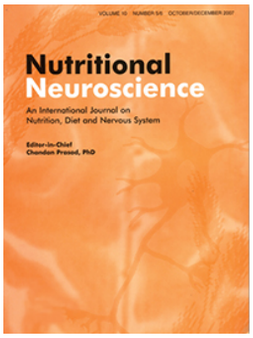

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# Evaluation of dietary intake in children and college students with and without attention-deficit/hyperactivity disorder

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**Objectives:** To evaluate dietary intake among individuals with and without attention-deficit hyperactivity disorder (ADHD), to evaluate the likelihood that those with ADHD have inadequate intakes.
**Methods:** Children, 7–12 years old, with ($n = 23$) and without ($n = 22$) ADHD, and college students, 18–25 years old, with ($n = 21$) and without ($n = 30$) ADHD comprised the samples. Children's dietary intake was assessed by a registered dietitian using 24-hour recalls over 3 days. College students kept a detailed food record over three days. Dietary information for both groups was entered into the Nutrition Data Systems for Research database, and output was analyzed using SAS 9.4. Nutrient analyses included the Healthy Eating Index-2010, Micronutrient Index (as a measure of overall micronutrient intake), and individual amino acids necessary for neurotransmission. Logistic regression was used to model the association of nutrient intake with ADHD. Models were adjusted for age, sex, IQ (or GPA), and energy intake (or total protein intake) as appropriate. Significance was evaluated at $P = 0.05$, and using the Benjamini–Hochberg corrected $P$-value for multiple comparisons.
**Results:** No evidence existed for reduced nutrient intake among those with ADHD compared to controls in either age group. Across both groups, inadequate intakes of vitamin D and potassium were reported in 95% of participants. Children largely met nutrient intake guidelines, while college students failed to meet these guidelines for nine nutrients. In regards to amino acid intake in children, an increased likelihood of having ADHD was associated with higher consumption of aspartate, OR = 12.61 ($P = 0.01$) and glycine OR = 11.60 ($P = 0.05$); and a reduced likelihood of ADHD with higher intakes of glutamate, OR = 0.34 ($P = 0.03$). Among young adults, none of the amino acids were significantly associated with ADHD, though glycine and tryptophan approached significance.
**Discussion:** Results fail to support the hypothesis that ADHD is driven solely by dietary micronutrient inadequacy. However, amino acids associated with neurotransmission, specifically those affecting glutamatergic neurotransmission, differed by ADHD status in children. Amino acids did not reliably vary among college students. Future larger scale studies are needed to further examine whether or not dietary intake of amino acids may be a modulating factor in ADHD.

**Keywords:** ADHD, Diet, Nutrition, Vitamin D, Amino acids, Neurotransmission, Aspartate, Glutamate, Glycine, Tryptophan, Tyrosine

## Introduction

Attention-deficit hyperactivity disorder (ADHD), characterized by heterogeneous combinations of inattention, impulsivity, and hyperactivity symptoms,[1] is one of the most commonly diagnosed childhood psychiatric disorders, with an estimated worldwide prevalence of 4–5%.[2,3] Although once considered only a childhood disorder, ADHD is now known to persist well into adulthood in a substantial portion of cases.[4] ADHD is associated with poor short- and long-term academic, social, and occupational outcomes,[5] in addition to poor health outcomes,[6] including an association with obesity in teenage girls and adults with ADHD.[7] In terms of etiology, ADHD is thought to involve both genetic liability as well as activating environmental effects, with gene × environment interaction effects likely.[8]

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One of the earliest and most enduring environmental factors theorized to be related to ADHD etiology is diet and nutrient intake.[9] More than 40 years ago, an American pediatric allergist, Dr Benjamin Feingold, suggested his patients' hyperactive and inattentive symptoms were associated with dietary intake of certain foods and additives.[10] Although subsequent studies called into question the effectiveness of this diet on hyperactivity,[11,12] double-blind placebo controlled studies conducted in the twenty-first century confirmed that artificial colors and preservatives contribute a small component to hyperactivity in children.[13,14] Furthermore, genetic polymorphisms on the histamine gene were identified as potentially moderating the effects of food additives on hyperactive behavior,[15] further supporting a causal effect. A meta-analysis of food additives in relation to ADHD suggests a statistically significant, albeit small, effect size of 0.18–0.29.[16]

Epidemiological[17] and randomized studies[18] have confirmed that diet plays a role in mood and neurological functioning. Certain dietary intake patterns, such as the Western Diet[19] or low adherence to a Mediterranean diet, are associated with ADHD symptoms.[20] These dietary-disorder associations may be bi-directional, in that those with ADHD may choose less healthy food options, or the diet itself may contribute to ADHD symptomology.[20] Furthermore, a nutrient-poor diet, both in terms of a pregnant mother's nutrient intake,[21,22] and a child's diet in infancy, may be a factor in ADHD symptomatology.[23]

Deficiencies in some individual nutrients are hypothesized to impact the expression and severity of ADHD symptoms based on their role in neurotransmission. In particular, zinc deficiency is associated with impaired attention and concentration in human and animal studies,[24] and restlessness in infants.[25] Zinc, an essential nutrient for more than 90 enzymes,[25] is involved in metabolic pathways relevant to ADHD. For example, zinc co-modulates neurotransmission of glutamate,[26] an excitatory neurotransmitter thought to be potentially dysregulated in ADHD. Iron deficiency is another putative factor in ADHD etiology, based on its role in the production and reuptake of monoamines such as dopamine and norepinephrine.[27,28] Iron-deficient animals have shown decreased dopamine receptor density.[29] In humans, the association is less clear. Lower serum ferritin levels (indicating less stored iron) have been observed in some children with ADHD relative to controls,[30] but not in all samples.[31]

Nutrient supplementation as a therapy for ADHD remains a controversial, yet promising area with emerging data. The research using single nutrient supplementation has yielded mixed or modest outcomes. In a double-blind study of zinc with 400 children, those receiving zinc demonstrated significant improvement in hyperactivity, impulsivity and peer relationships compared to placebo, although the placebo group improved as well.[32] In an open-label trial of iron in 14 boys with ADHD, parents, but not teachers, reported a significant decrease in children's ADHD ratings,[33] and among 23 children randomized to iron or placebo, only clinicians reported a decrease in ADHD symptoms in those taking iron.[34] Recently, supplementation with a broad spectrum micronutrient formula has yielded promising results in an open-label study and a randomized controlled trial (RCT) of adults with ADHD,[35,36] and in an open-label study with children.[37]

In addition to the examples of zinc and iron above, other individual micronutrients play an important supportive role for optimal neurotransmission. For example, vitamin B6 also serves as an essential cofactor in the production of these neurotransmitters, in addition to iron and vitamin C.[38] Vitamin B12 and folate are essential players in the interconnected cycles of methionine and folate that help keep tetrahydrobiopterin in its reduced state, providing the necessary cofactor (BH4) for the production of dopamine, epinephrine, and serotonin (see Fig. 3).[39] Magnesium also acts as an important blockade for the N-methyl-D-aspartate receptor (NMDA) glutamate receptor, helping to prevent excitotoxicity.[40] Thus, the intake of micronutrients may affect ADHD symptomatology through modulation of neurotransmission.

