Article

Pilot Associations between Adverse Childhood Experiences, Executive Function, and Brain-Derived Neurotrophic Factor (BDNF) among Adults with Excess Adiposity

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Abstract: Adverse childhood experiences (ACEs) may predict markers of neurocognitive performance (i.e., executive function; EF) and brain health/plasticity (i.e., brain-derived neurotrophic factor; BDNF). This pilot examined: (1) ACES history and current EF performance, (2) ACEs history and current BDNF levels, and (3) current EF performance and BDNF levels. We hypothesized that higher ACEs would be associated with lower EF scores and that these patterns would be associated with serum BDNF levels. Given the pilot nature of the study, emphasis was placed on effect size vs. significance. Participants were 37 middle-aged women. Higher ACEs were not directly associated with EF scores (β = 0.08, p = 0.635) but showed potentially meaningful negative beta coefficients with proBDNF levels (β = -0.22, p = 0.200) and positive coefficients with mature BDNF (β = 0.28, p = 0.094). EF scores and proBDNF showed a positive relationship that did not reach significance (r = 0.28, p = 0.100) similar to EF scores and mature BDNF (r = 0.14, p = 0.406). In a modest pilot sample of middle-aged women with excess weight, higher ACEs were potentially associated with lower proBDNF and higher mature BDNF. Larger follow-up studies are warranted given the size of the detected coefficients and theoretical implications of ACEs and obesity as neurocognitively toxic for brain health and performance.

Keywords: cognitive function; obesity; overweight; adverse childhood experiences; early life adversity; neurotrophins; neurotrophic factor

1. Introduction

Adverse childhood experiences (ACEs) and obesity are two interrelated and highly prevalent predictors of negative biopsychosocial health outcomes, including relative neurocognitive deficits. ACEs impact an estimated 64% of adults (≥1 ACE) and include traumatic events such as abuse and neglect. Like ACEs, excess adiposity is also widespread among adults, with 72% of adults aged 20 or older qualifying as overweight or obese [1]. Meta-analyses indicate that persons with childhood maltreatment are 1.4 times more likely to develop obesity [2] and that the risk follows a dose-response relationship [3]. ACEs and obesity also show a dose-response effect on health, such that the risk of multiple adverse outcomes increases in a graded fashion as a person’s ACE score and/or obesity levels increases. Such increases may result in neurocognitive injury via various sources, including cognitive deprivation (e.g., in the case of neglect) [4], dysregulation of the body’s stress regulative systems [5], and inflammation [6].
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ACEs and obesity are linked to one another, and both appear to impact brain and neurocognitive health independently. Accordingly, indicators of neurocognitive function and brain health (e.g., neuropsychological performance, neurotrophins, white matter integrity, etc.) should be examined in an effort to understand the implications of ACEs history on adult obesity status. One such neurocognitive domain that appears to be highly impactful for obesity onset and progression is executive function (EF), a performance domain of fluid cognition. EF is a subdomain of neurocognition that typically includes the following cognitive abilities: inhibitory control, cognitive flexibility, and working memory. These EF skills are essential for the planning, organizing, problem-solving, initiation, self-monitoring, and inhibition behaviors critical for implementing complex goal-directed behaviors, such as obesity prevention or treatment in an obesogenic environment. Unfortunately, the biologic substrates and candidate mechanisms that characterize high ACEs and fluid cognition or lower EF in obesity are unclear. One possible candidate is neurotrophic factors, such as brain-derived neurotrophic factors (BDNF) [15–18].

BDNF is part of the family of growth factors that also includes the nerve growth factor, neurotrophin-3, and neurotrophin-4/5 [19]. BDNF is synthesized in the cell as a precursor molecule pro-BDNF and later converted into mature BDNF [20]. Indeed, BDNF is the only neurotrophin secreted in an activity-dependent manner which has been shown to be critical for hippocampus-dependent memory in humans [21] and potentially ET. Both BNDF isoforms are biologically active, and some speculation is around their different functional role; therefore, the need to identify which of the BDNF isoforms are related to the ET in the sample of our study [22,23]. BDNF has a long history of being associated with adverse mental health conditions, such as depression. This factor [24] is of most interest to the current study given that its serum/plasma levels, as well as certain BDNF genetic variants (e.g., Val66Met polymorphism rs6265 [25], T-allele carriers for variant rs10767664 [26]), have also been implicated in hippocampal size, memory recovery [21] and the hypothalamic melanocortin pathways that control body weight and response to weight loss interventions and, thus, BDNF likely contribute to functions that control eating, drinking, body weight, and changes to insulin parameters [26–29]. BDNF also changes in response to exercise and/or energy expenditure [30], and lower serum levels have been linked to sedentary behaviors like higher television screen time [31].

