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Micronutrient Supplementation in Adolescents and Adults with Autism Spectrum Disorder: An Open-Label Trial

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Essay article

Abstract

Aim: To investigate the change in core and associated behaviours of autism spectrum disorder (ASD) following micronutrient supplementation.

Methods: Adolescents and adults with ASD (N=16, aged 11-22) participated in an 8-week open label study of micronutrients supplements. Measures of behaviour and social responsiveness, using Autism Behaviour Inventory – Short (ABI-S) and Social Responsiveness Scale (SRS) respectively, were completed by parents and teachers at baseline and end of the study. Paired t-tests were used to compare the pre- and post-treatment mean scores.

Results: Eleven participants completed the study. Mean scores on both clinical outcomes showed improvements (decreases) over the study period, but none were statistically significant. Parent-reported ABI-S scores decreased (improved) by 11.5% (effect size=-0.52, p=0.08), teacher-reported ABI-S scores improved by 3.7% (effect size=-0.16, p=0.31), and parent-reported SRS scores improved by 8.6% (effect size=-0.56, p=0.05). There were no adverse events reported.

Conclusion: This study adds to the mixed findings of micronutrient supplementation in individuals with ASD, consistent with previous studies. Micronutrients were safely tolerated. In the future, randomized controlled trials with a larger sample size are needed to provide more insight on the potential benefits of micronutrients in ASD.

Keywords: *Micronutrients, autism spectrum disorder (ASD), nutrition, supplements, clinical trial*

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1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by early deficits in social interactions and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013). The prevalence of ASD has been on the rise with the Centers for Disease Control (CDC) indicating a prevalence rate of 21.5 and 27.6 per 1,000 children aged 4 and 8, respectively (Shaw et al., 2023; Maenner et al., 2023). Additionally, the CDC estimates 2.21% of adults, over the age of 18, in the United States are on the spectrum (Dietz et al., 2020). To address these growing numbers, research efforts have increased to understand etiological factors contributing to ASD and identify potential interventions.

Among these, nutritional supplementation has been an area of focus. Previous studies have revealed imbalances in vitamins and minerals in children and adolescents with ASD, including lower levels of vitamin D, lithium, zinc, and methionine, along with elevated levels of vitamin B6, C, and beta-carotene (Adams et al., 2011a). These nutritional imbalances may contribute to impaired methylation, decreased glutathione levels, and increased oxidative stress, possibly playing a role in the presentation of ASD symptoms (Adams et al., 2011a). Furthermore, nutritional deficiencies have been found to increase the risk of ASD (Wang et al., 2020; Alzghoul et al., 2020) and exacerbate core symptoms (Cheng et al., 2020). A comparative study by Zhu et al. (2020) demonstrated correlations between insufficient micronutrient levels and the development of ASD, along with associated symptoms, in children.

The high incidence of this nutritional vulnerability in ASD has been associated with poor dietary patterns, such as consuming less varied diets and limited fruits and vegetables (Chistol et al., 2018). With these nutritional and dietary considerations, there are probable functional consequences. Gastrointestinal symptoms, such as diarrhea, constipation, and abdominal pain, are common among individuals with ASD, potentially affecting nutrient absorption and the composition of their gut microbiome (McElhanon et al., 2014). These gastrointestinal disturbances are thought to play a role in modulating the expression of social and behavioral symptoms (Karhu et al., 2020).

Various complementary and alternative interventions have been explored as possible therapies for the clinical symptoms of ASD. Several studies evaluating the efficacy of nutritional interventions in individuals with ASD showed nutritional supplementation to be effective in improving several symptoms, functions, and clinical domains (Adams et al., 2018; Fraguas et al., 2019; Kittana et al., 2021; Song et al., 2020;) or provided inconsistent results (Li et al., 2018; Monteiro et al., 2020). Another study assessing how nutritional interventions may affect other developmental disorders found clinical benefits of micronutrient supplementation in Attention Deficit/Hyperactivity Disorder (ADHD), which may translate as an effective intervention for ASD (Johnstone et al., 2022).