Other nutrients important for optimal neurotransmission are amino acids. Amino acids influence the production and function of multiple neurotransmitters, and as such, may be related to ADHD etiology. Disordered neurotransmission is suspected in ADHD, and includes potential dysregulation of the neurotransmitters dopamine and glutamate,[41] serotonin,[42] and possibly norepinephrine.[43] The production or function of these neurotransmitters could be affected by dietary intake of amino acids in two key ways: neurotransmitters are either produced from dietary amino acids, or are neurotransmitters themselves (see Fig. 3). For example, dopamine can be produced by the dietary amino acids tyrosine and phenylalanine (as a precursor to tyrosine), and dopamine can be further converted to the neurotransmitter norepinephrine.[44] Furthermore, brain dopamine levels have been shown to be reduced by depleting phenylalanine and tyrosine in animal diets.[45] Serotonin is produced from the dietary amino acid tryptophan, and is the precursor to melatonin.[46] Low serotonin may lead to reduced melatonin production, which could be a contributing factor in the common report of sleep problems in ADHD.[47] Similar to dopamine, tryptophan depletion has been associated with downregulated serotonergic neurotransmission[48] and ADHD symptoms.[49]

The amino acids glutamate, aspartate, and glycine have the ability to act as neurotransmitters themselves. Glutamate is the most ubiquitous excitatory neurotransmitter, with the ability to act on multiple types of receptors.[50] The amino acid, aspartate, shares a similar ability to stimulate neurons using one of the glutamate receptors, the NMDA receptor.[51] And lastly, glycine has the ability to act as a co-agonist of the NMDA receptor, causing excitatory neurotransmission, while also having its own inhibitory effects at the spinal cord.[52]

Neurotransmission may also be affected by the intake of omega-3 fatty acids. Omega-3 fatty acids are known to improve cortical connectivity in monkeys,[53] and improve cell membrane fluidity, which, in turn, increases absorption or release of neurotransmitters.[54] The body of research examining the role of omega-3 fatty acids in relation to ADHD has been expanding in recent years. A meta-analysis of 16 studies ($n = 1408$) reported that supplementation with omega-3s improved hyperactivity, as reported by parent and teacher, and inattention, as reported by parent, with an effect size of 0.26.[55] Fatty acids may also play a role in ADHD due to their essential function in optimal neural development and signaling.[55]

Despite the increasing evidence for an association between diet, nutrient and amino acid intake and ADHD symptoms, few studies have examined overall diet quality in ADHD, particularly in regards to specific nutrient or amino acid intake. One study of amino acids, in children with ADHD versus controls, revealed no differences between blood and urine concentrations of tyrosine, phenylalanine, or tryptophan between the two groups, but the authors did not measure intake.[56]

A crucial research question is whether people with ADHD generally have poorer micronutrient or fatty acid intake, or altered consumption of amino acids, relative to people without ADHD. The objective of this report was to begin to answer this question by comparing overall diet quality, micronutrient, amino acid, and omega-3 intake in two age groups with and without ADHD. Based on the growing body of literature reporting an association between poor diet quality and prevalence of ADHD,[19,20] we hypothesized that the children and college students with ADHD would report poorer dietary intake overall, lower intake of omega-3s, and an altered intake of amino acids between the ADHD and control groups.

## Methods

### *Sample*

The study samples were composed of two age groups: 7–12-year-old children from the Pacific Northwest ($n = 45$), and 18–25-year-old college students from the East Coast ($n = 51$). The children were recruited from the local community via mass mailings using commercial mailing lists, to elicit volunteers for a study of ADHD in children and typically developing age-matched controls. The children were screened and evaluated in detail by the research team to identify true cases and valid non-cases based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria. The evaluation included parent and teacher standardized clinical ratings, a clinical interview of parent[57] and child, as well as child and parent observations and child cognitive testing. Children with IQ < 75 were excluded. Children who already had a diagnosis of ADHD at baseline, underwent the same standardized interview procedure. A previous ADHD diagnosis was recorded and was taken into consideration as a further piece of evidence toward the child having ADHD, but in and of itself, was not the only thing considered. Final diagnostic assignment required independent consensus of two experienced clinicians (a child psychiatrist and a child clinical psychologist) based on review of all available information. The sample is a sub-set of a larger cohort described elsewhere[58] who volunteered for a nutritional add-on study. This study was approved by the local Institutional Review Board (IRB) and written informed consent (and child assent) were obtained.

College students age 18–25 were recruited from a university campus on the East Coast via flyers or campus announcement platforms. Cases were defined as those having a current written diagnosis of ADHD from a clinician, and controls had to be free of any physical or mental illness and have no prior diagnosis of ADHD, based on self-report. All college students also completed the Adult ADHD Rating Scale to confirm their diagnostic status. All subjects with ADHD significantly differed from controls on this measure ($P < 0.0001$). Approval for this research was given by the local IRB and all participants provided written informed consent. Stimulant medication usage was recorded for both populations.

### *Dietary assessment*

Dietary intake data were collected over three days: two weekdays and one weekend day, in both groups. For the children, dietary assessment was conducted using a 24-hour recall with the multi-pass method,[59] where a registered dietitian interviewed the parent and child together, aiding the parent and child in recalling the foods and drinks the child consumed in the past 24-hour period. College students underwent detailed training on how to keep an accurate food diary of every item consumed in a 24-hour period, including how to estimate serving sizes and how to record ingredients and condiments as appropriate. Students were

instructed to keep the food record in real time, over the three specified days, which included two weekdays and one weekend day.

All dietary assessment data were entered into Nutrition Data Systems for Research (NDSR©) nutritional analysis software, which calculated nutrient data, including diet quality and micronutrient (vitamin and mineral) intake. Output from the program includes estimates for the intake of specific food groups, carbohydrates, protein, fatty acids, vitamins, and minerals. These estimates were averaged over the three days of dietary assessment to obtain values for each nutrient. Participants' diets were examined in four ways, as described below.

First, overall diet quality was assessed using the Healthy Eating Index (HEI), which is based on the 2010 Dietary Guidelines for Americans.[60] The HEI-2010 is computed using information on the adequacy of intake of fruits, vegetables, whole grains, dairy, total protein including meat, beans, or seafood; and unsaturated fatty acids; while also deducting points for excess consumption of saturated fats, refined grains, sodium, and empty calories. An HEI score is computed from 0 to 100, with a higher score implying a better diet that adheres closer to the guidelines set forth for Americans.