In addition to its links with metabolic/energy indicators, BDNF levels may also be useful as indicators of cognitive impairment in young, otherwise healthy adults with obesity [18]. Thus, BDNF may be critical to obesity and its behavioral concomitants via neurocognitive pathways—though it should be noted that null findings for BDNF-obesity relationships have also been reported in the literature [32]. These patterns—if present—may be especially important given previous evidence that higher ACEs have also been linked to lower levels of BDNF in various samples [15–17]. It seems possible that the cognitive and brain alternations observed in individuals with ACEs, obesity, or both may be linked to disruptions in BDNF. However, the relationships between ACEs history and markers of cognitive performance and brain health in individuals with excess weight have not been widely examined. Accordingly, the present study will clarify and advance the science of ACEs and obesity by simultaneously examining the relationships between (1) ACEs history and current EF, (2) ACEs history and current BDNF isoform, and (3) EF and BDNF in a sample with overweight/obesity. This pilot will test if the adverse effects of ACEs are detectable using EF performance and a neurotrophic marker in a preliminary.
sample of women with excess weight. Such results may point to valuable targets in the shared neurobiological pathways by which ACEs contribute to future obesity. We hypothesized that higher ACEs would be meaningfully associated with lower EF scores. We also hypothesized that higher ACEs and lower EF scores would be meaningfully associated with serum BNDF levels but made no a priori hypotheses about the direction of the associations, given mixed findings in the literature.

2. Materials and Methods

2.1. Participants

Participants (n = 37) were English-speaking women with overweight or obesity (BMI ≥ 25) with no significant medical or psychiatric comorbidities who were seeking weight loss treatment. Exclusion criteria included: (1) not using weight loss medications or participating in a weight loss program, (2) not pregnant or breastfeeding, (3) no history of bariatric surgery, (4) not participated in vigorous exercise in the past 24 h, and (5) not taken any anti-inflammatory medications in the past 24 h. These criteria were included given that these behaviors or conditions may be associated with cognitive function or BDNF levels [33]. See Table 1 for participant characteristics. Basic clinical variables are included in Table 1 as indicators of the health of the sample: fasting glucose, blood pressure, C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and cortisol.

Table 1. Participant Demographics, Clinically Relevant Biomarkers, and Key Study Variables (n = 37).

| Demographics          | Mean (SD), n (%)          |
|-----------------------|--------------------------|
| Age (years)           | 31.7 (7.933), 26 (70.3%) white |
| Race/ethnicity        | 11 (29.7%) Other/more than one race, 34 (91.9%) Non-Hispanic, 3 (8.1%) Hispanic/Latino/a, 12 (32.4%) Some college/associate’s degree |
| Highest level of education | 16 (43.2%) Bachelor’s degree, 6 (16.2%) Master’s degree, 3 (8.1%) Professional degree, 3 (8.1%) < High school graduate, 9 (24.3%) High school graduate |
| Mother’s highest level of education | 9 (24.3%) Some college/associate’s degree, 9 (24.3%) Bachelor’s degree, 5 (13.5%) Master’s degree, 2 (5.4%) Professional degree |

| Clinical Biomarkers   | Mean (SD), n (%)          |
|-----------------------|--------------------------|
| Fasting glucose (mg/dL) | 97.0 (29.9)              |
| Systolic blood pressure (mmHg) | 110.9 (16.2)           |
| Diastolic blood pressure (mmHg) | 74.0 (12.7)            |
| C-reactive protein (CRP)  | 5.2 (5.8)               |
| Interleukin-6 (IL-6)  | 0.5 (0.4)                |
| Tumor necrosis factor-alpha (TNF-α) | 2.4 (1.6)            |
| Cortisol (mcg/L)      | 10.4 (5.1)               |

| Key Study Variables   | Mean (SD), n (%)          |
|-----------------------|--------------------------|
| BMI (kg/m²)           | 32.54 (6.3)              |
| Body fat (%)          | 42.78 (5.5)              |
| Total ACE score (1–10) | 2.24 (1.98)              |
| Fluid cognition/executive function T-score | 49.38 (12.58) |
| MatureBDNF pre-task (ng/mL) | 24.22 (5.08)            |
| ProBDNF pre-task (ng/mL)  | 1.48 (4.37)              |
2.2. Measures