Prior studies studying the effects of micronutrient supplementation in individuals with ASD have shown some promising findings. One study found autism severity scores to correlate with levels of vitamins, minerals, and amino acids (Adams et al., 2011a). A double-blind, randomized, placebo-controlled trial of a vitamin/mineral supplement in 141 children with autism found numerous improvements in nutritional biomarkers as well as a statistically significant improvement in parent ratings of child functioning (with specific questions on language, behavior, social function, sleep, gastrointestinal symptoms, and eye contact). There was no improvement in the Social Responsiveness Scale (SRS) or the Pervasive Developmental Disorder Behavior Inventory (PDD-BI) (Adams et al., 2011b). A more recent open-label study by the same team collected evaluations from 161 people with autism about the effectiveness of the vitamin/mineral supplement from the double-blind RCT (Adams et al., 2022). When compared to the placebo group of the previous study, the participants of the open-label study had greater improvements in parent-reported child functioning across a wide range of symptoms. Another study from the group evaluated a more complex intervention that included a nutritional supplement as well as digestive enzymes, carnitine, essential fatty acids, Epsom-salt baths, and a healthy gluten-free, casein-free, soy-free diet. The study found improvements in autism symptoms but was limited by the single-blind study design (Adams et al., 2018).

Despite the potentially beneficial results, these studies were limited in design - open-label or single-blind for most - and were few in number, only four studies by the same group. Therefore, there exists the need for more research examining the effect of micronutrient supplementation in individuals with ASD. The current study aims to investigate the changes in clinical outcomes before and after micronutrient supplementation in adolescents and adults with ASD. Understanding the potential impact of micronutrient treatment on clinical outcomes can aid in developing effective therapies for ASD. By addressing this research question, the present study seeks to fill the existing knowledge gap and shed further light on micronutrient supplementation in individuals with ASD.

2. Material and methods

2.1 Participants

This study was approved by the UCSF Institutional Review Board on July 14, 2022 and was registered on ClinicalTrials.gov (NCT59463) on March 4, 2022 prior to performing any study activities. The UCSF investigative team has an ongoing relationship with a local, non-public school (Oak Hill School, San Anselmo, CA) that specializes in the education of

children and young adults with autism and related neurodevelopmental disorders (ages 5-22, grades K-12).

This unique academic-school-parent partnership was created with the goal of improving overall care and communication between parents, clinical providers, and teachers. The teaching techniques and school environment at Oak Hill School are detailed in the book, The Oak Hill Method (Bent et al., 2022). The families of all students attending the school (n=50 at study initiation) were invited to participate in the study via e-mail and informational flyers.

Adolescents and young adults were eligible to participate if they were enrolled in the school, had a formal diagnosis of ASD, reported no use of micronutrient supplements within the last 3 months and had no current multivitamin supplementation, were willing to hold other treatments constant for the 8-week study period, and had parents who were willing to complete online surveys at specified intervals.

ASD is defined as being present if the individual has a diagnosis from a medical professional trained to diagnose autism, or if the student is determined by school staff and the study psychiatrist to meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text-Revision (DSM–5-TR) criteria for ASD. Informed consent was obtained from the parent of all study participants.

2.2 Intervention

This study was open-label, and all clinicians, parents, and teachers were aware of the treatment initiation and duration of 8 weeks. All enrolled participants were provided micronutrient supplementation, containing 36 different vitamins, minerals, amino acids, and antioxidants (EMPowerPlus Advanced, TrueHope Nutritional Support Ltd.). This supplement brand was chosen due to its bioavailability and proprietary direct-to-cell (DTC) technology that delivers essential nutrients on the cellular level using sublingual absorption, bypassing the gut. The size of an average human cell is 10 microns, and these DTC supplements are less than 0.5 microns in diameter, while off-the-shelf supplements are typically 74 microns. It is hypothesized that nutrients are effectively absorbed and used by the body when smaller than human cell.

The micronutrient supplementation came in powder form and was packaged in individual pouches called "Lightning Sticks" for daily consumption (2.9 mg of micronutrients per stick). The components of each Lightning Stick are provided in Supplementary Table 1. Treatment involved taking one Lightning Stick sublingually daily for 8 weeks. Those enrolled completed baseline measures (described below), commenced treatment on the same day (November 14, 2022), and finished treatment on the same day (January 8, 2023).

2.3 Objectives and Measures

The primary goal of the study was to examine whether there were any changes in clinical symptoms after treatment with micronutrients. We used batch enrollment where the parents of all potentially eligible participants were screened for eligibility and asked to go through an informed consent process. Once the final "set" of eligible student participants was identified, they were given the study medication on the same day. During the screening visit, participants also had a brief physical examination including height and weight. Micronutrient supplements supply was provided at the screening visit along with dosing instructions, but participants did not begin the treatment until the study initiation day.