Second, nutrient intake estimates for vitamins and minerals were compared to the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) for each age group.[61] A dichotomous variable was created for each micronutrient, with 0 = 'not meeting the RDA/AI', or 1 = 'meeting the RDA or AI'. These were summed to form a novel Micronutrient Index (MNI), which estimated the overall number of micronutrients consumed at or above the RDA/AI levels. Scores ranged from 0 to 17, depending on whether or not the individual's diet met the RDA or AI for the following vitamins: thiamin, riboflavin, niacin, pantothenic acid, B6, folate, B12, C, A, D, E, and K; and minerals: calcium, iron, magnesium, potassium, and zinc.

Third, intakes of specific amino acids important for neurotransmission were analyzed using the gram estimates from the NDSR output. These included aspartate, glutamate, glycine, tryptophan, and tyrosine.

Further, a sensitivity analysis was completed on available venous, non-fasting blood samples from a convenience sample of 34 children ($n = 17$ in both groups) to substantiate the reported dietary intake of vitamin D and omega-3s. The omega-6/omega-3 fatty acid ratio was calculated by dividing the sum of the omega-6 fatty acids by the sum of the omega-3 fatty acids. (Due to monetary constraints, other nutrient variables were not analyzed.)

### *Statistical methods*

SAS® software, version 9.4, was used for all analyses. For preliminary analyses, uncorrected bivariate comparisons were provided for each continuous micronutrient variable using Wilcoxon rank sum for non-parametric data and Chi-square or Fisher's Exact (as appropriate) for categorical data.

When group differences for nutrient intake did not meet the statistical threshold for rejecting the null hypothesis, equivalency tests were conducted using formulas provided by Rogers *et al*.[62] The equivalency test, unlike the traditional hypothesis test, allows inference as to whether two groups actually have equivalent scores. Equivalency testing is achieved by defining, *a priori*, what value constitutes equivalency, or 'the minimum difference between two groups that would be important enough to make the groups nonequivalent'.[62] Then, two simultaneous one-sided $t$ tests are performed. If the mean intake values fall outside the pre-defined equivalence range, equivalence is rejected, but otherwise equivalence can be inferred. In this case, a difference of less than 20% between ADHD and non-ADHD groups served as the definition of equivalence.

Bivariate analyses were used to compare nutrient intakes by group as a preliminary analysis. Continuous variables were observed to be non-normally distributed, so non-parametric tests were used to compare median intakes between groups. For the amino acids, bivariate analyses included an assessment in grams, as well as a percentage of the total protein intake, to adjust for overall availability of amino acids.

Further in depth-analyses were conducted using two types of models. First, multivariable logistic regression was used to compare HEI scores and amino acids of interest among those with and without ADHD, in the child and college student samples. Second, the MNI score was compared among groups using multivariable ordinal logistic regression, where probabilities are cumulated over the higher ordered values.

Multivariable logistic regression models were adjusted for age, sex, and intellectual quotient (IQ) (for the children) or grade point average (GPA) (for the college students). In traditional nutrition analyses, it is typical to adjust for total energy intake, which we also included in the models of HEI and MNI. However, in relation to the amino acids, we chose to instead adjust for total protein intake, because this measure accounts for the availability of other amino acids that may affect neurotransmission. (Total energy intake would not accurately represent amino acid intake, because an adequate calorie diet could be deficient in protein).

We evaluated significance at the $P = 0.05$ level, but also utilized a Benjamini–Hochberg correction for

multiple comparisons as well, using a false discovery rate of 10%.

## Results

### *Demographics and bivariate nutrient results*

Table 1 presents the demographic characteristics, median and interquartile ranges for macronutrient intake, and bivariate results for dietary measures, reported by ADHD status. Among the children, there were more males than females (as is typical in ADHD populations); however, there was a higher proportion of females with ADHD among the college-age sample. Children with ADHD had lower IQ scores ($103 \pm 15$) than children without ADHD ($115 \pm 11$), $F\ (1,\ 43) = 0.1,\ P = 0.01$, as is commonly observed, but both groups had normal range IQ. Thirty percent of the children with ADHD, and 90% percent of the college students, were prescribed stimulant medication when the nutrient information was collected. No significant differences were reported between those with and without ADHD in either age group for macronutrient intake, the intake of omega-3 fatty acids, overall dietary quality as measured by the HEI, nor the overall number of micronutrients consumed at the RDA/AI recommended levels (MNI).

In post-hoc measures of equivalency, intake was observed to be equivalent (less than 20% different) for all the micronutrients examined in both age groups except vitamins B12, D, and K for children; and folate, vitamin C, vitamin A, and vitamin D for the college students. For these six nutrients, the data are inconclusive and we cannot reliably comment on equivalency or intake differences between groups. These results are reported in Table 2.

### *Nutrient comparison*

In terms of individual nutrients, more than 50% of the children in both the ADHD and control groups met the RDA or AI levels for the vitamins and minerals, with the exception of five nutrients: vitamin D, potassium, vitamin E, vitamin K, and calcium. Notably, only one child met the RDA for vitamin D and only two children met the AI for potassium. These results

**Table 1 Demographic characteristics and average macronutrient intake of children age 7–12 and college students age 18–25 years with and without ADHD**

