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Dietary and nutrient status of children with attention-deficit/hyperactivity disorder: a case-control study

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Running title: Diet and nutrients in ADHD

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ABSTRACT

Background and Objectives: Nutritional and dietary habits may affect children's behaviors and learning. The etiology of attention-deficit/hyperactivity disorder (ADHD), a common neurodevelopmental disorder in children, may be associated with unhealthy diets or nutrients deficiencies. The purpose of this study was to examine whether children with ADHD exhibited different dietary habits or nutrient profiles from healthy control subjects. **Methods and Study Design:** We recruited 42 patients with ADHD (mean age: 8.1 years) and 36 healthy children as the control group (mean age: 9.8 years). We adopted the ADHD Rating Scale and the Swanson, Nolan, and Pelham Version IV Scale to interview both the ADHD patients and the control subjects and then evaluated participants' dietary intake with a food frequency questionnaire. Logistic regression models were utilized to produce a composite dietary/nutrient score, while receiver operating characteristic (ROC) was adopted to differentiate between the two participant groups. **Results:** Compared to the control children, children with ADHD demonstrated a higher intake proportion of refined grains (p=0.026) and a lower proportion of dairy (p=0.013), calcium (p=0.043), and vitamin B2 (p=0.024). We observed that the composite score of dietary and nutrient could significantly distinguish patients with ADHD from healthy controls (p<0.001). The composite dietary/nutrient score demonstrated a significant correlation with the severity of ADHD clinical symptoms (p<0.05). **Conclusions:** ADHD children and healthy controls have different dietary patterns and that dietary and nutrient factors may play a role in the pathophysiology of ADHD. Clinicians should consider dietary habits and specific nutrients in the routine assessment of children with ADHD.

Key Words: ADHD, diet, nutrition, calcium, grains

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), a psychiatric disorder that often affects children and adolescents, is characterized by inattention, hyperactivity, and impulsivity.[1] This disorder affects 3% to 10% of school-age children worldwide,[2] with one study reporting a local prevalence of 7.5% in Taiwan.[3] ADHD is generally considered a highly genetic disorder, but environmental factors may also contribute to children's susceptibility to ADHD.[4] Current evidence supports the belief that nutritional and dietary habits affect children's behavior and learning.[5] For example, the intake of sweetened desserts, fried foods, and salt has already been associated with children's learning and behavioral problems.[6] In contrast, healthy dietary habits and balanced nutrients intake have been observed to benefit children's learning achievement.[6] Since ADHD is a neurodevelopmental disorder characterized by behavioral problems and learning disabilities, some researchers have proposed that ADHD may be associated with "unhealthy" diets or nutrient deficiencies.[5,7,8] Therefore, dietary habits and certain nutrients should be considered when evaluating children with ADHD.

Nearly half of ADHD children have suboptimal nutrition, while only 11.1% of typically developed children demonstrate such a condition.[9] Compared to the healthy controls, ADHD patients were more likely to have a poor diet, regardless of whether they were undergoing drug therapy.[10] A "Western-style" diet, which is high in fat and refined sugars, resulted in an increased risk of ADHD, while a "healthy diet" that contained fiber, folate, and omega-3 fatty acids was considered a protective factor against ADHD.[8] Previous evidence has shown that fatty acids may influence hyperactivity in children with specific learning disabilities. Furthermore, some food additives (colorings, flavorings, and preservatives) may increase hyperactivity in children with behavioral problems.[7] Another study has indicated that poor adherence to a Mediterranean diet may contribute to developing ADHD.[11] Not only does a child's nutrients deficiency act as a risk factor of ADHD, but an unhealthy prenatal diet may also be associated with ADHD in the subsequent offspring due to increased epigenetic changes.[12] However, whether specific dietary habits or nutrient deficiencies contribute to ADHD is still with a matter of considerable debate.

Dietary habits and nutrient status vary across different countries and cultures. However, studies on the diet and nutrient status of ADHD children in Taiwan is scarce. Only one prior study has indicated that no dietary differences were observed in children with ADHD except for the intake of iron and vitamins.[13] In this study, we have hypothesized that children with ADHD exhibit an unhealthy dietary pattern and nutrient deficiency. This study aimed to investigate whether children with ADHD and healthy controls demonstrated distinguishable dietary and nutrient patterns, as well as examine the potential correlation between ADHD symptoms and dietary/nutrient status.

