Original Article

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Nutrition Bio Shield (NBS) Supplement for Adult Attention-Deficit/Hyperactivity Disorder: A Randomized Controlled Trial

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Abstract

Background: Micronutrient interventions for Adult Attention-Deficit/Hyperactivity (ADHD) could be helpful. We used a naturally processed whole wheat grains supplement containing higher doses of micronutrients named Nutrition Bio Shield (NBS). We aimed to determine its effects on ADHD symptoms in adults.

Methods: Fifty-two medication-free adults with ADHD were randomly assigned to receive 5 *g* of NBS supplement or placebo daily for eight weeks.

Results: Twenty-three participants in the NBS group and 24 participants in the placebo group completed the study. After 8 weeks, compared with the placebo, the ADHD scores significantly decreased (mean difference 95%CI): -4.9 (-8.6 to -1.1); p=0.01; Cohen's d=0.74), and quality of life significantly improved (mean difference 95%CI): 5.6 (0.12 to 11.3); p=0.04; Cohen's d=0.59) in the NBS group. The observed side effects were minimal and did not differ statistically between groups.

Conclusion: Quality of life increased during consumption of the NBS supplement, compared to the placebo. However, despite the statistically significant findings, these changes in ADHD symptoms were small and the clinical significance may be low (about 5%).

Keywords: Adult, Attention deficit disorder with hyperactivity, Micronutrients, Quality of life, Trace elements, Triticum, Whole grains

Introduction

Adult Attention-Deficit/Hyperactivity Disorder (ADHD) is a disruptive behavior disorder with a prevalence of about 3.8% (1). It is usually associated with serious psychiatric disorders such as depression, alcohol or drug abuse, and social dysfunctions such as education and job instability. Adult ADHD is also associated with higher rates of divorce (2). The core features of adult ADHD include mild to severe inattention, distractibility, and impulsiveness (3). Furthermore, adult ADHD is a manifestation of untreated childhood ADHD. If patients with ADHD do not receive a timely treatment, this disorder can seriously affect the life quality of the patients and people living with them (4). The first line medication to treat ADHD is methylphenidate; however, its common negative side effects such as sleep disorders and loss of appetite as well as stigmatization associated with the diagnosis may cause many patients with ADHD go untreated (5). Investigations have shown that the duration of untreated illness for adult ADHD is about 17 years (6).

ADHD is a disorder with a multifactorial etiology, and nutrition may be one of its contributing factors (7). Sun *et al*, in a systematic review, reported lower serum zinc levels in children with ADHD (8). Also, Robberecht *et al* have assessed the association of some minerals including iron, zinc, copper and selenium with ADHD. Magnesium and iron levels were lower in the serum of ADHD clients (9). Landaas *et al* revealed lower levels of vitamins B2, B6, and folate in adults with ADHD compared to healthy controls (10). However, these were cross-sectional studies that only assessed the associations. Therefore, they cannot be used to infer causality or completely describe nutritional status.

In addition, efforts made to evaluate the effects of single nutrient supplements to improve ADHD symptoms have reported conflicting results of no or limited effects for single nutrients or low dose nutritional supplements. In a pilot trial, Arnold *et al* combined zinc glycinate with amphetamine and reported an ambiguous result for zinc glycinate effects on ADHD. They reported a 37% lower optimal amphetamine in the zinc group compared to the placebo group (11). In a 6-week trial of zinc supplementation, Noorazar *et al* reported improvement in inattention symptoms of children with ADHD, but not in their hyperactivity (12). In a review, Händel *et al* evaluated the effects of polyunsaturated fatty acids (PUFAs; omega 3 and omega 6) in the treatment of children and adolescents with ADHD and reported that PUFAs had no clear benefit for ADHD (13). However, some studies show that micronutrients can have a positive effect in ADHD. In a 6-week placebo controlled randomized controlled trial, Akhondzadeh *et al* augmented zinc supplement to methylphenidate treatment and concluded that zinc augmentation could significantly increase the therapeutic effect of methylphenidate (14). Konofal *et al* administered iron supplements to ADHD children and reported improvement on the Clinical Global Impression-Severity score. However, iron did not achieve significance for improvements on the teacher and parent Conner's rating scales (15). Sever *et al* administered iron supplements to 14 non-anemic boys with ADHD for 4 weeks and reported reduction of symptoms in Conner's parent rating scale but not the teachers of symptoms (16). Starobrat-Hermelin *et al*, in an open-label trial, administered a magnesium supplement to magnesium-deficient children with ADHD and reported improvement in symptoms compared to the control group (17). Coleman *et al* conducted a pilot clinical trial on six children with ADHD and concluded that vitamin B6 combined with methylphenidate could decrease hyperactivity better than vitamin B6 alone or placebo (18).