Two measures were used to assess the change in core and associated features of autism: the Autism Behavior Inventory, Short Form (ABI-S) and the Social Responsiveness Scale (SRS).

The ABI-S is an observer-reported outcome scale designed specifically to measure change and severity of ASD symptoms and has been shown to have content validity when completed by parents (Pandina et. al., 2021). The SRS is one of the most commonly used outcome measures in clinical trials of ASD and focuses on social responsiveness and interaction (Duke et al., 2013). Parents and teachers were asked to complete both measures at baseline, 4 weeks, and 8 weeks using an online and secure platform.

2.4 Safety Assessments

Parents and teachers were advised to report any concerns about a new medical problem immediately to the study investigators, who were available at all times to receive reports of possible adverse effects. At the 4-week and 8-week online questionnaires, parents were asked to report any new medical problems or concerns for possible side effects.

2.5 Statistical Analysis

Baseline characteristics and variables were summarized using descriptive statistics. Repeated measures analysis using mixed-effects models was used to determine whether there were statistically significant changes in the mean score of ABI-S and SRS across the timepoints, with 'subject ID' being defined as the random effect.

Change in both clinical variables was computed as post-treatment (8 weeks) score minus pre-treatment (baseline) score. Shapiro-Wilk test was used to test for normality of the data. Since all variables were normally distributed, one-sided paired t-test was used to compare the pre- and post-treatment mean scores.

Parent and teacher-reported measures were analyzed separately.

The open-label effect sizes were calculated by dividing the mean difference in score (end of study scores minus baseline scores) by the standard deviation of the difference. We also examined the number of participants who were "responders", defined a priori as those who showed an improvement of at least 10% in at least two out of the four surveys.

Supplementary Table 1 Composition and supplement facts for daily dose of micronutrient supplement

Supplement Facts	**Amount per 1 Lightning Stick**	**% Daily Value**
Vitamin A (as retinyl palmintate)	768 IU	16
Vitamin C (as ascorbic acid & sodium ascorbate)	80 mg	134
Vitamin D (as cholecalciferol)	192 IU	48
Vitamin E (as dl-alpha-tocopheryl acetate)	48 IU	160
Vitamin B6 (as pyridoxine HCl)	4.8 mg	240
Folate (as folic acid)	192 µg	48
Vitamin B12 (as cyanocobalamin)	120 µg	2000
Vitamin B1 (as Thiamine Hydrcochloride)	2.4 mg	160
Vitamin B2 (Riboflavin)	1.8 mg	106
Vitamin B3 (as Niacin & Niacinamide)	12 mg	60
Vitamin B5 (Panthothenic Acid as Calcium-D-Panthothenate)	2.8 mg	29
Biotin	144 µg	48
Iodine (as potassium iodide)	27.2 µg	18
Zinc (as zinc gluconate)	6.4 mg	43
Inositol	Inside blend	
Magnesium	80 mg	20
Selenium	27.2 µg	38
Manganese	1.28 mg	65
Chromium	83.2 µg	70
Molybdenum	19.2 µg	27
Potassium	32 mg	1
Calcium	176 mg	18
Iron	1.8 mg	10
Phosphorus	112 mg	11
Copper	0.96 mg	48
Proprietary blend (Choline, DL, phenylalanine, vanadium chelate, citrus bioflavonoids, inositol, l-glutamine, l-methionine, boron, grape seed extracts, ginkgo biloba, germanium, nickel)	355 mg	N/A

3. Results

Sixteen students enrolled in the school completed the informed consent process for the study. Four participants withdrew before completing post-baseline information due to the inability to take the micronutrients supplements as instructed. They all withdrew earlier on in the study; two participants withdrew after two days, one after one week and one after two weeks. None of them could tolerate the sensation of the powder form and therefore could not take the micronutrients. Another participant was lost to follow-up early on in the study (shortly after the baseline visit) despite numerous attempts to reach them throughout the study period. (Figure 1). The characteristics of the 11 participants who completed the study are shown in Table 1. All participants had a diagnosis of ASD, 82% were male and the mean age was 17.7 years. Neither of the participants who were taking medications had any changes in their medications during the course of the 8-week study period. None of the participants reported any adverse events during the study period.