2.2.1. ACES

Participants completed the ACES checklist, which included 10 different adverse events that may have occurred before the age of 18 [34]. Adverse events include abuse (physical, emotional, and sexual), neglect (physical and emotional), and household dysfunction, which includes having a household member with a substance use or psychological disorder, having a household member incarcerated, having a mother treated violently, and having divorced parents.

2.2.2. Executive Function

Participants completed a portion of the NIH Toolbox-Cognition Battery (NIHTB-CB) [35]. This NIHTB-CB is a neuropsychological battery delivered via iPad that assesses multiple cognitive domains, including executive function, attention, speed, and/or fluid cognition subscales. The NIHTB-CB was created by the NIH and is normed for participants aged 3 to 85 years and was chosen because it is valid, time- and cost-efficient, and allows researchers to compare results across existing NIHTB-CB studies. All tests in the battery have been validated against gold-standard instruments and normed for use in the age range in the current study [35]. The specific tests chosen for the present investigation were Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, List Sorting Working Memory Test, Pattern Comparison Processing Speed Test, and Picture Sequence Memory. This battery takes approximately 25 min to administer. A fluid cognition $T$-score composite ($M = 50$, $SD = 10$) was generated by compiling scores from the aforementioned tests and correcting for age and gender.

2.2.3. Brain-Derived Neurotrophic Factor (BDNF)

Participants provided a fasted blood sample when they arrived in the lab for their baseline assessment. Whole blood was collected via venipuncture into vacutainer tubes to obtain serum per tube manufacturer instructions. Serum was aliquoted and stored in a $-80^\circ$ C freezer until time of assay. Serum levels of pro- and mature peripheral BDNF (proBDNF and mBDNF, respectively) were analyzed using Biosensis (catalog# BEK2241) [36] human ELISA kits. Cortisol was analyzed using human ELISA kits from R&D Systems. BDNF and cortisol plates were read on a Bio-Rad iMark plate reader. Serum samples were analyzed for levels of CRP, TNFα, and IL-6 using Meso Scale Discovery (MSD) V-PLEX kits and a MESO QuickPlex SQ 120 instrument. Samples were analyzed in duplicate according to the manufacturer’s instructions.

2.3. Procedure

Participants were recruited locally through the university and community by online/phone screenings. Eligible participants interested in enrolling provided written informed consent. All procedures were approved by the university’s IRB and adhered to APA ethical guidelines. Demographic variables, ACES, and eligibility criteria (e.g., medical and psychiatric comorbidities, BMI) were assessed via online surveys. At the start of the baseline assessment, a trained phlebotomist took a fasted blood draw between approximately 8 and 8:30 am. Then, neurocognitive testing was administered by trained research staff. Participants received USD 60 reimbursement for completing the visit.

2.4. Data Analysis

First, bivariate associations were run for each key study variable and demographic factors. Then, EF variables (i.e., fluid cognition composite) were regressed on ACES. Next, BDNF variables (i.e., proBDNF and mBDNF) were regressed on ACES. Finally, the BDNF variables were regressed on EF variables. Analyses were run using SPSS (Version 26.0, IBM Corp, 2017) and adjusted for BMI, given that our cognitive composite was already corrected for age and gender.
3. Results

Bivariate correlations between all key study variables are presented in Table 2. The variables that were most strongly associated were age and mBDNF, with higher age significantly associated with higher mBDNF level at a strong effect size magnitude ($r = 0.54$, $p = 0.001$). The next strongest associations were the small-to-medium effects observed between both BDNF variables and ACEs ($rs = −0.22$ to $0.26$) or the EF fluid cognition composite ($rs = 0.20$ to $0.26$). BMI also showed a small-to-medium association with mBDNF ($r = 0.21$).