Later, investigators tried to assess the effects of wide-ranging micronutrients on ADHD symptoms. In one of those investigations, Rucklidge *et al* investigated the effects of a multivitamin and mineral supplement on adult ADHD and found a significant improvement in self-reported symptoms of ADHD (19). In a recent work, Johnstone *et al* investigated the effects of a vitamin and mineral supplement on symptoms of ADHD among youths and found a significant effect on clinician-rated scores (20).

While there is growing interest regarding the association between ADHD symptoms and dietary intake, there is a lack of clinical trials on the possible effects of natural products enriched with broad-spectrum micronutrients and bioactive compounds in a single supplement. Nutrition Bio Shield (NBS) is a brand name for a supplement naturally processed

from the whole wheat grain and is a patented blend. In this product, a new method of grain processing is used yielding a higher dose of micronutrients. This product's contents are between the Recommended Dietary Intake (RDA) and upper tolerable intake levels (UL) for most nutrients. It contains a broad spectrum of micronutrients such as vitamins B1, B2, B3, B5, B6, B9, C, D, K, A and alpha-tocopherol; magnesium; manganese; zinc; copper; phosphorus; calcium; potassium; sulfur; boron; iron; phenolic compounds; and ingredients such as fatty acids including omega-3, 6 and 9 (Table 1). Hence, due to the adequate and broad spectrum of micronutrients and bioactive compounds in this product, and considering the possible role of the single or complex vitamins and minerals in improving mental health, especially ADHD, we proposed that adults with ADHD could benefit from the over-the-counter NBS product. Thus, we designed a randomized controlled trial and determined the effects of NBS supplement on adults with ADHD.

Materials and Methods

Study design and process

This study was a double-blind, placebo-controlled randomized clinical trial performed from July 2020 to August 2021. Clients referring to a psychiatric clinic were assessed for ADHD symptoms by a psychiatrist. The diagnosed clients were invited to participate in this trial after explaining the intervention process and objectives of the study. This way, 79 adults were invited to join the trial. Of them, 52 eligible clients signed the informed consent form and were recruited. They were randomly assigned to receive 5 *g/day* of the NBS supplement or 5 *g/day* of placebo produced by the same factory. The placebo was whole wheat flour. The organoleptic properties of the placebo and NBS were similar and they were presented in the same packaging, in a way that they were indistinguishable from each other. To reduce selection bias, we performed simple randomization using the computerized random allocation in an Excel sheet using the function=RAND. Furthermore, the allocation concealment was done using sequentially numbered containers. In this way, the allocation sequence was concealed from the research team. Therefore, the person who randomized the patients did not know whether each subject was allocated to the treatment or placebo group. The patients were instructed to mix the powder in a glass of water and consume it before breakfast early in the morning for 8 weeks. We monitored the adherence to treatment by phone. Also, the participants were told to bring the supplement container with them at the final visit to check the remaining amount and proper consumption. Those who consumed less than 80% of their supplement were excluded in the per-protocol analysis. Assessments were done at the baseline and end of the trial at week 8. The primary outcome was the change in the ADHD score during the study and the secondary outcome was the change in the quality-of-life score during the study. The study design was registered in a clinical trial registry approved by the World Health Organization (WHO) under registration number (IRCTID): IRCT20140203016465N6.