| | Children age 7–12 yrs | | | College students age 18–25 yrs | | |
|---|---|---|---|---|---|---|
| | No ADHD *N* = 22 | Yes ADHD *N* = 23 | *P*-value* | No ADHD *N* = 30 | Yes ADHD *N* = 21 | *P*-value* |
| | Number (%) | | | Number (%) | | |
| Male | 12 (55%) | 15 (65%) | 0.47 | 7 (23%) | 9 (43%) | 0.14 |
| Caucasian | 16 (73%) | 18 (78%) | 0.67 | 16 (53%) | 16 (76%) | 0.68 |
| Current stimulant medications | 0 | 7 (30%) | N/A | 0 | 19 (90%) | N/A |
| | Median (IQ† range) | | | Median (IQ† range) | | |
| Age (years) | 9.1 (1.5) | 9.0 (1.5) | 0.61 | 19.5 (2.0) | 19.0 (1.0) | 0.98 |
| IQ | 116 (18) | 104 (22) | 0.01 | | | |
| GPA | | | | 3.8 (0.34) | 3.6 (0.40) | 0.20 |
| Energy intake (kcal) | 1956 (476) | 1932 (551) | 0.55 | 2219 (769) | 2226 (1385) | 0.81 |
| Carbohydrate intake (g) | 276 (116) | 266 (99) | 0.71 | 268 (101) | 233 (140) | 0.59 |
| Total sugars (g) | 118 (76) | 128 (72) | 0.66 | 95 (54) | 85 (71) | 0.90 |
| Total fat intake (g) | 71 (25) | 69 (32) | 0.36 | 79 (36) | 92 (62) | 0.87 |
| Trans fats (g) | 2.6 (1.9) | 2.4 (1.6) | 0.37 | 2.8 (3.1) | 2.6 (2.1) | 0.99 |
| Saturated fats (g) | 25 (11) | 24 (14) | 0.97 | 27 (18) | 27 (25) | 0.64 |
| Monounsaturated fats (g) | 25 (10) | 23 (13) | 0.41 | 30 (11) | 37 (22) | 0.30 |
| Polyunsaturated fats (g) | 12.6 (3.8) | 13.3 (7.7) | 0.41 | 19.3 (9.9) | 19.5 (11.9) | 0.35 |
| Protein intake (g) | 66 (18) | 74 (29) | 0.57 | 74 (40) | 82 (51) | 0.83 |
| Aspartate (g) | 5.5 (1.9) | 6.3 (2.5) | 0.27 | 6.85 (3.36) | 6.60 (3.86) | 0.72 |
| Glutamate (g) | 14.4 (4.2) | 13.7 (6.8) | 0.76 | 14.97 (8.12) | 14.89 (8.64) | 0.93 |
| Glycine (g) | 2.4 (0.97) | 2.7 (1.3) | 0.18 | 3.11 (1.44) | 3.36 (1.99) | 0.28 |
| Phenylalanine (g) | 2.99 (0.88) | 3.25 (1.31) | 0.61 | 3.35 (1.71) | 3.60 (1.88) | 0.93 |
| Tryptophan (g) | 0.83 (0.26) | 0.81 (0.39) | 0.99 | 0.92 (0.36) | 0.93 (0.59) | 0.99 |
| Tyrosine (g) | 2.35 (0.62) | 2.43 (0.89) | 0.85 | 2.60 (1.55) | 2.87 (1.73) | 0.92 |
| Amino acids as % of total protein | | | | | | |
| % Aspartate | 7.92% (0.8%) | 8.43% (1.0%) | 0.008 | 8.57% (1.1%) | 8.67% (1.0%) | 0.71 |
| % Glutamate | 21.55% (1.6%) | 20.78% (2.0%) | 0.04 | 20.46% (1.8%) | 19.57% (2.6%) | 0.17 |
| % Glycine | 3.56% (0.4%) | 3.69% (0.8%) | 0.10 | 3.85% (0.6%) | 3.98% (0.4%) | 0.08 |
| % Phenylalanine | 4.51% (0.3%) | 4.51% (0.2%) | 0.35 | 4.51% (0.4%) | 4.46% (0.5%) | 0.13 |
| % Tryptophan | 1.23% (0.1%) | 1.23% (0.2%) | 0.90 | 1.20% (0.1%) | 1.19% (0.1%) | 0.13 |
| % Tyrosine | 3.53% (0.2%) | 3.52% (0.2%) | 0.25 | 3.42% (0.4%) | 3.43% (0.3%) | 0.52 |
| HEI‡ | 54.5 (11.2) | 57.8 (15.6) | 0.20 | 56.2 (11.7) | 55.0 (11.2) | 0.80 |
| MNI§ | 13.0 (1.0) | 13.0 (2.0) | 0.16 | 9.5 (7.0) | 8.0 (8.0) | 0.55 |

* Wilcoxon rank sum for continuous variables and Chi-square for categorical data.
† Interquartile range.
‡ 2010 HEI.
§ MNI is a novel measure which summarizes the number of micronutrients which were consumed at the RDA/AI levels.

**Table 2 Post-hoc equivalency testing of mean average micronutrient intake in children and college students with and without ADHD**

| | Children | | | | College students | | | |
|---|---|---|---|---|---|---|---|---|
| Micronutrient | Control mean* | ±20% Of control mean | ADHD mean | Equal intake supported?† | Control mean* | ±20% Of control mean | ADHD mean | Equal intake supported?† |
| Thiamin (mg) | 1.77 | 1.42–2.12 | 1.81 | Yes | 1.98 | 1.58–2.38 | 1.74 | Yes |
| Riboflavin (mg) | 2.23 | 1.79–2.68 | 2.23 | Yes | 2.08 | 1.66–2.50 | 2.02 | Yes |
| Niacin (mg) | 21.21 | 16.97–25.45 | 22.24 | Yes | 25.32 | 20.26–30.38 | 26.6 | Yes |
| Pantothenic acid (mg) | 4.39 | 3.51–5.26 | 4.73 | Yes | 5.23 | 4.18–6.28 | 5.53 | Yes |
| Vitamin B6 (mg) | 1.58 | 1.26–1.90 | 1.88 | Yes | 1.92 | 1.54–2.30 | 2.06 | Yes |
| Folate (mcg) | 668.57 | 534.86–802.28 | 602.22 | Yes | 662.48 | 529.98–794.98 | 528.96 | No↓ |
| Vitamin B12 (mcg) | 4.75 | 3.80–5.70 | 6.69 | No↑ | 4.12 | 3.30–4.94 | 3.73 | Yes |
| Choline (mg) | 229.47 | 183.57–275.36 | 261.95 | Yes | 306.37 | 245.10–367.64 | 352.03 | Yes |
| Vitamin C (mg) | 80.65 | 64.52–96.78 | 95.04 | Yes | 72.71 | 58.17–87.25 | 97.69 | No↑ |
| Vitamin A (mcg) | 563.52 | 450.81–676.22 | 534.70 | Yes | 582.15 | 465.72–698.58 | 368.42 | No↓ |
| Vitamin D (mcg) | 4.87 | 3.90–5.84 | 6.08 | No↑ | 5.44 | 4.35–6.53 | 4.09 | No↓ |
| Vitamin E (mg) | 6.93 | 5.55–8.32 | 7.92 | Yes | 9.52 | 7.62–11.42 | 8.78 | Yes |
| Vitamin K (mcg) | 59.06 | 47.25–70.87 | 75.41 | No↑ | 169.85 | 135.88–203.82 | 196.68 | Yes |
| Calcium (mg) | 1118.18 | 894.54–1341.81 | 1102.78 | Yes | 1080.18 | 864.14–1296.22 | 893.19 | Yes |
| Iron (mg) | 16.29 | 13.03–19.55 | 16.82 | Yes | 16.92 | 13.54–20.30 | 14.71 | Yes |
| Magnesium (mg) | 241.31 | 193.05–289.57 | 282.69 | Yes | 331.61 | 265.29–397.93 | 305.75 | Yes |
| Potassium (mg) | 2113.64 | 1690.91–2536.37 | 2464.67 | Yes | 2468.27 | 1974.62–2961.92 | 2532.25 | Yes |
| Sodium (mg) | 3029.98 | 2423.99–3635.98 | 3313.55 | Yes | 3506.39 | 2805.11–4207.67 | 3437.01 | Yes |
| Zinc (mg) | 10.89 | 8.72–13.07 | 11.24 | Yes | 11.17 | 8.94–13.40 | 9.75 | Yes |

* Derived from those without ADHD.
† 'Yes' if ADHD group mean intake falls within ±20% of control mean, 'No' if not; arrow indicates whether ADHD group mean intake is higher or lower.

are illustrated in Fig. 1. In contrast to the relatively well-nourished children, the college students, across both the ADHD and non-ADHD groups, reported insufficient intake of 14 of the 19 nutrients studied. Sodium was the only nutrient meeting minimum intake recommendations among all the students, but the level exceeded recommended upper limits, again suggesting unhealthy intake levels. Similar to the children, only one college student met RDA for vitamin D and only two met the AI for potassium. These results are illustrated in Fig. 2. The only significant nutrient intake difference between ADHD and controls in either group was a higher percentage of individuals meeting the recommended intake level for iron among college students with ADHD, as compared to controls (57% versus 30%, $P = 0.05$).