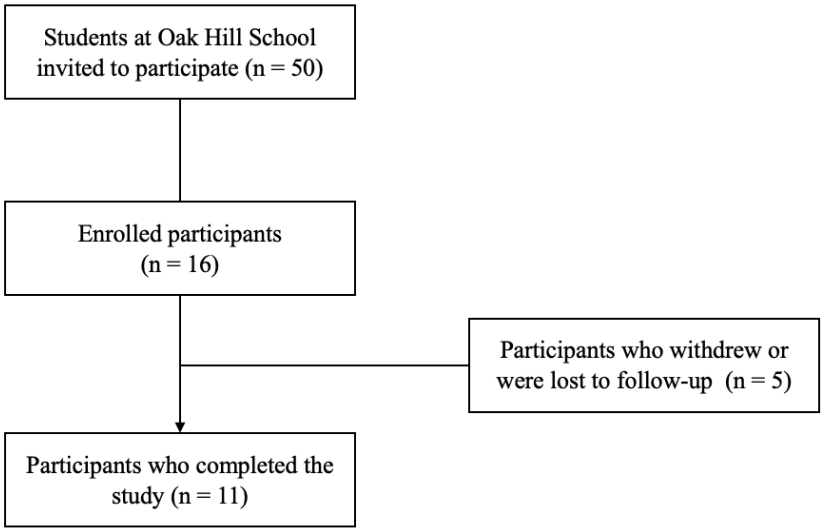

Fig. 1: Flow of participants through the study

Table 1: Characteristics of participants who completed the study

		Subjects (*N* = 11)	
		%	**N**
Gender	Female	18	2
	Male	82	9
Age (Range 11-22)	11-14	18	2
	15-21	73	8
	22+	9	1
	Mean Age		17.7 *SD=3.2*
Current medications	Cetirizine	18	2
	Dupilumab	9	1
	Fluoxetine	9	1
	Guanfacine	9	1
	Methylphenidate	9	1
	Sertraline	18	2

3.1 Change in Symptoms

The change in ABI-S and SRS scores at baseline and the end of the study, as well as the effect sizes, are shown in Table 2. Mean scores on both measures showed improvements (decreases) at the end of the study, but none of these changes were statistically significant. Parent-reported ABI-S improved -2.9 points (95% CI -7.1 to 1.4), teacher-reported ABI-S improved -0.8 points (95% CI -4.4 to 2.8), and parent-reported SRS improved -8.1 points (95% CI: -18.4 to 2.2). While parent-reported measures showed moderate improvement (effect size = -0.52 and –0.56 for ABI-S and SRS respectively), the change in teacher-reported measures were negligible (Table 2). Figure 1 demonstrates the mean scores for ABI-S and SRS over the 2-month study period.

Table 2: Mean ABI-S and SRS scores at baseline and end of study and effect sizes

		Adjusted Mean Scores (95% CI)		Change from Baseline (95% CI)		
		Baseline	**End of Study**	**End of Study**	**p**	**Effect Size**
ABI-S	**Parent**	25.3 [22.6, 27.9]	22.3 [17.5, 27.2]	-2.9 [-7.1, 1.4]	0.08	-0.52
	Teacher	21.6 [13.9, 29.3]	20.8 [14.0, 27.6]	-0.8 [-4.4, 2.8]	0.31	-0.16
SRS	**Parent**	94.4 [77.4, 111.4]	86.3 [66.3, 106.3]	-8.1 [-18.4, 2.2]	0.05	-0.56
	Teacher	69 [51.8, 86.2]	69.8 [54.9, 84.7]	0.8 [-9.8, 11.4]	0.56	0.05

Table 3: Responders vs. non-responders to micronutrient supplementation

	ABI-S Score Change				**SRS Score Change**				**Responder**
ID	**Parent**		**Teacher**		**Parent**		**Teacher**		**Yes/No**
	Score	**%**	**Score**	**%**	**Score**	**%**	**Score**	**%**	
001	-6	-28.6%			-25	-25.5%			Yes
002	-4	-16%	-7	-23.3%	-25	-27.5%	-27	-23.9%	Yes
005	1	4.8%	-5	-41.7%	5	6.6%	0	0%	No
007	-3	-12.5%	0	0%	-15	-18.1%	4	4.9%	Yes
008			-3	-7.5%			26	37.7%	No
009	-14	-51.9%	1	4%	-24	-39.3%	-2	-2.5%	Yes
011	-6	-21.4%	-7	-41.1%	3	2.8%	-12	-16.4%	Yes
012	-1	-3.5%	0	0%	13	13.7%	7	9.7%	No
014	4	13.3%	9	128.6%	-3	-2.5%	18	47.4%	No
015	3	13.6%	4	57.1%	5	7.0%	-6	-11.3%	No
016			0	0	-15	-10.8%	0	0%	No