Study tools

Study tools included the validated Persian version of the Adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1) Symptoms Checklist from the World Health Organization (WHO) Composite International Diagnostic Interview. This instrument comprises a checklist of 18 ADHD symptoms from Diagnostic and Statistical Manual of Mental Disorders (DSM) that are ranked on a scale of 0 to 4, leading to a total score up to 72. A higher ASRS-V1.1 score indicates higher ADHD symptoms. We used the change in the total score of the questionnaire as our primary outcome. It has sufficient validity to distinguish the current symptoms of ADHD in over the 18-year-old clients. A cutoff of 30 on the ADHD checklist has been used to diagnose ADHD with an 81.82% sensitivity and 62.5% specificity (21). Mousavi *et al* have validated the translated version of this tool among adult clients. Its Cronbach's alpha of 0.85 shows an acceptable internal consistency (22).

The other study tool was the World Health Organization Quality of Life (WHOQOL-BREF) scale. This instrument is developed by the WHO to measure the quality of life in 15 countries. WHOQOL-BREF has 26 Likert scale questions, each of which can have a score of 1 to 5. It comprises five subscales of physical health (7 questions), mental health (6 questions), social health (3 questions), environmental health (8

Table 1. Macronutrients, Micronutrients, and Phenolic compounds in the NBS supplement according to food chemistry laboratory, the High-Performance Liquid Chromatography (HPLC), and Atomic Absorption Spectroscopy (AAS) analyses

	Nutrient	Value	Reference method
Macronutrients	Moisture	8.6%	-
	Total ash	1.8%	-
	Fiber	10.58%	-
	Digestible nutrients	60.7%	-
	Carbohydrate	42.53 *g* in 100 *g*	-
	Fat	6.2%	-
	Protein	17.8%	-
	Cellulose	6%	-
Vitamins	B1 (thiamin)	41.9 *mg*/100 *g*	HPLC
	B2 (Riboflavin)	1.5 *mg*/100 *g*	HPLC
	B3 (Niacin)	34.7 *mg*/100 *g*	HPLC
	B5 (Pantothenic acid)	14.2 *mg*/100 *g*	USP 43
	B6	1.3 *mg*/100 *g*	HPLC
	B9 (Folate)	2.9 *mg*/100 *g*	HPLC
	A	362 *IU*/100 *g*	HPLC
	C	56.2 *mg*/100 *g*	HPLC
	D3 (Cholecalciferol)	648.2 *IU*/100 *g*	HPLC
	K,	63.6 *mcg*/100 *g*	HPLC
	E (alpha-tocopherol)	37.9 *mg*/100 *g*	HPLC
Minerals	Iron	22 *mg*/100 *g*	Spectrophotometry
	Zinc	2.5 *mg*/100 *g*	AAS
	Manganese	4.93 *mg*/100 *g*	-
	Copper	1.31 *mg*/100 *g*	-
	Magnesium	0.29%	-
	Potassium	2.31%	-
	Calcium	0.95%	-
	Phosphorus	0.42%	-
	Sulfur	0.28%	-
	Boron	0.62%	-
Fatty acids	Omega-3	48.42 *mg/g*	-
	Omega-6	60.62 *mg/g*	-
	Omega-9	22.16 *mg/g*	-
	Oleic Acid	13.24	HPLC
	Alpha Linoleic acid	26.8	USP 43
Phenolic compounds	Arctigenin	2.34	HPLC
	Gallic Acid	2.41	HPLC
	Quercetin	9.42	HPLC
	Inulin	2.64	HPLC

USP: United States Pharmacopeia quality standard

questions), and general health and quality of life (2 questions). After obtaining the raw scores of each subscale, they should be converted to a standard score from 0 to 100. The local version of this tool is validated by Nejat *et al*. The factor analysis and intraclass correlation for the scale and sub-scales were convincing and the Cronbach's alpha values were above 0.7 for the subscales (23).

Participants

Inclusion criteria: we enrolled the medication-free adults (18-55 year-old subjects not currently or actively using ADHD medicines during the past year) who were diagnosed with ADHD after a clinical interview performed by a psychiatrist based on the DSM-5 criteria.