As a sensitivity analysis of reported intake for vitamin D and omega-3s, we examined available blood concentrations on a convenience sample of 34 children ($n = 17$ in each group) (Table 3). No significant differences were noted between children with and without ADHD for vitamin D, nor for any of the fatty acids analyzed, including the omega-3s. Serum nutrient concentrations of vitamin D in the sub-set of children reflected the reported intake of the larger child group, and confirmed that in 95% of children, in both the ADHD and control groups, vitamin D levels were insufficient or deficient (data not shown).

Table 4 compares the mean diet quality of those with and without ADHD, by age group, using the HEI score and the MNI score (as a summation of the number of micronutrients being consumed at or above the RDA/AI). After adjustment for covariates, the likelihood of a child or college student with ADHD having a higher HEI score than those without ADHD, did not differ reliably in children, OR (95% CI) = 1.06 (0.97–1.15), $P = 0.19$; nor in the college students, OR = 1.03 (0.95–1.11), $P = 0.48$. Evaluation of the MNI suggested that children with ADHD had a qualitatively healthier diet than non-ADHD children, but this was shy of statistical significance, OR = 1.74 (0.91–3.34), $P = 0.09$. Among the college students, the ADHD group had a qualitatively poorer diet when evaluating the MNI, but groups did not differ reliably, OR = 0.52 (0.18–1.50), $P = 0.22$.

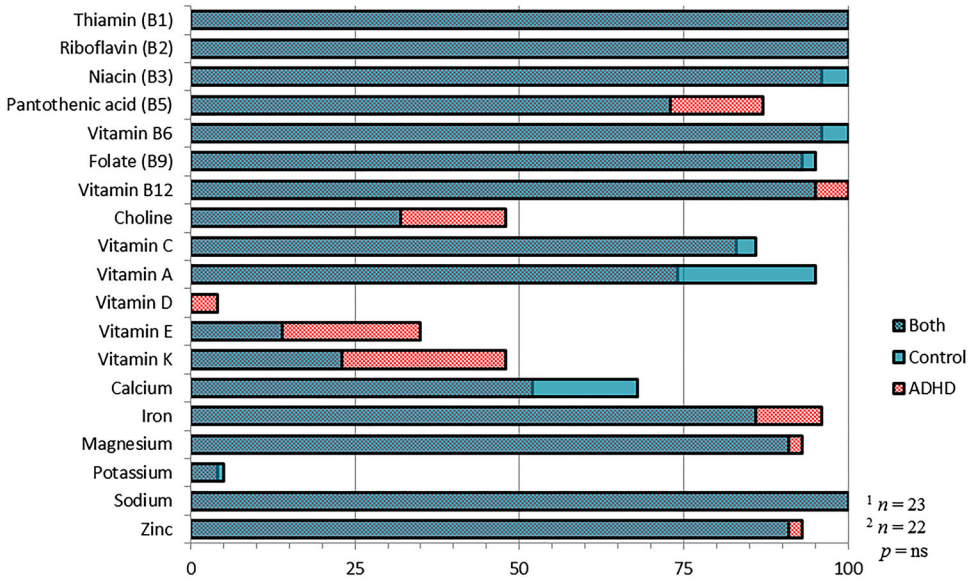


**Figure 1 Comparison of micronutrient intake relative RDA or AI values, in children age 8–12 years old, with and without ADHD.**

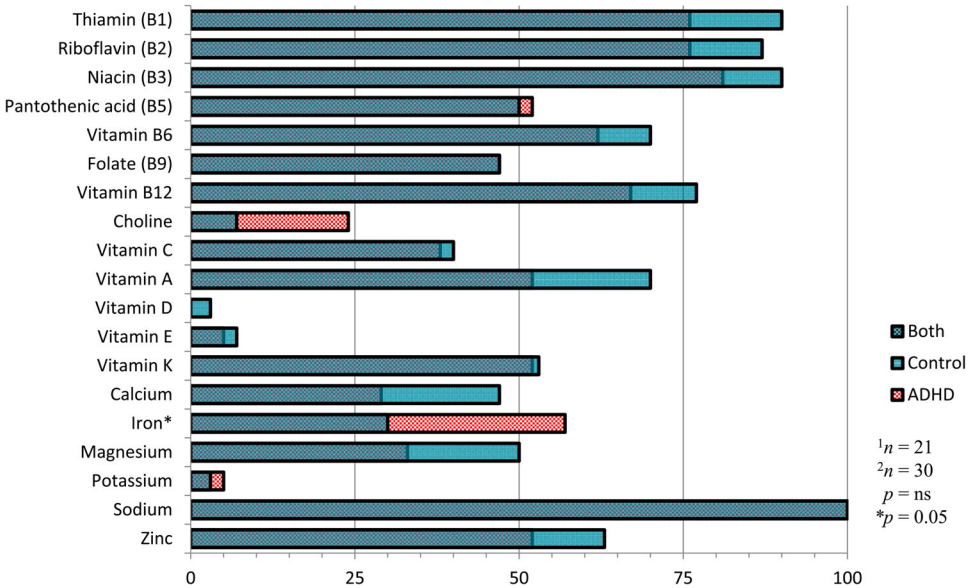


**Figure 2 Comparison of micronutrient intake relative RDA or AI values, in college students age 18–25 years old, with and without ADHD.**

### *Amino acid comparison*

In initial uncorrected bivariate analyses (Table 1), no reliable differences were detected between groups when comparing gram intakes of amino acids. However, when comparing intakes of each amino acid as a percent of the overall protein intake, bivariate group differences were noted in % aspartate and % glutamate (with % glycine approaching significance) among the children; while in contrast, only % glycine approached significance among the college students. This association held in multivariable logistic regression models evaluating the association of ADHD and gram amino acid intake, while adjusting for age, sex, IQ (or GPA) and total protein intake (Table 5). Among the child cohort, higher consumption of both aspartate and glycine were associated with an increased likelihood of having ADHD, OR (95% CI) = 12.61 (1.79–88.91), $P < 0.01$ and 11.60 (1.02–131.68), $P = 0.05$ respectively; while higher intakes of glutamate were associated with a reduced likelihood of ADHD, OR = 0.34 (0.13–0.90), $P = 0.03$. These associations maintained significance when using the more conservative Benjamini–Hochberg correction for multiple comparisons. Among the college students, none of the amino acids met significance at $P = 0.05$, nor at the more conservative corrected *P*-value level. Higher glycine intakes approached significance for an *increased* likelihood of ADHD, OR = 5.88 (0.91–37.93), $P = 0.06$, while higher tryptophan intakes approached