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MATERIALS AND METHODS

Study participants

Our research protocol was approved by the Institutional Review Board (IRB) at Chang Gung Memorial Hospital in Taiwan (IRB number: 105-0354C). We recruited 42 patients with ADHD treated in the outpatient Department of Child Psychiatry at Chang Gung Children's Hospital in Taiwan and 36 healthy control children.

The criteria for ADHD patients consisted of the following: (a) a clinical diagnosis of ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) through structured interviews conducted using the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, epidemiologic version (K-SADS-E);14 (b) between the ages of 6 and 16 years old; and (c) never treated for their ADHD with medications. We excluded patients who had major physical illnesses (such as genetic, gastrointestinal, or infectious diseases) or a history of major comorbid neuropsychiatric diseases (such as intellectual disabilities, autism spectrum disorder, bipolar disorders, major depressive disorders, psychotic disorders, substance use disorders, epilepsy, or severe head trauma).

The healthy control participants were children without ADHD, Han Chinese ethnicity, and between the ages of 6 and 16 years old within the same catchment area. Children were excluded if they had any known major physical illness or any of the aforementioned major neuropsychiatric diseases. The study procedures and data analysis are summarized in the conceptual diagram in Figure 1.

Dietary intake assessment

We used a validated food frequency questionnaire (FFQ) in order to evaluate participants' dietary intake during the previous year.[15] This questionnaire included the frequencies and amounts of 49 food items consumed from eight food groups. It had a fixed format and open-ended questions regarding major staple foods, oils/fats, sugars, and supplements and their consumption frequency. We recorded the standard portion size and frequency in order to estimate the daily intake of foods and nutrients. Daily dietary patterns and nutrient intake levels were calculated by multiplying the amount of food eaten daily, the level estimated from frequency, and the nutrient concentrations, while energy intake level was determined by adding up the calories from the food consumed. All nutrients were represented as nutrient density (each nutrient index divided by total energy intake). To complete the FFQ, the participants and their caregivers were interviewed by a trained research assistant. The validity of this FFQ has been verified for both adults and children in previously published studies.[16-20]

Clinical measurements

A senior psychiatrist interviewed both the ADHD and healthy control children using the K-SADS-E diagnostic tool and ADHD Rating Scale (ADHD-RS), and an experienced child psychologist conducted the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-

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IV) with individual subjects in a room designed to reduce variability in testing conditions. The Swanson, Nolan, and Pelham Version IV Scale (SNAP-IV) parent form and SNAP-IV teacher form were completed by the subjects' parents and teachers, respectively.

The K-SADS-E is a semi-structured diagnostic interview designed to evaluate current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria.[14] The K-SADS-E was used in this study to interview the parent(s) and the child to achieve summary ratings. The validity and reliability of the Chinese version of K-SADS-E has been previously established in Taiwan.[21]

The WISC-IV Chinese version is an individually administered and norm-referenced instrument created to measure the intelligence of children between the ages of 6 and 16.[22] The WISC-IV contains 10 core and 5 supplemental subtests. The core subtests form four factor indexes, including the Verbal Comprehension Index (VCI), the Perceptual Reasoning Index (PRI), the Working Memory Index (WMI), and the Processing Speed Index (PSI), while the Full Scale Intelligence Quotient (FSIQ) was formed from the 10 core subtests. The factor indexes and FSIQ each have a population mean of 100 and a standard deviation of 15.[23]

The SNAP-IV is a 26-item questionnaire used to evaluate ADHD symptoms and their severity to be completed by parents and teachers.[24] The 26 items include 18 items that address ADHD symptoms (9 for inattention and 9 for hyperactivity/impulsivity) and eight for oppositional defiant disorder (ODD) symptoms as defined in the DSM-IV. Each item is scored on a Likert scale from 0 to 3. The Chinese version of the SNAP-IV parent form[25] and the SNAP-IV teacher form[26] has satisfactory levels of reliability and concurrent validity.