Exclusion criteria: we excluded the volunteers who consumed any medication or dietary supplement that could affect the outcomes; those on specific diets had a pre-existing chronic illness, major neurological conditions such as CNS tumors and multiple sclerosis, major psychiatric disorders such as bipolar mood disorders and major depressive disorder. Furthermore, subjects with celiac disease, alcohol or substance use disorder; or those who were pregnant or were in lactation, were excluded.

Statistical analysis

We gathered the data and then checked for outliers and assumptions. No outlier value was detected and normality of the dependent variable in each group was checked by the histogram and the Stem-and-leaf plot. Furthermore, normality was confirmed through the non-significant Shapiro-Wilk test. Moreover, equality of variances was confirmed. Hence, we used independent t-test and chi-square test to compare baseline characteristics between groups. Then, we assessed the null hypothesis of the similarity of primary and secondary outcomes between the two groups using the independent sample t-test. Furthermore, we performed an ANCOVA model, controlling for baseline ADHD and mental health, as well as age and gender. We performed analyses on completers without significant protocol deviations. We used SPSS ver. 19 software and the significance level was set at α=0.05. Also, the groups were blinded to the person who analyzed the data.

Ethical approval

This work conforms to the requirements of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Subjects gave informed consent, and patient privacy was preserved. The study design was approved by the Ethical Committee of Tehran University of Medical Sciences under the study number of VCR.REC.1398.702.

Results

23 participants (18 female/5 male) in the NBS group and 24 (18 female/6 male) in the placebo group completed the study (Figure 1). The baseline characteristics of the participants are listed in table 2. After eight weeks of NBS consumption, ADHD symptoms decreased by -4.2±7.5, but in the placebo group, ADHD symptoms remained almost unchanged (0.6±5.1) and this difference, which was about 5% between groups, was statistically significant; mean difference (95% CI): -4.9 (-8.6 to -1.1); p=0.01; Cohen's d=0.74 (Table 3). In the ANCOVA model, after controlling for baseline ADHD, mental and physical health scores, as well as age and gender, and with the Intention to Treat (ITT) approach, the difference between the groups remained significant; F(1, 46)=5.96, p=0.019 (observed power=0.66). Using the cutoff point, improvement in ADHD symptoms was 21.7% in the NBS group *vs*. 4.2% in the placebo group. The quality of life increased by 3.9±10.1 in the NBS group and decreased in the placebo group by -1.7±8.8. This difference between the groups was statistically significant with the mean difference (95% CI): 5.6 (0.12 to 11.3); p=0.04; Cohen's d=0.59 (Table 3).

Changes in ADHD score after eight weeks are shown in figure 2, and changes in quality of life are shown in figure 3. At the end of the study, we assessed side effects using a routine symptoms checklist in which subjects were asked whether they experienced any of the following side effects during the study: nausea, vomiting, skin rash, headache, tingling, itching, irritation, discomfort, intolerance, insomnia, confusion, drowsiness, anxiety, and stress. Then, we compared the reported side effects between the groups. In the NBS group, one case reported intolerance and one case reported nausea. In the placebo group, two cases reported headache and one case reported