Table 2. Bivariate Correlations of Key Study Variables.

|   | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Age | - | - | - | - | - |
| 2. BMI | 0.17 | - | - | - | - |
| 3. ACES | 0.17 | -0.09 | - | - | - |
| 4. Fluid cognition/executive function | 0.15 | 0.15 | 0.09 | - | - |
| 5. proBDNF | 0.17 | 0.07 | -0.22 | 0.26 | - |
| 6. Mature BDNF | 0.54 ** | 0.21 † | 0.26 † | 0.20 † | 0.19 |

Note. BMI = body mass index; ACES = Adverse Childhood Experiences Scale; ** $p < 0.001$. * Fluid cognition/executive function is a composite variable of Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, List Sorting Working Memory Test, Pattern Comparison Processing Speed Test, and Picture Sequence Memory. † Meaningful effect size $\geq 0.20$ (small-to-medium).

3.1. ACEs and Executive Function

Regressions adjusting for BMI showed that higher levels of ACEs were not directly associated with overall EF fluid cognition composite scores ($\beta = 0.08$, $p = 0.635$), suggesting that the effect size between adversity in childhood and adult EF scores was not substantial in the present pilot sample with excess adiposity.

3.2. ACEs and BDNF

ACES did show a meaningful negative effect with non-significant but trending $p$-values for proBDNF levels ($\beta = −0.22$, $p = 0.200$) and a meaningful positive effect with similar significance levels for mBDNF levels ($\beta = 0.28$, $p = 0.094$) adjusting for BMI. Figure 1 shows the levels of the pro- and mature BDNF across the different levels of ACE exposure (low = 0, medium = 1–2 ACEs, and high = 3+ ACEs) to show a potential dose-response pattern for these variables. These findings suggest that adversity in childhood may have small-to-moderate and opposing effects on two measures of brain health in adulthood in the present pilot sample over and above any effects of weight status. Such associations might reach significance in a well-powered sample.

Figure 1. Levels of pro− and mature BDNF across ACEs levels.
3.3. Executive Function and BDNF

EF fluid cognition composite scores showed a meaningful positive coefficient that did not reach significance with proBDNF ($\beta = 0.28, p = 0.100$). EF fluid cognition scores showed a smaller positive coefficient that did not reach significance with mBDNF ($\beta = 0.14, p = 0.406$). Again, the magnitude of these effects for proBDNF, especially, could suggest that they may also be detectable and reach significance in a larger sample, suggesting additional study is needed.

4. Discussion

The present study advanced the science of ACEs and obesity by simultaneously examining the relationships between ACEs, EF, and BDNF in a pilot sample of women with excess weight and adjusting for weight status. Our first hypothesis that higher ACEs would be associated with poorer EF scores was not supported, as the effect sizes between these variables were not substantive in this sample. This lack of association contrasts with prior literature, showing that higher ACEs are linked to poorer function on EF indices [37,38] and could be due to the restricted range in the EF variable in the present sample and/or the fact that the entire sample exhibited excess adiposity. Specifically, prior work from our laboratory and others has shown that samples with obesity have relatively lower EF performance, especially in the domain of inhibitory control [37,38].

Our hypothesis that higher ACEs would be associated with BDNF levels was supported—in a nuanced pattern—depending on whether examining mature BDNF or its precursor proBDNF. The mature form of BDNF is synthesized from a precursor protein (i.e., proBDNF), which serves different functions than its mature counterpart [20,39,40]. Notably, in this pilot sample, higher ACE levels exhibited negative associations with proBDNF levels but positive associations with mature BDNF, possibly in a dose-response manner for both. This pattern is consistent with previous work in animal models of depression or chronic social defeat. In said animal models, the expression of proBDNF was reduced, but that of mature BDNF was enhanced in brain regions in the reward circuit, such as the nucleus accumbens and amygdala [41]. These seemingly opposing effects make sense in light of the “yin-yang hypothesis” in which BDNF and its precursor cause opposite biological cascades [40].