The ADHD-RS is a validated instrument through which clinicians assign ratings based on information from a child and his or her parent(s).[27] This 18-item checklist is derived from the 18 criteria outlined in the DSM-IV for diagnosing ADHD. Each item is scored on a 4-point Likert scale from 0 to 3 points. The instrument provides a total score (the sum of all 18 items) and is divided into the inattentive (odd numbered items) and hyperactive/impulsive (even numbered items) subscales. A higher score indicates more severe ADHD symptoms. This scale has been proven to have good inter-rater reliability.[28]

Statistical analysis

We analyzed data using the statistical software package SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA). Variables were presented as either mean ± standard deviation or frequency. Two-tailed p-values < 0.05 were considered statistically significant.

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We applied the Chi-square test or Fisher's exact test to compare gender distribution between the ADHD patients and the control subjects. An independent t-test was utilized to determine the potential difference in age and clinical assessments between the two groups. Furthermore, we adopted multivariate analysis of covariance (MANCOVA), for which we controlled for age and gender. Differences in the nutrient density of each dietary index between the two groups were also analyzed, while Pearson correlation was used to assess the correlation between dietary patterns and the nutrient index. Raw scores of dietary/nutrient indices were transformed into Z-scores, which were expressed in terms of standard deviations from their means.

We adopted logistic regression to examine the predicted probability score (β-value and 95% Confidence Interval) of each dietary/nutrient index on differentiating ADHD patients and controls, controlling for age and sex. A composite diet score and a composite nutrient score were calculated by adding the dietary and nutrient coefficients, respectively. Then we utilized receiver operating characteristic (ROC) curves and the area under the curve (AUC) to assess both the specificity and sensitivity of the two composite probability scores obtained from the logistic regression model. Finally, we used Pearson correlation to analyze the correlation between the probability scores and ADHD symptoms in all subjects.

RESULTS

Demographic data and nutrient status

The characteristics of both the ADHD patients and the healthy controls are summarized in Table 1. We recruited a total of 42 ADHD patients (mean age 8.1 years, 78.6% male) and 36 healthy control children (mean age 9.8 years, 52.8% male). Compared to the control group, the ADHD group was more likely to be male (p=0.016) and younger (p=0.001), with a lower height (p<0.001), lower body weight (p=0.002), lower intelligence quotient (p=0.001), higher inattention scores (p<0.001), and higher hyperactivity/impulsivity scores (p<0.001) as rated by parents, teachers, and clinicians.

The dietary and nutrient status results measured by the FFQ of the ADHD group and the control group are provided in Table 2. Relative to the control group, children with ADHD demonstrated a higher intake proportion of refined grains (p=0.026) and a lower proportion of dairy (p=0.013), as well as lower intake of calcium (p=0.043) and Vitamin B2 (p=0.024). No other dietary or nutrients differences were observed between the two groups.

With regard to the correlation between dietary patterns and nutrient index, the intake of refined grains demonstrated a negative correlation with vitamin B-2 (r=-0.347, p=0.002),

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while the intake amount of dairy was positively correlated with calcium (r=0.896, $p<0.001$) and vitamin B-2 (r=0.878, $p<0.001$).

Logistic regression model and the composite diet/nutrient scores

We adopted logistic regression to evaluate the predicted probability scores of two diet indices and two nutrient indices with regard to differentiating ADHD patients from healthy controls (Table 3). We found that refined grains, dairy, calcium, and Vitamin B2 all significantly differentiate ADHD patients and controls in the adjusted model (controlling for age and sex).

We also applied the composite diet score (refined grains and dairy) and composite nutrient score (calcium and Vitamin B2) obtained from the logistic regression model to differentiate between ADHD cases and controls, respectively. The ROC curve revealed that the composite diet score demonstrated a sensitivity of 75% and a specificity of 76.2% (Figure 2A, AUC: 0.806, $p<0.001$), while the composite nutrient score showed a sensitivity of 63.9% and a specificity of 78.6% (Figure 2B, AUC: 0.771, $p<0.001$).