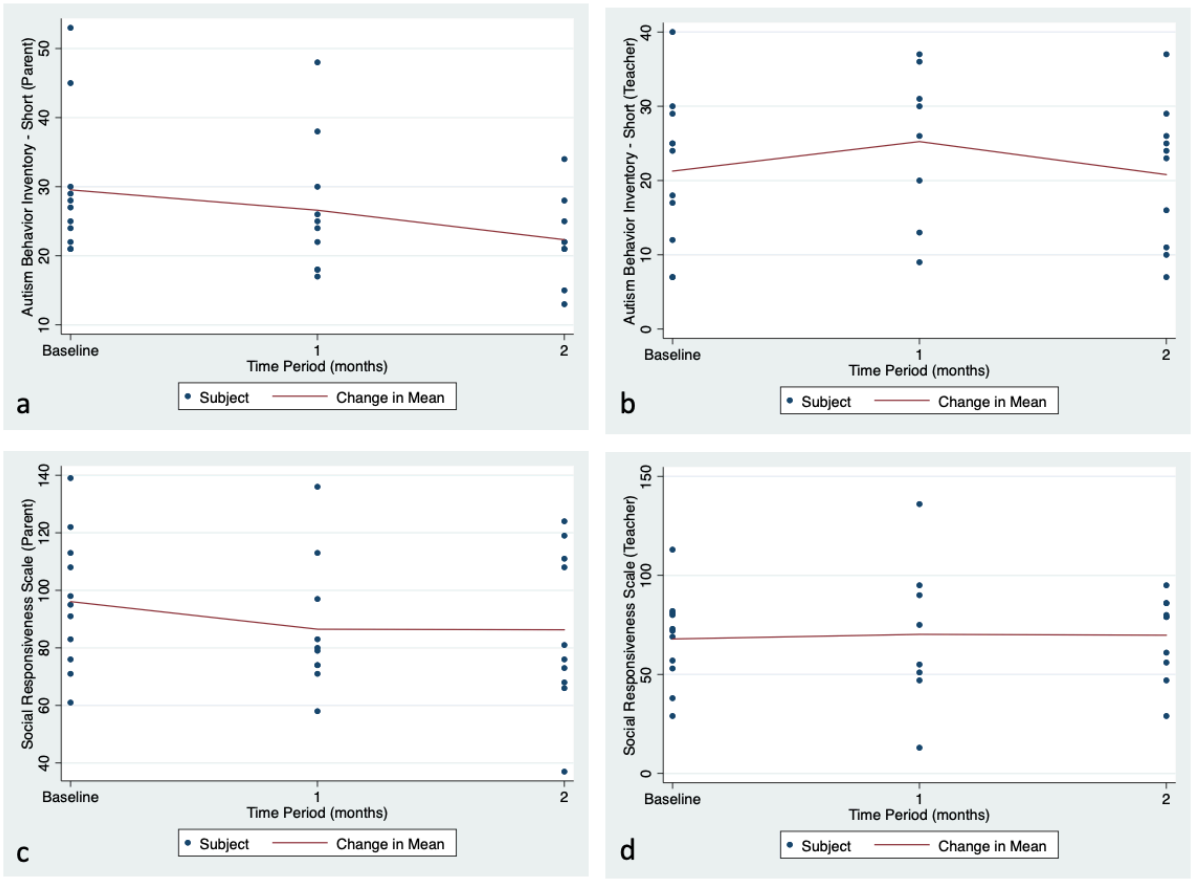

Fig. 2: Change in mean scores over time. a) Change in parent-reported Autism Behavior Inventory-Short (ABI-S). b) Change in teacher-reported ABI-S. c) Change in parent-reported Social Responsiveness Scale (SRS). d) Change in teacher-reported SRS.