Specifically, proBDNF is known for its role in synaptic pruning, apoptosis, and promotion of long-term depression (LTD) (i.e., a decrease in synaptic strength), whereas mature BDNF stabilizes neural terminals, signals the receptor tyrosine kinase TrkB, and is essential for early phase long-term potentiation (LTP) (i.e., an increase in synaptic strength) [20]. Thus, our results, if replicated in larger samples, could suggest that individuals with greater adversity in early life might experience higher levels of BDNF as a response to chronic stress. BDNF expression plays a critical role in resilience to chronic stress and is highly...
dependent on corticosterone secretion [42]. Thus, our study’s “see-saw” tendency of pro-
and matureBDNF levels can represent an adaptative response to previous exposure to
ACES. Such a pattern in the context of obesity may help elucidate parallel alterations
in reward pathways that contribute to an inability to resist palatable foods and/or be
hypersensitive to their appetitive properties (e.g., “brake” dysfunction in the context of
a sensitive “accelerator”). It should be noted that these BDNF patterns observed in the
reward circuit may not be the same as those found for hippocampal or prefrontal cortex
brain regions, in which BDNF has been found to be consistently lower [43], and that the
present pilot study cannot disentangle whether the pro- and mature BDNF level observed
are driven by alternations in specific brain regions, as the study variables were derived
from peripheral serum levels of pro- and mature BDNF.

Notably, proBDNF also showed a potentially small, positive relationship with per-
formance on neurocognitive tests of fluid cognition. This finding is consistent with those
of Katuri et al. (2021), who also found that lower serum BDNF levels were related to
multiple markers of greater cognitive decline in a sample with obesity, including several
markers of sustained attention, reaction time, and working memory [18]. Our finding is
also interesting in that fluid cognition (and executive function) encapsulates the ability
to inhibit so that higher scores can indicate greater inhibitory control. If this finding is
replicated and is shown to be significant in a larger sample, it could indicate that the ability
to perform well on tasks of inhibition might be paralleled by the brain’s levels of a peptide
that has a role in inhibiting synaptic strength.

Although the current brief report and pilot study illuminates some interesting potential
pathways linking ACEs with markers of brain health and plasticity in a sample with excess
weight, their preliminary and pilot nature requires additional, more extensive studies to
clarify the role of BDNF in early life adversity and obesity. Additionally, our study is
primarily middle-aged women with excess adiposity, so these patterns may not generalize
to younger, older, or other-gendered or weight status populations. Lastly, it would be
helpful to prospectively collect data on these topics to clarify the role of weight change
on observed associations. Although we controlled for BMI in the present analyses, being
able to track weight fluctuations over time and their relations to ACEs history and BDNF
expression will be a critical next step.

In conclusion, the current pilot results encourage the following specific recommen-
dations for future work. First, larger follow-up studies in more powered and diverse
samples over time are warranted to explore the relationship between ACEs, neurocog-
nitive performance indicators, and neurotrophic levels. Second, the size and opposing
directions of the detected coefficients for mature BDNF versus its precursor also call for
a nuanced analysis of this biomarker of brain health and plasticity. Failure to examine
mature vs. proBDNF levels may help explain inconsistencies in the literature. Third, the
potential differential patterns of BDNF response across hippocampal versus reward regions
need further explication in the context of weight status. If replicated and extended, the
current implications could be that ACEs are neurocognitively toxic for brain health and
performance in a manner associated with obesity.

Author Contributions: Conceptualization, M.A.W.H.; methodology, C.E.T., C.T., T.K.T., M.A.W.H.
and M.E.S.; software, M.E.S.; validation, C.E.T., M.A.W.H. and A.R.M.; formal analysis, M.E.S.;
resources, T.K.T. and L.W.; data curation, C.E.T. and M.E.S.; writing—original draft preparation,
M.A.W.H., C.E.T. and M.E.S.; writing—review and editing, C.E.T., M.E.S., A.R.M., L.W., D.V.S.,
C.T., T.K.T. and M.A.W.H.; supervision, M.A.W.H. and T.K.T. All authors have read and agreed to
the published version of the manuscript.

Funding: This project was supported via pilot funding through the Center for Integrated Research
on Child Adversity (CIRCA) and the National Institute of General Medical Sciences (NIGMS) of the
National Institutes of Health (P20GM109097) awarded to Hawkins. Hawkins was also supported via
a Career Development Award by the National Institute of Diabetes and Digestive and Kidney Disease
(K23DK103941). Tsotsoros was supported via the National Institute on Aging (NIA) of the National
Institute of Health (R36AG072342). The funding sources had no role in the design and conduct of
the study: collection, management, analysis, and interpretation of the data; preparation, review, or approval of the paper; and decision to submit the paper for publication.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Oklahoma State University (parent protocol code AS-19-65, approved on 14 June 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets analyzed for this study can be accessed by contacting the corresponding author.