We observed that the composite diet score was negatively correlated with the inattentive symptoms evaluated by parents (r=-0.428, $p<0.001$), teachers (r=-0.451, $p<0.001$) and clinicians (r=-0.546, $p<0.001$), as were the hyperactivity/impulsivity symptoms evaluated by parents (r=-0.492, $p<0.001$), teachers (r=-0.509, $p<0.001$), and clinicians (r=-0.570, $p<0.001$).

The composite nutrient score was also negatively correlated with the inattentive symptoms evaluated by parents (r=-0.458, $p<0.001$), teachers (r=-0.390, $p=0.001$) and clinicians (r=-0.493, $p<0.001$), as were the hyperactivity/impulsivity symptoms evaluated by parents (r=-0.507, $p<0.001$), teachers (r=-0.518, $p<0.001$), and clinicians (r=-0.549, $p<0.001$).

DISCUSSION

This study's results indicate that dietary patterns and nutrient status may be involved in the underlying pathophysiology of ADHD. Compared to healthy controls, we found ADHD patients to have fewer intakes of calcium and Vitamin B2. Various minerals, such as zinc, phosphorus, selenium, and calcium, have previously been found to be protective against ADHD symptoms in Chinese children.[29] Intracellular calcium signaling has a crucial role in microglial functions and also contributes to the process of neurodevelopment.[30] Mutations of the voltage-gated calcium channel genes have been associated with neurodevelopment disorders.[31] Furthermore, vitamins may play a vital role in neuron development,[32] with a lack of B vitamins being associated with ADHD diagnosis and B-2 and B-6 deficiencies potentially being related to high ADHD symptom severity.[33] Folic acid, B-12, B-6, and B-2

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are sources of coenzymes that contribute to carbon metabolism and have been linked to thymidine synthesis. Thymidine is used to synthesize purines, which are involved in RNA and DNA structure formation.[34] In general, our findings herein support the important role of calcium and vitamin B-2 in ADHD.

Compared to the control group, the ADHD patients had a higher intake proportion of refined grains. The processing of refined grains removes many essential vitamins and minerals, so they offer less nutritional value.[35] In contrast, whole grains are relatively more natural and typically minimally processed and are thus rich in vitamins, minerals, and fiber. We found that ADHD patients had lower Vitamin B2 than controls, which was associated with a greater intake of refined grains. Currently, no data have directly shown a correlation between refined/whole grains and ADHD. Only one Iranian study has demonstrated that the consumption of refined grains was significantly associated with depression and anxiety in women.[36] Therefore, the intake proportion of refined/whole grains may be related to individuals' moods or behaviors. Our study showed that ADHD subjects may intake more refined grains in their diets than healthy children, which may be due to either the children's own preference or the children's parents' provision. This finding suggests that while children with ADHD had a similar intake of grains as the healthy children, they may receive fewer vitamins, minerals, and fiber from their diet. We also observed that compared to the control group, children with ADHD had a lower dairy intake. Furthermore, calcium and Vitamin B2 intakes were positively correlated with dairy intake, which is an important source of calcium and Vitamin B. This finding supports that nutrients deficiency, which is derived from ones' dietary habits, may be associated with a susceptibility to ADHD.

We found that both the composite diet score (refined grains and dairy) and composite nutrient score (calcium and vitamin B-2) could significantly differentiate patients with ADHD from healthy controls. The composite scores were also significantly correlated with the severity of ADHD clinical symptoms. A higher intake of sweetened desserts, fried foods, and salt have been associated with an increased risk of ADHD,[6,8] and our findings generally support this point of view. One possible explanation is that children with ADHD are commonly impulsive, have difficulty waiting, and seek instant satisfaction. Therefore, they favor foods with low nutrient density as such foods tend to be crispy, sweet, or tasty.[10] Furthermore, the association between unhealthy dietary habits and ADHD may be related to underlying poor nutrients intake. Nutrient deficiencies may cause insufficient brain function and lead to inattention and hyperactivity/impulsivity symptoms in children. However, due to

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the nature of the cross-sectional study, the relationship between nutrient deficiencies and ADHD requires additional investigation in the future.