**Table 3 Sensitivity analysis: Comparison of fatty acid and vitamin D3 plasma concentrations in a sub-set of children, 7–12 years old, with and without ADHD**

| Type | | Children age 7–12 Yrs | | |
|---|---|---|---|---|
| | | No ADHD ***N*** = 17 | ADHD ***N*** = 17 | ***P***-value* |
| | | Median (IQ† range), mmol/L | | |
| SFA | Myristic acid (14:0) | 543 (333) | 307 (529) | 0.40 |
| MUFA, *n*-5 | Myristoleic acid (14:1) | 6.6 (6.8) | 5.0 (8.6) | 0.66 |
| SFA | Palmitic acid (16:0) | 2397 (1013) | 2344 (706) | 0.40 |
| MUFA, *n*-7 | Palmitoleic acid (16:1) | 141 (75) | 170 (100) | 0.84 |
| MUFA, *n*-9 | Oleic acid (18:1) | 1155 (610) | 1182 (809) | 0.71 |
| PUFA, *n*-6 | Linoleic acid (18:2) | 1403 (536) | 1495 (725) | 0.43 |
| PUFA, *n*-3 | Alpha-linolenic acid (18:3) | 38 (13) | 40 (20) | 0.45 |
| PUFA, *n*-6 | Arachidonic acid (20:4) | 564 (302) | 708 (240) | 0.40 |
| PUFA, *n*-3 | Eicosapentaenoic acid (EPA) (20:5) | 59 (18) | 61 (27) | 0.97 |
| PUFA, *n*-3 | Docosahexaenoic acid (DHA) (22:6) | 150 (23) | 151 (80) | 0.78 |
| PUFA, *n*-6/*n*-3 | Omega-6 to omega-3 ratio | 8.5 (2.1) | 9.5 (3.2) | 0.12 |
| | | Median (IQ range), ng/mL | | |
| | Vitamin D3 | 21 (7) | 22 (7) | 0.92 |

Note: SFA = saturated fatty acid, MUFA = monounsaturated fatty acid, PUFA = polyunsaturated fatty acid.
* Wilcoxon rank sum.
† Interquartile range.

**Table 4 Association of diet quality measures and ADHD in children age 7–12 years and college students age 18–25 years**

| | Children age 7–12 yrs | | College students age 18–25 yrs | |
|---|---|---|---|---|
| | OR (95% CI) | ***P***-value | OR (95% CI) | ***P***-value |
| HEI | | | | |
| Crude | 1.04 (0.97–1.11) | 0.30 | 0.99 (0.93–1.06) | 0.78 |
| Adjusted* | 1.06 (0.97–1.15) | 0.19 | 1.03 (0.95–1.11) | 0.48 |
| MNI | | | | |
| Crude | 1.51 (0.88–2.57) | 0.13 | 0.73 (0.28–1.94) | 0.53 |
| Adjusted† | 1.74 (0.91–3.34) | 0.09 | 0.52 (0.18–1.50) | 0.22 |

* Adjusted for age, sex, average energy intake (kcal), and IQ.
† Adjusted for age, sex, average energy intake (kcal), and GPA.

significance for a *decreased* likelihood of having ADHD, OR < 0.01 (<0.001–1.43), $P = 0.06$.

## Discussion

### *Summary of main findings*

To our knowledge, this is the first study to describe overall dietary nutrient intake and amino acid intake in individuals with and without ADHD. While limited by small sample sizes, the data provide a first look at this critical element of the nutrition puzzle in relation to ADHD.

In that vein, we observed that overall adequacy of dietary intake among the two age groups with ADHD was similar to the controls, based on analyses of the HEI and MNI. Based on equivalency testing, we can also reliably confirm individual nutrient intake equivalence in both samples, for those with ADHD and controls, for most of the micronutrients. However, amino acid intake appears to differ between those with and without ADHD, with differences between age groups. Specifically, in children with ADHD versus those without, gram intakes of aspartate and glycine were higher, and glutamate intake was lower. In college students, none of the amino acids met significance, however higher glycine intake was marginally associated with an increased likelihood of ADHD, while higher tryptophan intake appeared to be marginally protective, presenting as a slightly reduced odds of having ADHD. Interpretation of these findings, relative to the existing literature, is discussed below.

### *Comparisons to the dietary literature*

Among both age groups, regardless of ADHD status, inadequate vitamin D intake was apparent in 95% of the total sample relative to normative recommendations.[61] Blood tests confirmed vitamin D deficiency and insufficiency in the sub-set of children with samples available. These results are consistent with studies showing that vitamin D deficiency/insufficiency is an overlooked health concern that has potential mental health consequences,[63–65] particularly in northern climates, where inadequate UV exposure leads to reduced blood vitamin D concentrations. In particular, vitamin D impacts serotonin function, with inadequate levels reducing brain serotonin synthesis.[66] In our college sample, we observed slightly lower intakes of tryptophan (the precursor to

**Table 5 Likelihood of having ADHD based on amino acid intake (g) in each age group**

| | Children age 7–12 years | | | | College students age 18–25 years | | | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for total protein intake | | Adjusted for age, sex, IQ and total protein intake | | Adjusted for total protein intake | | Adjusted for age, sex, GPA and total protein intake | |
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Aspartate (g) | 7.62 (1.41–41.35) | 0.02 | 12.61 (1.79–88.91) | 0.01* | 1.38 (0.51–3.73) | 0.53 | 1.89 (0.61–5.81) | 0.27 |
| Glutamate (g) | 0.53 (0.27–1.04) | 0.06 | 0.34 (0.13–0.90) | 0.03* | 0.71 (0.49–1.05) | 0.08 | 0.75 (0.49–1.14) | 0.18 |
| Glycine (g) | 6.13 (0.76–49.42) | 0.09 | 11.60 (1.02–131.68) | 0.05* | 7.30 (1.18–45.28) | 0.03 | 5.88 (0.91–37.93) | 0.06 |
| Phenylalanine (g) | 0.06 (<0.001–9.36) | 0.27 | 0.07 (<0.001–25.47) | 0.38 | 0.07 (0.004–1.18) | 0.06 | 0.09 (0.003–2.52) | 0.16 |
| Tryptophan (g) | 0.12(<0.001–82.67) | 0.52 | 0.02(<0.001–142) | 0.38 | <0.001(<0.001–0.39) | 0.03 | <0.001(<0.001–1.43) | 0.06 |
| Tyrosine (g) | 0.02 (<0.001–1.70) | 0.08 | 0.01 (<0.001–2.57) | 0.11 | 0.10 (0.003–3.09) | 0.19 | 0.08 (0.001–4.40) | 0.22 |

* Meets the more stringent Benjamini–Hochberg corrected *P*-value criteria for multiple comparisons.

serotonin) in ADHD subjects, in addition to poor vitamin D intake. The combination of these two factors may have compounding effects on serotonin function. Lower serotonin levels have been associated with impulsivity and poor long-term planning, two behaviors commonly associated with ADHD.[66] Since vitamin D plays an important role in gene regulation, it would be of interest to ask whether a vitamin D deficiency may be part of an activating environment for people carrying a genetic liability for ADHD. Future work on gene x environment interplay (e.g. using the vitamin D receptor gene) would be of interest in pursuing this hypothesis. Supplementation with omega-3 fatty acids has been shown to have a small, but reliable, effect on ADHD symptoms.[55] However, fish consumption may have a potentially greater benefit on ADHD since it can improve both vitamin D and omega-3 fatty acid intake concurrently.