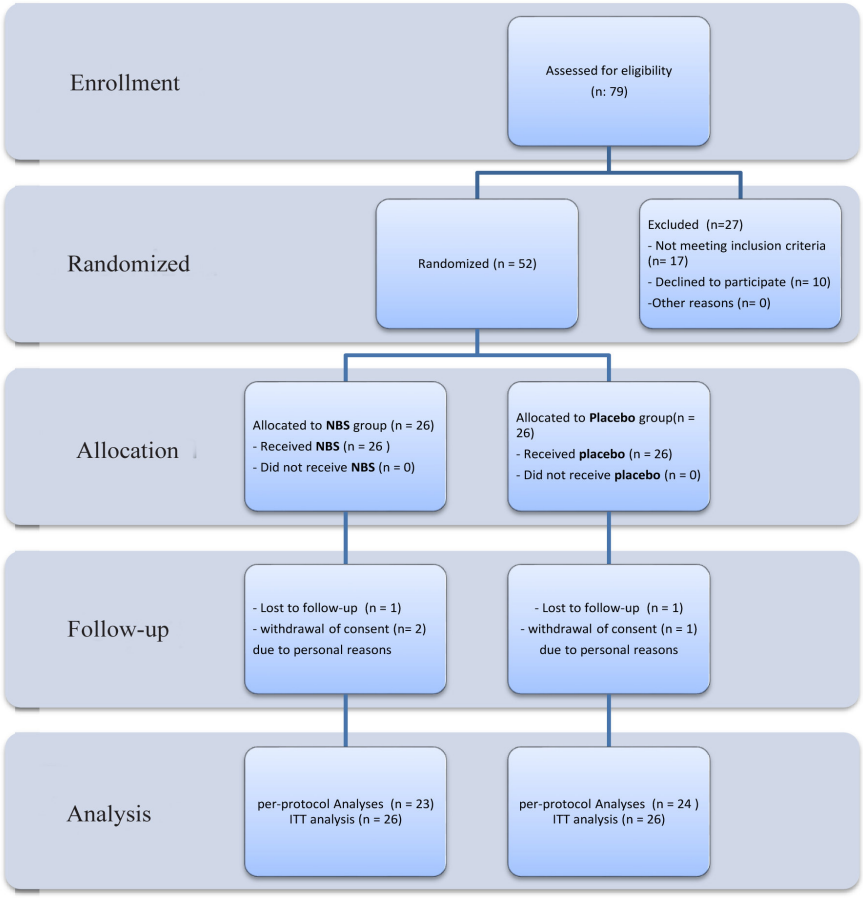

Figure 1. Consort flow diagram for the study showing the enrollment of subjects, and their allocation to groups during the trial.

Table 2. Baseline characteristics and general health status of the participants in each group compared using the independent sample t-test, and chi-square test, or fisher's exact test

		NBS (N=23) Mean ± SD	Placebo (N=24) Mean ± SD	p-value
Age (year)		38.5±11.8	38±13.4	0.99
Height (*cm*)		159.7±5.8	160.3±9.8	0.80
Weight (*kg*)		73.6±14.6	72±15.0	0.71
gender		18f/5 *m*	18f/6 *m*	0.79 Δ
Education level	High school diploma or bellow Undergraduate Upper graduate	16 (69.6%) 7 (30.4%) 0 (-)	12 (50%) 9 (37.5%) 3 (12.5)	0.28 Δ
Income	Low Middle High	7 (30.4%) 16 (69.6%) 0 (-)	10 (41.7%) 14 (58.3%) 0 (-)	0.42 Δ
ADHD score		50.1±16.9	49.9±10.6	0.95
Physical health		53.5±24.8	61.8±16.8	0.18
Mental health		42.7±16.3	50.8±13.0	0.07
Social health		49.5±29.6	48.9±24.9	0.93
Environmental health		48.6±22.4	45.5±20.8	0.61
Life quality		53.6±22.2	54.6±15.0	0.85

Δ Chi-square or fisher's exact test

Table 3. dependent variables at different time points of the trial are compared between groups using independent sample t-test

		Baseline Mean ± SD	Post test Mean ± SD	Change from baseline± SD	t-value	Mean difference	95% confidence interval	p-value	Effect size (cohen's d)
ADHD (ITT)	NBS (N=26)	49.1±16.1	45.4±16.0	-3.7±7.2	-2.5	-4.37	-0.93 to -7.8	0.01	0.70
	Placebo (N=26)	49.6±10.2	50.2±9.6	0.6±4.9					
ADHD (per-protocol)	NBS (N=23)	50.1±16.9	45.9±16.9	-4.2±7.5	-2.6	-4.9	-1.1 to -8.6	0.01	0.74
	Placebo (N=24)	49.9±10.6	50.5±9.9	0.6±5.1					
Physical health	NBS	53.5±24.8	60.3±21.0	6.8±13.6	1.7	7.5	-1.1 to 16.2	0.08	0.50
	Placebo	61.8±16.6	61.1±16.4	-0.7±15.8					
Mental health	NBS	42.7±16.3	49.0±19.1	6.2±11.02	0.3	1.3	-6.5 to 9.1	0.74	0.09
	Placebo	50.8±13.0	55.8±18.1	4.9±15.2					
Social health	NBS	49.5±29.6	50.2±27.5	0.7±10.7	0.5	2.1	3.7 to -5.3	0.56	0.16
	Placebo	48.9±24.9	47.3±24.4	-1.4±14.5					
Environmental health	NBS	48.6±22.4	51.4±21.9	2.7±10.5	0.06	0.3	-7.0 to 7.5	0.94	0.02
	Placebo	45.5±20.8	48.0±16.2	2.4±14.0					
Life quality	NBS	53.6±22.2	57.6±20.8	3.9±10.1	2.0	5.6	0.12 to 11.3	0.04	0.59
	Placebo	54.6±15.0	52.9±15.0	-1.7±8.8					