This study has several limitations that need to be mentioned at this time. First, the nutrient status in this study was based solely on FFQ measurements. No laboratory assessments were performed to determine biochemical markers. Second, our sample size was small, thus reducing the study's statistical power. Furthermore, while we used a logistic regression model and ROC curve to differentiate ADHD patients from controls, no additional participants were recruited to verify our findings. Third, ADHD patients and controls were not age- and gender-matched. Although we set age and gender as covariates in the MANCOVA model, the imbalanced demographic characteristics between groups still may have influenced the results. ADHD is generally heterogeneous and can be categorized into different subtypes, while psychiatric comorbidities can be observed in most ADHD patients.[37] The nutrient index was based on nutrients density. Although the nutrient status was standardized using data from previous studies,[15] the heterogeneity of ADHD and controls may have confounded our findings. Fourth, multiple test corrections were not performed in this study, so the potential for false positives cannot be excluded. Finally, dietary habits may differ based on country and culture. Additional research is needed to confirm this study's findings.

In conclusion, the findings of this study indicate that children with ADHD tend to intake more refined grains and less dairy, calcium, and Vitamin B2 compared to healthy controls. The composite score of dietary patterns and of nutrient status was capable of significantly differentiating ADHD patients from healthy controls and were significantly correlated with ADHD clinical symptoms. These results indicate that dietary and nutrient factors may contribute to the pathophysiology of ADHD.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

All authors declare to have no conflicts of interest. This work was supported by a grant from the Chang Gung Research Project (CMRPG8E1441).

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Table 1. Characteristics of patients with ADHD and healthy controls[†]

Characteristics	ADHD (N=42)	Controls (N=36)	Statistic (χ^2 or t)	*p*-value
Gender			5.804	0.016*
Male	33 (78.6)	19 (52.8)		
Female	9 (21.4)	17 (47.2)		
Age (years)	8.1±1.7	9.8±2.7	3.342	0.001*
Height (cm)	129.1±10.0	140.8±15.3	3.893	<0.001*
Weight (kg)	29.3±9.4	37.5±12.2	3.292	0.002*
BMI (kg/m^2)	17.2±3.9	18.4±3.1	1.442	0.153
FSIQ of the WISC-IV	99.1±10.6	108.7±12.8	3.623	0.001*
Clinical measures				
SNAP-IV parent form (I)	16.2±6.7	4.6±5.5	8.272	<0.001*
SNAP-IV parent form (H)	14.1±6.8	3.1±4.5	8.461	<0.001*
SNAP-IV teacher form (I)	15.5±6.1	3.5±3.9	10.143	<0.001*
SNAP-IV teacher form (H)	12.1±7.1	2.4±3.0	7.697	<0.001*
ADHD-RS (I)	8.6±0.7	0.5±1.6	30.829	<0.001*
ADHD-RS (H)	7.0±2.8	0.4±1.5	13.289	<0.001*
Primary caregiver			2.274	0.209
Mother	37 (88.1)	35 (97.2)		
Other	5 (11.9)	1 (2.8)		
Caregiver's age	38.8±5.0	40.1±2.2	1.467	0.149

[†]Data are expressed as N (%) or mean±SD.
FSIQ: Full Scale Intelligence Quotient; WISC-IV: Wechsler Intelligence Scale for Children–Fourth Edition; I: inattention scores; H: hyperactivity/impulsivity scores.
*$p<0.05$

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Table 2. Dietary and nutrient status between children with ADHD and healthy control children[†]