In addition to poor vitamin D intake, nearly all participants in both age groups had inadequate intake of potassium, which indicates low consumption of fruits and vegetables. Additionally, the majority of participants in both age groups had low intakes of choline and vitamins E and K. These results suggest that consumption of eggs, nuts, seeds and leafy greens is too low. In the college population, a majority of students also had low intakes of folate, vitamin C, calcium, and magnesium. Moreover, pantothenic acid and iron intakes were low for almost half the college sample. More college students with ADHD met the RDA for iron than controls, but 43% of the ADHD group still did not meet recommendations. Iron is necessary for the production of dopamine,[67] which has been shown to be altered in ADHD.[68] Research on iron status and ADHD is ongoing and deserves further attention.[69]

For most nutrients, children and college students with and without ADHD had similar intakes, as shown in the equivalency testing results. These results, along with the HEI and MNI comparisons, suggest that micronutrient intake and diet quality were unrelated to ADHD in these two samples. Stimulant medication usage and food availability may be two factors involved in overall diet quality in these samples. The high prevalence of prescription stimulant use in college students with ADHD may negatively impact diet quality due to the appetite suppressing effects of this type of medication.[70] Students may not have an appetite until the medication wears off, then they feel quite hungry, and select whatever is readily available, rather than choosing thoughtfully what they will eat. Typically, the types of foods readily available on a college campus are high in calories, but low in nutrient value. Students may also be choosing based on price. Inexpensive, mass-produced convenience foods tend to lack nutrients and contain high

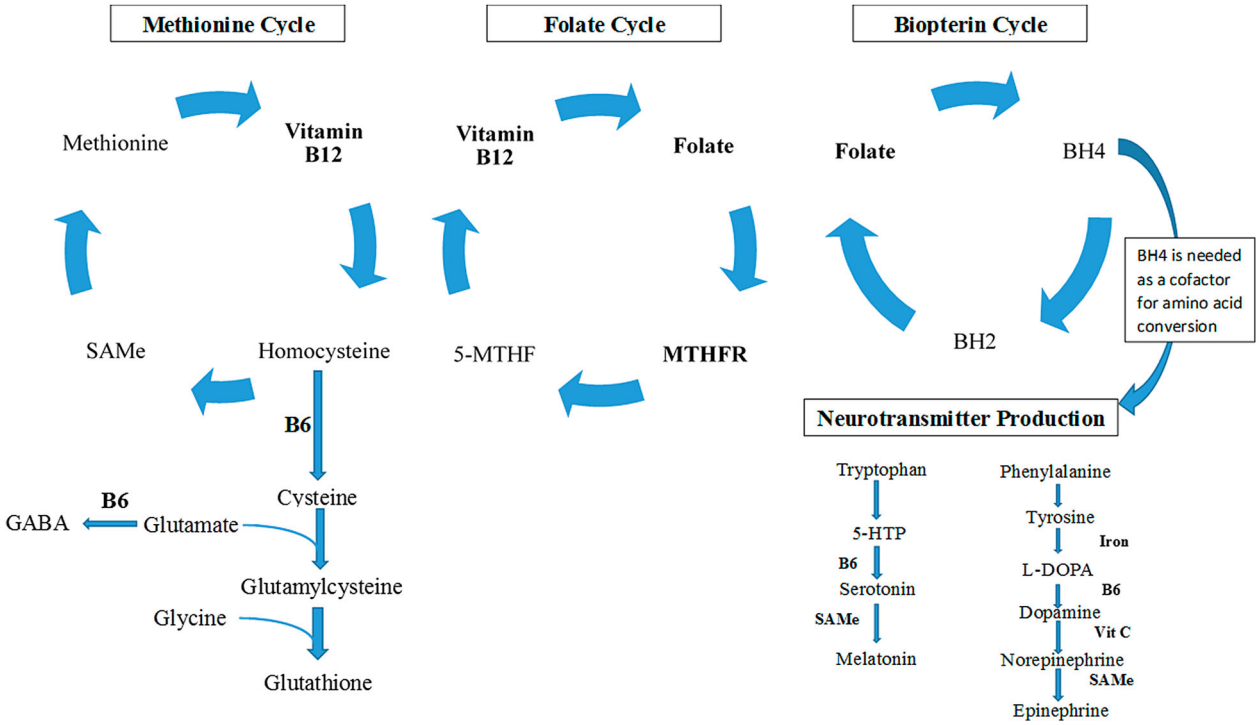


**Figure 3 An overly simplified schematic showing the inter-related cycles for methionine, folate, and tetrahydrobiopterin, and how specific nutrients are necessary for the production of monoamine neurotransmitters. Note: enzymes are not included. Abbreviations: SAMe = s-adenosyl methionine; 5-MTHF = L-5-methyltetrahydrofolate; MTHFR = methylene tetrahydrofolate reductase; BH4 = tetrahydrobiopterin; BH2 = dihydrobiopterin; 5-HTP = 5-hydroxytryptophan; L-DOPA = L-3,4-dihydroxyphenylalanine; GABA = gamma-aminobutyric acid.**

sodium, compared to healthful choices. In contrast, the 8–12-year-old children are still living at home and eating food purchased by their parents/guardians, which impacts the type and quality of food available, likely for the better. Parents may make healthier purchases, driven less by price, compared to college students. Selection bias may be a factor in the child group as well, because motivated parents interested in nutrition may have been more apt to participate in this research. Individual food choices in relation to food availability and medication usage is an area worthy of future research.