Acknowledgments: The authors thank all the research participants and wish to acknowledge the contributions of Brenda Davis and Ashlee Taylor from the Oklahoma University Integrative Immunology Center toward analyzing the study blood samples.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Center for Disease Control National Center for Health Statistics. Overweight and Obesity. 3 May 2017–11 December 2018. Available online: https://www.cdc.gov/nchs/fastats/obesity-overweight.htm (accessed on 1 January 2020).

2. Danese, A.; Tan, M. Childhood maltreatment and obesity: Systematic review and meta-analysis. Mol. Psychiatry 2014, 19, 544. [CrossRef] [PubMed]

3. Hemmingsson, E.; Johansson, K.; Reynisdottir, S. Effects of childhood abuse on adult obesity: A systematic review and meta-analysis. Obes. Rev. 2014, 15, 882–893. [CrossRef] [PubMed]

4. Merz, E.C.; Noble, K.G. Neural Development in Context: Differences in Neural Structure and Function Associated with Adverse Childhood Experiences. In The Wiley Handbook of Early Childhood Development Programs, Practices, and Policies; Wiley: Hoboken, NJ, USA, 2017; pp. 135–160.

5. Shonkoff, J.P.; Garner, A.S.; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012, 129, e232–e246. [CrossRef] [PubMed]

6. Miller, A.A.; Spencer, S.J. Obesity and neuroinflammation: A pathway to cognitive impairment. Brain Behav. Immun. 2014, 42, 10–21. [CrossRef] [PubMed]

7. Kellar, D.; Craft, S. Brain insulin resistance in Alzheimer’s disease and related disorders: Mechanisms and therapeutic approaches. Lancet Neurol. 2020, 19, 758–766. [CrossRef]

8. Carvalho, J.C.N.; Donat, J.C.; Brunnet, A.E.; Silva, T.G.; Silva, G.R.; Kristensen, C. Cognitive, Neurobiological and Psychopathological Alterations Associated with Child Maltreatment: A Review of Systematic Reviews. Child Indic. Res. 2015, 9, 389–406. [CrossRef]

9. Irigaray, T.; Pacheco, J.B.; Grassi-Oliveira, R.; Fonseca, R.P.; Leite, J.C.D.C.; Kristensen, C.H. Child maltreatment and later cognitive functioning: A systematic review. Psicol. Reflex. Crit. 2013, 26, 376–387. [CrossRef]

10. Sylvestre, A.; Bussieres, E.-L.; Bouchard, C. Language problems among abused and neglected children: A meta-analytic review. Child Maltreatment 2016, 21, 47–58. [CrossRef] [PubMed]

11. Smith, L.; Toussaint, L.; Micoli, A.; Lynch, B. Obesity, putative biological mediators, and cognitive function in a national sample of children and adolescents. Prev. Med. 2021, 150, 106659. [CrossRef] [PubMed]

12. Prickett, C.; Brennan, L.; Stolwyk, R. Examining the relationship between obesity and cognitive function: A systematic literature review. Obes. Res. Clin. Pract. 2015, 9, 93–113. [CrossRef] [PubMed]

13. Lee, C.M.; Woodward, M.; Batty, G.D.; Beiser, A.S.; Bell, S.; Berr, C.; Bjertness, E.; Chalmers, J.; Clarke, R.; Dartigues, J.-F.; et al. Association of anthropometry and weight change with risk of dementia and its major subtypes: A meta-analysis consisting 2.8 million adults with 57,294 cases of dementia. Obes. Rev. 2020, 21, e12989. [CrossRef] [PubMed]

14. Qu, Y.; Hu, H.-Y.; Ou, Y.-N.; Shen, X.-N.; Xu, W.; Wang, Z.-T.; Dong, Q.; Tan, L.; Yu, J.-T. Association of body mass index with risk of cognitive impairment and dementia: A systematic review and meta-analysis of prospective studies. Neurosci. Biobehav. Rev. 2020, 115, 189–198. [CrossRef] [PubMed]

15. Şimşek, Y.; Yüksel, T.; Kaplan, I.; Uysal, C.; Alaca, R. Examining the levels of BDNF and cortisol in children and adolescent victims of sexual abuse—A preliminary study. Compr. Psychiatry 2015, 61, 23–27. [CrossRef] [PubMed]