Δ Cohen›s d=(M2 - M1)/SD_{pooled} where SD_{pooled}= $\sqrt{((SD_1^2 + SD_2^2)/2)}$. ITT: Intention-To-Treat approach.

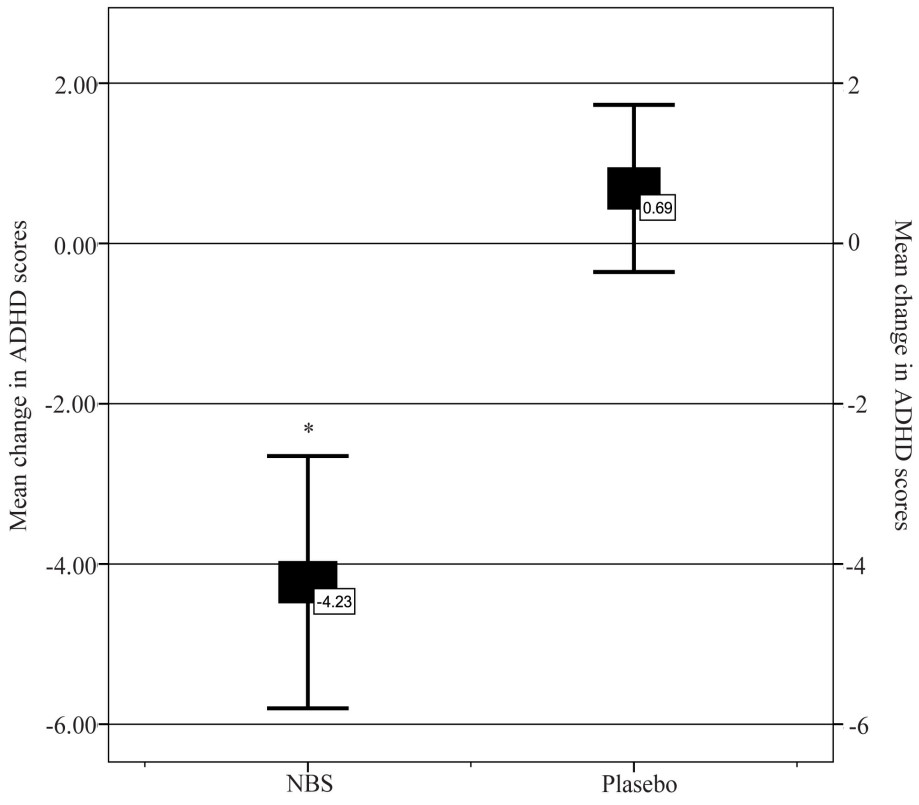

Figure 2. Mean change in ADHD scores ± SE during the study period in the NBS and placebo groups. The mean difference between groups was significant.