Given the relative equivalency of the micronutrient intake between those with and without ADHD, perhaps it is micronutrient absorption or utilization, rather than low intake relative to population recommendations, which is disrupted in ADHD. Investigating this possibility is an important direction for future research. Even when dietary intake is sufficient, a number of factors influence an individual's ability to absorb and metabolize vitamins and minerals, including gut health[71] and genetic polymorphisms.[72] Gut health may be influenced by medication usage, as gastro-intestinal symptoms are more common in those taking ADHD medications than in those who are not.[73] Furthermore, there is growing interest in the potential for the microbiota to influence gut health as well as the gut–brain axis and neuroimmune modulation.[74] Beneficial bacteria in the gastro-intestinal tract play a key role in maintaining gut barrier health.[75] In regards to genetic polymorphisms, gene mutations can result in a decreased binding affinity for vitamins that serve as important coenzymes.[76] Reviewing more than 50 genetic variants resulting in physical health issues, Ames and colleagues noted improvements when patients were administered high vitamin doses to restore key enzymatic activity.[76] Enzymatic interactions possibly related to ADHD include genetic variants of methylenetetrahydrofolate reductase (MTHFR),[77–79] which alter the function of enzymes essential for one carbon metabolism (see Fig. 3).[80] These enzymes are important for proper amino acid metabolism and DNA methylation.[80] Individuals with this mutation require supplementation with high levels of B vitamins in their bio-active form to attain sufficient concentrations.[80] Another metabolic consideration relevant to ADHD is that the availability of nutrients through ingestion may not translate into adequate brain levels. This hypothesis is supported by findings from a group of adults with ADHD whose symptoms improved after taking high doses of vitamins and minerals; although the participants' baseline serum nutrient levels did not predict who would benefit from micronutrient treatment.[81] While these speculations cannot be answered by this study, the results suggest that it will

be important to reconcile reported benefits from nutrient supplementation in ADHD with data on nutrient intake. It is extremely important that future studies looking at nutritional therapeutics in ADHD carefully evaluate nutrient intake prior to treatment.

### *Comparisons to the amino acid literature*

The disparate findings around amino acid intake in children, with aspartate being associated with an increased likelihood of ADHD, while glutamate was associated with a reduced likelihood of ADHD, are quite surprising. Aspartate and glutamate are very similar compounds, and both have the ability to act as excitatory neurotransmitters in the nervous system.[50,51] While glutamate can act on multiple types of receptors (NMDA, AMPA, kainate, and metabotropic receptors),[50] aspartate only has the ability to bind to one of these, the NMDA receptor.[51] Interestingly, the NMDA receptor is further activated by glycine as a co-agonist.[52] High brain glycine levels have been shown to inhibit dopamine release, and this effect is thought to be mediated through co-stimulation of the NMDA receptor, which in turn stimulates inhibitory interneurons.[82] The fact that glutamate was associated with a reduced likelihood of having ADHD suggests potential dysfunction of the NMDA receptor, or an ability for glutamate to affect ADHD symptoms by action mediated through one of its other receptor types. The hypo-glutamatergic hypothesis,[41] related to neurotransmitter dysfunction in ADHD, is supported by these findings.

Finally, the observation that college students who have higher intakes of tryptophan have a lower likelihood of having ADHD, is consistent with the fact that depression, which has been strongly associated with decreased serotonin levels, is highly comorbid with ADHD.[83] Furthermore, research has also suggested that altered levels of 5-HT (serotonin) may be associated with hyperactive and impulsive components of the disorder.[42] Acute tryptophan depletion has also been associated with aggression[84,85] and attentional performance[49] in ADHD. However, Berwerff *et al*. failed to show differences in blood spot or urine concentrations of tryptophan among children age 6–13 with and without ADHD.[56] Thus, more research is needed to determine the potential role of serotonin (mediated by tryptophan intake) on ADHD symptoms.

It is also worth noting that aspartate and glycine can be found in food additives, especially protein additives like gelatin, soy protein isolate, and aspartame. Gelatin is a major source of glycine and aspartate in the diet, and is commonly packaged with artificial colors in foods like candy, jello, yogurt, and even gummy vitamins. Low sugar variations of these products also commonly contain aspartame (as an additional source of aspartate in the diet). Thus, gelatin and aspartame could be mediating factors in previous literature concerning the positive effects of removing artificial food colors from the diet.[86]

Interestingly, no significant differences were noted between groups in tyrosine intake, which serves as a precursor to dopamine production. Altered dopaminergic neurotransmission is implicated in ADHD,[31,58] however high glycine intake may be inhibiting the release of dopamine, rather than insufficient tyrosine intake decreasing its production.

### *Limitations and strengths of the study*

Study results must be viewed as preliminary due to the small sample sizes, large confidence intervals, differences between age groups, and limited power to detect only large effects. Furthermore, serum measures were unavailable except for a sub-sample of the child participant group, which only had serum vitamin D and omega-3 fatty acid concentrations available for analysis. Despite these limitations, the results provide some of the first descriptive data about overall diet, micronutrient, and amino acid intake in samples of individuals with and without ADHD, who are not part of a dietary intervention study. Other study strengths include two community-based samples, one on each coast, representing different age groups. The participants were enrolled in the same time period, thus eliminating comparison confounders, and stringent diagnostic criteria were used for ADHD classification among the children and a previous written physician diagnosis of ADHD (with confirmation based on ADHD rating scale) was required for the college students. Serum vitamin D and omega-3 data in a sub-set of the children supported the dietary intake reports for both nutrients and confirmed that there were no significant differences between children with and without ADHD, with respect to fatty acid intake. Finally, the participants' diets were analyzed in several ways, thus providing a model for an approach that can be used in future, more ambitious, studies in this vein.

### *Implications for future research*

Studies comparing larger samples with and without ADHD, measuring dietary intake of vitamins, minerals, amino acids, omega-3 fatty acids, the omega-6/omega-3 fatty acid ratio, as well as blood nutrient concentrations are important next steps. This study only collected data in children age 7–12 and young adults age 18–25 years; future research could also examine the ages 13–18 as a time period with changing dietary intake and significant brain development through puberty. Future work examining the association of dietary intake of amino acids and ADHD should include total protein, rather than overall

caloric intake, in statistical modeling. The relationship between amino acid intake and ADHD status requires further investigation, and the method used herein may guide future hypothesis generation to inform larger scale studies. Diet intervention studies would be useful to assess whether altering intake of amino acids affects symptoms, with exposure to gelatin and other food additives being of particular interest.

Examination of potential mechanistic factors, such as changes in the microbiota or gastro-intestinal function, are also needed. Considering personalized treatment by examining genetic polymorphisms such as MTHFR or the histamine gene, would also be a useful next step. It is also worthwhile to note the extremely poor intake of nutrients among this group of college students. These students attend a selective, private university in an urban environment, and yet the majority were eating inadequate amounts of nutrient-dense foods. Improved nutrition education about the role of diet in overall health is needed, particularly among this age group.

## Conclusions

Across both age groups of young people, nutrient intake was not associated with ADHD, suggesting that ADHD symptomatology is not likely driven by dietary nutrient inadequacy alone. If these results were to hold up in larger follow up studies, it would raise the possibility that any nutrient effects present in ADHD may be more related to digestion or utilization factors, rather than solely to dietary intake. Consumption of dietary aspartate, glycine, and glutamate was associated with ADHD in children, but significant associations were not observed in college students. These preliminary results support the possibility that altered glutamatergic neurotransmission is occurring in ADHD. More research is needed to understand if dietary modification of amino acids may be able to affect symptoms in ADHD, and whether or not dietary effects differ by age.

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## Disclaimer statements

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