16. de Castro Bins, H.D.; Panichi, R.M.D.; Taborda, J.G.V.; Ferrão, Y.A. Childhood trauma, psychiatric disorders, and criminality in women: Associations with serum levels of brain-derived neurotrophic factor. Int. J. Law Psychiatry 2020, 71, 101574. [CrossRef] [PubMed]

17. Soares, S.; Rocha, V.; Kelly-Irving, M.; Stringhini, S.; Fraga, S. Adverse Childhood Events and Health Biomarkers: A Systematic Review. Front. Public Health 2021, 9, 649825. [CrossRef]

18. Katuri, R.B.; Gaur, G.S.; Sahoo, J.P.; Bobby, Z.; Shannagavel, K. Association of Circulating Brain-Derived Neurotrophic Factor with Cognition among Adult Obese Population. J. Obes. Metab. Syndr. 2021, 30, 163–172. [CrossRef] [PubMed]
19. de Assis, G.G.; de Almondes, K.M. Exercise-dependent BDNF as a modulatory factor for the executive processing of individuals in course of cognitive decline. A systematic review. Front. Psychol. 2017, 8, 584. [CrossRef] [PubMed]

20. Je, H.S.; Yang, E.; Ji, Y.; Nagappan, G.; Hempstead, B.L.; Lu, B. Role of pro-brain-derived neurotrophic factor (proBDNF) to mature BDNF conversion in activity-dependent competition during developing neuromuscular synapses. Proc. Natl. Acad. Sci. USA 2012, 109, 15924–15929. [CrossRef]

21. Egan, M.F.; Kojima, M.; Callicott, J.H.; Goldberg, T.E.; Kolachana, B.S.; Bertolino, A.; Zaitsev, E.; Gold, B.; Goldman, D.; Dean, M.; et al. The BDNF val66met Polymorphism Affects Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function. Cell 2003, 112, 257–269. [CrossRef]

22. Huang, E.J.; Reichardt, L.F. Neurotrophins: Roles in Neuronal Development and Function. Annu. Rev. Neurosci. 2001, 24, 677–736. [CrossRef]

23. Massague, J. The transforming growth factor-beta family. Annu. Rev. Cell Biol. 1990, 6, 597–641. [CrossRef] [PubMed]

24. Jin, Y.; Sun, L.H.; Yang, W.; Cui, R.J.; Xu, S.B. The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disorders. Front. Neurosci. 2019, 10, 515. [CrossRef] [PubMed]

25. Martinez-Esquero, J.D.; Rendon-Macias, M.E.; Zamora-Mendoza, G.; Serrano-Meneses, J.; Rosales-Rodriguez, B.; Escalante-Bautista, D.; Rodriguez-Cruz, M.; Sánchez-González, R.; Arellano-Pineda, Y.; López-Alarçon, M.; et al. Association Between the Brain-derived Neurotrophic Factor Val66Met Polymorphism and Overweight/Obesity in Pediatric Population. Arch. Med. Res. 2017, 48, 599–608. [CrossRef]

26. Primo, D.; Izaola, O.; Lopez, J.J.; de Luis, A.A. Brain derived neurotrophic factor (BDNF) polymorphism rs 10,767,664 affects matur BDNF as punishment and reward signals for synapse elimination at mouse neuromuscular junctions. J. Neurosci. 2011, 31, 1944–1953. [PubMed]

27. Wisse, B.E.; Schwartz, M.W. The skinny on neurotrophins. Nat. Neurosci. 2003, 6, 655–656. [CrossRef]

28. Department of Health & Human Services. BDNF Gene. Lister Hill National Center for Biomedical Communications; 2018. Available online: https://ghr.nlm.nih.gov/gene/BDNF#resources (accessed on 1 January 2020).