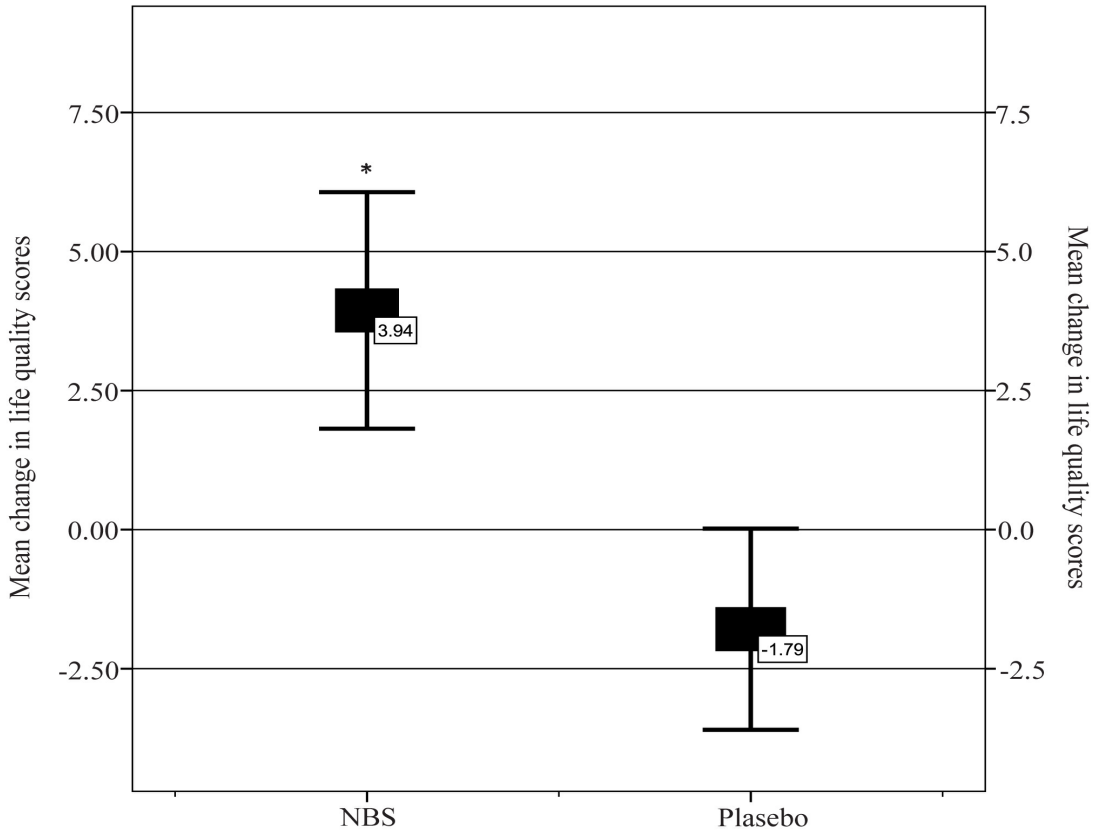

Figure 3. Mean change in life quality scores ± SE during the study period in the NBS and placebo groups.

* The mean difference between groups was significant.

nausea. The difference between the two groups was not significant (Fisher's Exact test; p=0.52).

Discussion

The main finding of this randomized clinical trial was that ADHD symptoms decreased slightly (about 5%) in the treatment group during the study. These symptoms remained almost unchanged in the placebo group, and the difference between groups was statistically significant with an almost large effect size (Cohen's D=0.74). The improvement rate of ADHD was 21.7% in the NBS group *vs*. 4.2% in the placebo group.

We have to interpret these results in terms of NBS ingredients. This supplement is a whole wheat product enriched with micronutrients, polyunsaturated fatty acids, and bioactive compounds. Hence, the NBS supplement could reduce symptoms of ADHD possibly through the effects of micronutrients on improving the symptoms of inattention and impulsivity. There are many theories about the possible mechanisms for micronutrients effects on decreasing ADHD symptoms, including coenzyme activity (24), the role of micronutrients in dopamine syntheses (25), the antioxidant role, and the modification of neuronal membrane functioning (26).

Our findings are in line with some previous studies on the use of different vitamins or minerals in improving mental health status. New evidence supports the use of integrative multivitamins and minerals rather than a single micronutrient. In a trial on the use of multivitamin and mineral supplementation in ADHD clients, Rucklidge *et al* reported improvement in attention deficit (but not impulsivity) and a reduction in aggression and emotional dysregulation (27). Harding *et al* compared the effects of Ritalin with a nutritional supplement containing a combination of micronutrients, phytochemicals, probiotics, phospholipids, essential fatty acids and amino acids in children with ADHD and reported similar improvement in self-control and attention in both groups (28). Some other studies have also reported the positive effects of multivitamin-mineral supplements on ADHD. In a preliminary