Characteristics	ADHD (N=42)	Controls (N=36)	Statistic (F-value)	*p*-value
Dietary index				
Grains, unit	3.85±0.76	3.72±0.60	1.129	0.291
Refined grains, unit	0.35±0.55	0.10±0.23	5.171	0.026[*]
Unrefined grains, unit	3.52±0.98	3.63±0.72	0.029	0.865
Meat (including seafood), unit	5.44±1.95	5.00±2.04	0.218	0.642
Vegetable, unit	2.45±2.18	2.33±1.34	0.206	0.651
Fruit, unit	1.24±1.12	1.28±0.97	0.205	0.652
Dairy, unit	0.95±0.76	1.27±0.79	6.450	0.013[*]
Oil, unit	4.06±2.40	4.58±2.67	0.028	0.867
Nuts/seeds/legumes, unit	0.11±0.17	0.22±0.41	3.007	0.087
Nutrient index[‡]				
Protein, g	74.55±11.49	74.39±12.85	0.522	0.472
Fat, g	0.33±0.10	0.36±0.10	1.034	0.312
Carbohydrate, g	0.73±0.30	0.73±0.19	0.160	0.691
Calcium, mg	589.04±248.64	669.29±251.66	4.230	0.043[*]
Phosphorus, mg	1208.61±198.85	1253.98±198.92	3.060	0.084
Ferritin, mg	1.14±0.28	1.01±0.27	0.685	0.411
Magnesium, mg	269.99±69.55	267.82±64.43	0.260	0.612
Zinc, mg	10.31±1.43	10.11±1.50	0.022	0.882
Potassium, mg	2439.15±738.07	2436.98±655.75	0.010	0.922
Vitamin A, ug	880.00±477.11	920.37±379.93	0.193	0.662
Vitamin D, ug	5.76±2.78	5.85±2.34	0.038	0.846
Vitamin E, mg	7.90±2.50	8.61±2.35	0.500	0.482
Vitamin B-1, mg	1.23±0.23	1.19±0.21	0.758	0.387
Vitamin B-2, mg	1.47±0.46	1.64±0.44	5.316	0.024[*]
Niacin. mg	19.35±5.83	18.32±5.39	0.198	0.657
Vitamin B-6, mg	1.56±0.38	1.49±0.35	1.205	0.276
Vitamin B-12, mg	5.36±2.66	5.70±3.73	1.103	0.297
Vitamin C, mg	145.20±82.73	137.48±61.29	1.257	0.266
Dietary fiber, g	15.92±6.61	15.68±5.54	0.460	0.500
Cholesterol, mg	285.94±134.96	312.04±109.92	1.479	0.228

[†]Data are expressed as N (%) or mean±SD.
[‡]All nutrients are represented as nutrient density (each nutrient index divided by total energy intake).
[*]$p<0.05$

Table 3. Effect of dietary and nutrient indices on participant groups (controls vs. ADHD)

Variables	Z-scores[†]		Unadjusted model		Adjusted model	
	ADHD	Controls	*β* (95% CI)	*p*-value	*β* (95% CI)	*p*-value
Refined grains	0.26±1.22	-0.30±0.52	0.18 (0.04-0.81)	0.025	0.19 (0.04-0.93)	0.040
Dairy	-0.18±0.97	0.22±1.01	1.69 (0.94-3.05)	0.081	2.26 (1.16-4.43)	0.003
Calcium	-0.15±0.99	0.17±1.00	1.00 (1.00-1.00)	0.162	1.00 (1.00-1.00)	0.050
Vitamin B2	-0.17±1.01	0.20±0.96	2.30 (0.82-6.44)	0.112	3.64 (1.15-11.56)	0.028

Unadjusted model: univariate logistic regression model; adjusted model: multivariate logistic regression model, controlling for age and sex; 95% CI: 95% confidence interval.
[†]Z-scores are expressed as mean±SD.