29. Bathina, S.; Das, U.N. Brain-derived neurotrophic factor and its clinical implications. Arch. Med. Sci. 2015, 11, 1164–1178. [CrossRef]

30. Szuhany, K.L.; Bugatti, M.; Otto, M.W. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J. Psychiatr. Res. 2015, 60, 56–64. [CrossRef]

31. Goldfield, G.S.; Cameron, J.D.; Sigal, R.J.; Kenny, G.P.; Holcik, M.; Prud’Homme, D.; Guerin, E.; Alberga, A.S.; D’Angiulli, A.; Tremblay, M.S.; et al. Screen time is independently associated with serum brain-derived neurotrophic factor (BDNF) in youth with obesity. Appl. Physiol. Nutr. Metab. 2021, 46, 1083–1090. [CrossRef]

32. Sandrini, L.; Di Minno, A.; Amadio, P.; Ieraci, A.; Tremoli, E.; Barbieri, S.S. Association between Obesity and Circulating Brain-Derived Neurotrophic Factor (BDNF) Levels: Systematic Review of Literature and Meta-Analysis. Int. J. Mol. Sci. 2018, 19, 2281. [CrossRef]

33. Zhang, X.Y.; Chen, D.-C.; Tan, Y.-L.; Tan, S.-P.; Wang, Z.-R.; Yang, F.-D.; Xiu, M.-H.; Hui, L.; Lv, M.-H.; Zunta-Soares, G.B.; et al. Gender difference in association of cognition with BDNF in chronic schizophrenia. Psychoneuroendocrinology 2014, 48, 136–146. [CrossRef]

34. Felitti, V.J. The relationship of adult health status to childhood abuse and household dysfunction. Am. J. Prev. Med. 1998, 14, 245–258. [CrossRef]

35. Weintraub, S.; Dikmen, S.S.; Heaton, R.K.; Tulsky, D.S.; Zelazo, P.D.; Bauer, P.J.; Carlozzi, N.E.; Slotkin, J.; Blitz, D.; Wallner-Allen, K.; et al. Cognition assessment using the NIH Toolbox. Neurology 2013, 80, 554–564. [CrossRef] [PubMed]

36. Polacchini, A.; Metelli, G.; Francavilla, R.; Baj, G.; Florene, M.; Mascaretti, L.G.; Tongiorgi, E. A method for reproducible measurements of serum BDNF: Comparison of the performance of six commercial assays. Sci. Rep. 2015, 5, 17989. [CrossRef]

37. Lavagnino, L.; Di Minno, A.; Amadio, P.; Ieraci, A.; Tremoli, E.; Barbieri, S.S. Association between Obesity and Circulating Brain-Derived Neurotrophic Factor (BDNF) Levels: Systematic Review of Literature and Meta-Analysis. Int. J. Mol. Sci. 2018, 19, 2281. [CrossRef]

38. Hawkins, M.A.; Keirns, N.G.; Baraldí, A.; Layman, H.M.; Stout, M.E.; Smith, C.E.; Gunstad, J.; Hildebrand, D.A.; Vohs, K.D.; et al. Association Between the Brain-derived Neurotrophic Factor Val66Met Polymorphism and Overweight/Obesity in Pediatric Population. Arch. Med. Res. 2017, 48, 599–608. [CrossRef]

39. Polacchini, A.; Metelli, G.; Francavilla, R.; Baj, G.; Florene, M.; Mascaretti, L.G.; Tongiorgi, E. A method for reproducible measurements of serum BDNF: Comparison of the performance of six commercial assays. Sci. Rep. 2015, 5, 17989. [CrossRef] [PubMed]

40. Lu, B.; Pang, P.T.; Woo, N.H. The yin and yang of neurotrophin action. Nat. Rev. Neurosci. 2005, 6, 603–614. [CrossRef]

41. Qiao, H.; An, S.-C.; Xu, C.; Ma, X.-M. Role of proBDNF and BDNF in dendritic spine plasticity and depressive-like behaviors induced by an animal model of depression. Brain Res. 2017, 1663, 29–37. [CrossRef]

42. Taliz, D.; Loya, A.; Gersner, R.; Haramati, S.; Chen, A.; Zangen, A. Resilience to Chronic Stress Is Mediated by Hippocampal Brain-Derived Neurotrophic Factor. J. Neurosci. 2011, 31, 4475–4483. [CrossRef]

43. Sartorius, A.; Hellweg, R.; Litzke, J.; Vogt, M.; Dormann, C.; Vollmayr, B.; Danker-Hopfe, H.; Gass, P. Correlations and Discrepancies between Serum and Brain Tissue Levels of Neurotrophins after Electroconvulsive Treatment in Rats. Pharmacopsychiatry 2009, 42, 270–276. [CrossRef]