open-label trial of multivitamin and mineral supplementation in 14 unmedicated adults ADHD, Rucklidge *et al* reported a significant improvement in ADHD symptoms (29). They have also reported an improvement in the quality of life of adults with ADHD after administration of micronutrients. This was also consistent with our results, showing a slight improvement (about 5.6%) in quality of life following micronutrient-enriched NBS supplementation (a medium effect size with Cohen's D=0.59). This could be due to an improvement in the perceived quality of life following mood improvements. In another study, Rucklidge *et al* found that after eight weeks of micronutrient supplementation, ADHD symptoms were significantly reduced (30). These studies were in line with ours.

However, there are studies that report minimal or no effect of micronutrients. Knowing this, negative results usually have less chance of being published. In one of these studies, Sinn and Bryan reported no additional therapeutic benefit of micronutrients on learning and behavioral problems associated with ADHD in children (31). In a systematic review of zinc and iron supplementation in children with ADHD, Granero *et al* concluded that zinc supplementation might improve baseline zinc status and ADHD symptoms. However, iron supplementation was more controversial, with benefits limited to individuals with low baseline iron/ferritin levels (32). Arnold *et al* also reported mixed effects with zinc glycinate on ADHD (11). In a systematic review and meta-analysis, Händel *et al* reported no beneficial effects of polyunsaturated fatty acids on ADHD core symptoms or quality of life in children and adolescents (13). The effects of vitamin supplementation on ADHD symptoms were inconsistent depending on the role of each vitamin in the etiology of ADHD (33). Contradictory results may also be due to different genetic phenotypes, different dietary backgrounds or previous micronutrient deficiencies, and using supplements with different micronutrient ingredients or dosages. Furthermore, studies with small sample sizes or lower quality may be another source of heterogeneity. The most positive results in ADHD come from broad-spectrum micronutrient trials, not a single dose or low dose of a vitamin or mineral.

Limitations

We used a study with a different dosing schedule and supplement to calculate the sample size, thus it is unclear whether the study was underpowered. Also, we did not assess baseline intake among participants. Hence, there is a lack of clarity on which micronutrient in this supplement has had a positive effect on adult ADHD. Also, the mechanism of action of this supplement on patients is unknown and future studies should shed light on this point. Another limitation of this study is the lack of follow-up of the patients after 12th week of trial. This study was performed during the lockdowns due to Covid-19 pandemic and fear of clients to participate in clinical trials during the outbreak of Covid-19. Although this limitation extended the duration of data gathering, we motivated the participants and ensured maximum protective measures against the virus. Fortunately, the clients cooperated well with us and no Covid-19 infection was reported during the study.

Conclusion

ADHD symptoms slightly decreased, and the life quality sub-scale of the World Health Organization Quality of Life (WHOQOL-BREF) scale was improved significantly. Quality of life increased during consumption of the NBS supplement, compared to the placebo. However, despite the statistically significant findings, these changes in ADHD symptoms were small and the clinical significance may be low (about 5%). This study is possibly the first trial to test the use of a natural product enriched with micronutrients in adults with ADHD. However, this product is still under investigation and further studies are needed to confirm the results of this preliminary study. This study does not recommend supplementation instead of medications. In addition, testing with non-proprietary products also requires more work.

Funding

The research was funded by the NBS and the research facilities were provided by the psychiatry and psychology research center.

Ethical approval

This work conforms to the requirements of the Declaration of Helsinki in 1995 (as revised in

Edinburgh, 2000). The subjects gave informed consent, and patient privacy was preserved. The study design was approved by the Ethical Committee of Tehran University of Medical Sciences (code: VCR.REC.1398.702).

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Conflict of Interest

The research was funded by the NBS and the research facilities were provided by the psychiatry and psychology research center, Tehran University of Medical Sciences. Investigators have not received any salary or other benefits from the supplement manufacturers and we do not have any ongoing relationships such as consultancies, *etc*. We confirm full academic independence to report and publish all the findings, and the industry was not involved in the study hypothesis/design, execution, analysis, or interpretation.

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