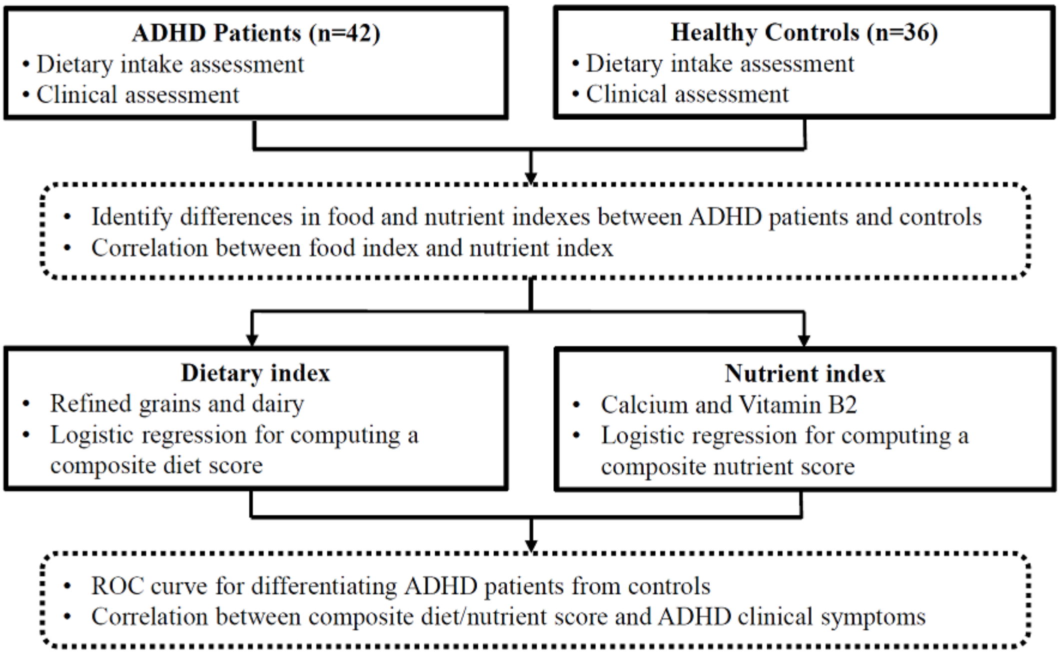

Figure 1. Conceptual diagram of study procedures and data analysis.

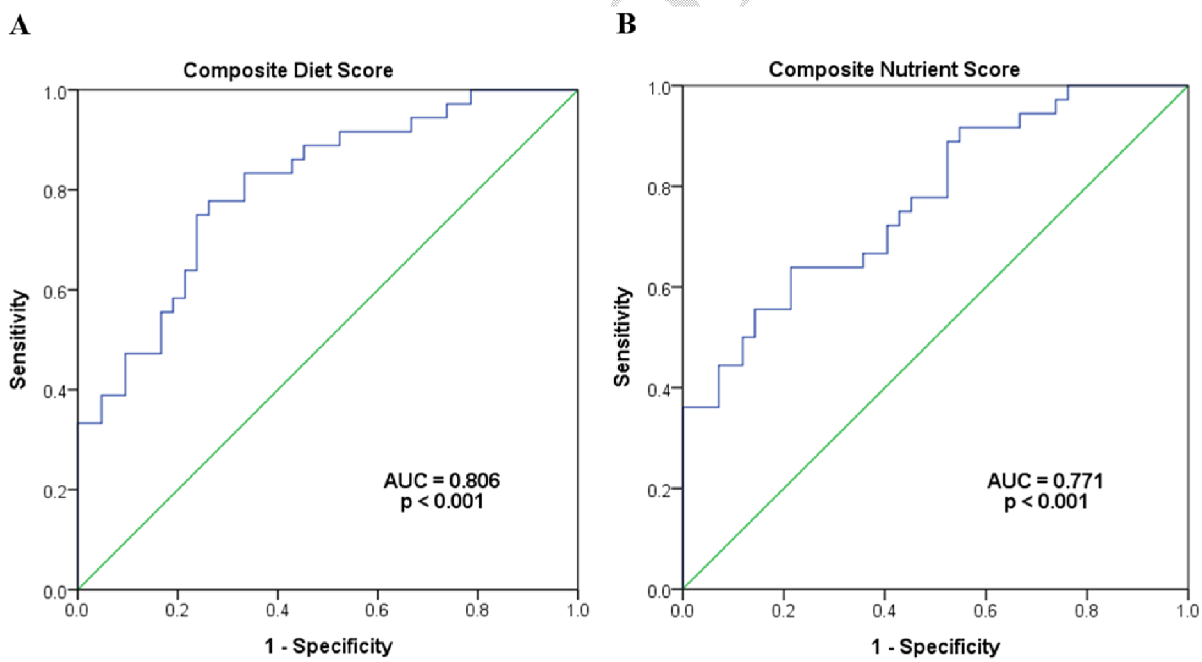

Figure 2. Receiver Operating Characteristic (ROC) curve of using the composite diet score (A) and the composite nutrient score (B) to differentiate children with ADHD from healthy controls. The composite diet score was obtained using refined grains and dairy as predictors in a logistic regression model; the composite nutrient score was obtained using calcium and vitamin B2 as predictors in a logistic regression model.