2014 Jul;66(2):283–97,
42 Shankara-Narayana N, Brooker L, Goebel C, Speers N, Handelsman DJ. Reliability of drug history to verify androgen abuse in men. J Clin Endocrinol Metab. 2022 Aug 18;107(9): e3790–96.
43 Shankara-Narayana N, Yu C, Savkovic S, Desai R, Fennell C, Turner L, et al. Rate and extent of recovery from reproductive and cardiac dysfunction due to androgen abuse in men. J Clin Endocrinol Metab. 2020 Jun 1; 105(6):dgz324.
44 Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metabo. 1981 Jul;53(1):58–68.
45 Conner JM, Yan Q, Varon S. Distribution of brain-derived neurotrophic factor in the rat pituitary gland. Neuroreport. 1996 Aug 12; 7(12):1937–40.
46 Sohrabji F, Lewis DK. Estrogen-BDNF interactions: implications for neurodegenerative diseases. Front Neuroendocrinol. 2006 Dec; 27(4):404–14.
47 Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, Egan JM, et al. Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS One. 2010 Apr 9;5(4):e10099.

48 de Ronde W, Smit DL. Anabolic androgenic steroid abuse in young males. Endocr Connect. 2020 Apr;9(4):R102–11.
49 Janne OA, Palvimo JJ, Kallio P, Mehto M. Androgen receptor and mechanism of androgen action. Ann Med. 1993 Feb;25(1):83–9.
50 Ottem EN, Beck LA, Jordan CL, Breedlove SM. Androgen-dependent regulation of brain-derived neurotrophic factor and tyrosine kinase B in the sexually dimorphic spinal nucleus of the bulbocavernosus. Endocrinology. 2007 Aug;148(8):3655–65.
51 Verhovshek T, Cai Y, Osborne MC, Sengelaub DR. Androgen regulates brain-derived neurotrophic factor in spinal motoneurons and their target musculature. Endocrinology. 2010 Jan;151(1):253–61.
52 Verhovshek T, Rudolph LM, Sengelaub DR. Brain-derived neurotrophic factor and androgen interactions in spinal neuromuscular systems. Neuroscience. 2013 Jun 3;239:103–14.
53 Hutchison JB. Gender-specific steroid metabolism in neural differentiation. Cell Mol Neurobiol. 1997 Dec;17(6):603–26.
54 Ivanova T, Kuppers E, Engele J, Beyer C. Estrogen stimulates brain-derived neurotrophic factor expression in embryonic mouse midbrain neurons through a membrane-mediated and calcium-dependent mechanism. J Neurosci Res. 2001 Oct 15;66(2):221–30.
55 Baumgartner NE, Black KL, McQuillen SM, Daniel JM. Previous estradiol treatment during midlife maintains transcriptional regulation of memory-related proteins by ERα in the hippocampus in a rat model of menopause. Neurobiol Aging. 2021 Sep;105:365–73.
56 Gross KS, Alf RL, Polzin TR, Frick KM. 17β-estradiol activation of dorsal hippocampal TrkB is independent of increased mature BDNF expression and is required for enhanced memory consolidation in female mice. Psychoneuroendocrinology. 2021 Mar;125:105110.
57 Sohrabji F, Miranda RC, Toran-Allerand CD. Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. Proc Natl Acad Sci USA. 1995 Nov 21;92(24):11110–4.
58 Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006 Jun 15;59(12):1116–27.
59 Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol. 2010 Feb;298(2):R372–7.
60 Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA. 2011 Feb 15;108(7):3017–22.
61 Antunes BM, Rossi FE, Teixeira AM, Lira FS. Short-time high-intensity exercise increases peripheral BDNF in a physical fitness-dependent way in healthy men. Eur J Sport Sci. 2020 Feb;20(1):43–50.
62 Daly RM, Gianoudis J, Prosser M, Kidgell D, Ellis KA, O'Connell S, et al. The effects of a protein enriched diet with lean red meat combined with a multi-modal exercise program on muscle and cognitive health and function in older adults: study protocol for a randomised controlled trial. Trials. 2015 Aug 8;16:339.
63 Walsh JJ, Scribbans TD, Bentley RF, Kellawan JM, Gurd B, Tschakovsky ME. Neurotrophic growth factor responses to lower body resistance training in older adults. Appl Physiol Nutr Metab. 2016 Mar;41(3):315–23.
64 Forti LN, Van Roie E, Njemini R, Coudyzer W, Beyer I, Delecluse C, et al. Dose-and gender-specific effects of resistance training on circulating levels of brain derived neurotrophic factor (BDNF) in community-dwelling older adults. Exp Gerontol. 2015 Oct;70:144–9.
65 Hakkinen K, Pakarinen A, Alen M, Kauhanen H, Komi PV. Relationships between training volume, physical performance capacity, and serum hormone concentrations during prolonged training in elite weight lifters. Int J Sports Med. 1987 Mar;8(Suppl 1):61–5.
66 Yamamoto H, Gurney ME. Human platelets contain brain-derived neurotrophic factor. J Neurosci. 1990 Nov;10(11):3469–78.
67 Blair P, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. Blood Rev. 2009 Jul;23(4):177–89.
68 Rosca AE, Vladareanu AM, Mititelu A, Popescu BO, Badiu C, Caruntu C, et al. Effects of exogenous androgens on platelet activity and their thrombogenic potential in supraphysiological administration: a literature review. J Clin Med. 2021 Jan 4;10(1):147.
69 Tamura S, Suzuki H, Hirowatari Y, Hatase M, Nagasawa A, Matsuno K, et al. Release reaction of brain-derived neurotrophic factor (BDNF) through PAR1 activation and its two distinct pools in human platelets. Thromb Res. 2011 Nov;128(5):e55–61.
70 Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, et al. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost. 2002 Apr;87(4):728–34.
71 Le Blanc J, Fleury S, Boukhatem I, Belanger JC, Welman M, Lordkipanidze M. Platelets selectively regulate the release of BDNF, but not that of its precursor protein, proBDNF. Front Immunol. 2020;11:575607.
72 Khetawat G, Faraday N, Nealen ML, Vijayan KV, Bolton E, Noga SJ, et al. Human megakaryocytes and platelets contain the estrogen receptor beta and androgen receptor (AR): testosterone regulates AR expression. Blood. 2000 Apr 1;95(7):2289–96.
73 Bjørnebekk A, Scarth M, Neupane SP, Westlye LT, Thorsby PM, Halvorsen B. Anabolic androgenic steroid use is associated with reduced brain derived neurotrophic factor in male weightlifters. PsyArXiv. 2022 March 16:2.