We also examined the number of participants who were responders, defined as an improvement in at least two out of the four surveys. Five participants were categorized as responders, while the remaining six were non-responders (Table 3). Sensitivity analyses among the two subgroups showed that the responders exhibited a 6.6-point (26.4%) decrease (improvement) in parent-reported ABI-S (p=0.03) and a 17.2-point (19.5%) decrease (improvement) in parent-reported SRS (p=0.03), compared to increases of 1.75 points (6.7%) in parent-reported ABI-S (p=0.2) and 1 point (1%) in parent-reported SRS (p=0.8) for non-responders. The changes in teacher-reported ABI-S and SRS were not significant among responders and non-responders alike.

4. Discussion

Individuals with ASD have been known to have nutritional deficiencies and prior studies have indicated that there may be clinical benefits to micronutrient supplementation. As such, we sought to examine any changes in clinical symptoms after micronutrient supplementation in adolescents and adults with ASD through an open-label clinical trial. Overall, there were no significant changes in the mean score of ABI-S and SRS at the end of the study compared to baseline, although there were some improvements at the individual level. Namely, among the eleven participants, six were considered responders and five were non-responders.

A small number of studies have studied micronutrient supplementation in ASD with potentially promising results. These include levels of vitamins, amino acids and minerals correlating with autism severity scores (Adams et al., 2011a), significant improvements in ratings of functioning across a number of different symptoms (Adams et al., 2011b; Adams et al., 2018; Adams et al., 2022). The findings from our study that showed no significant change in mean clinical symptoms after micronutrient supplementation contradict the (albeit limited) clinical benefits seen in these previous studies.

Although our results did not achieve statistical significance, we did see a trend towards improvement in ABI-S and SRS, mainly among parent-reported surveys which had moderate effect sizes. One reason for the negative findings could be the small sample size and resulting lack of power. Another could be that our study duration (8 weeks) was too short, and the micronutrients needed more time to show a significant effect. In contrast, all prior studies in this population were at least 12 weeks long.

Another interesting aspect of our findings was that parent-reported measures showed a greater absolute improvement compared to teacher-reported measures. One reason for this could be that the teacher ratings were influenced by comparison with other students in the class, whereas the parents did not have such a comparison point.

Although micronutrient supplementation in ASD has not been studied in detail, there have been some studies investigating general nutritional supplements in ASD populations, often showing mixed results. A meta-analysis (Fraguas et al., 2019) looking at specific dietary interventions on the symptoms, functions, and clinical domains in subjects with ASD found them to exert a nonspecific and small effect in ASD.

When looking at vitamin supplementation specifically, they observed small but statistically significant improvements in most of the outcomes measured. A more recent narrative review (Poudineh et al., 2020) looking at the effects of vitamins and other dietary supplements on ASD concluded that vitamins A, B6, B12, and D, iron supplements, L-carnosine, melatonin, Omega-3 and serotonin had growing positive evidence and thus showed some promise. However, the effects of multivitamin/mineral supplements, vitamin C, chelation, cyproheptadine, magnesium supplements, tryptophan and zinc supplements need further evaluation due to insufficient evidence.

Similarly, a systematic review (Li et al., 2018) also had mixed findings, where folinic acid and methyl B12 showed some improvements in ASD severity, vitamin D3 had inconsistent results in behavioral outcomes, and vitamin B6/Mg and omega-3 fatty acid were not helpful improving ASD symptoms. Another systematic review (Sathe et al., 2017) found methyl B12 and levocarnitine to show some improvement in symptoms severity and gluten/casein-free diets to have parent-rated improvements in communication and challenging behaviors, while omega-3 fatty acid did not affect challenging behaviors.

However, the authors observed insufficient or low strength of evidence for most of the studies. The consensus from prior literature is that while nutritional and dietary supplements show some promise in managing ASD symptoms, the results are mixed and inconsistent. Therefore, further research is required on this topic.

The micronutrient supplement used in this study was well-tolerated, as none of the participants who completed the study reported any adverse events during the course or at the end of the study. The micronutrients supplement used in this study was much lower in dose across all vitamins and minerals compared to the micronutrients used in the previous studies. The absence of adverse reactions aligns with other studies of micronutrients in ASD populations, which also observed them as safe and tolerable (Adams et al., 2011b; Adams et al., 2018; Adams et al., 2022). Interestingly, in a recent review summarizing the current evidence for using vitamins, minerals, and cofactors in ASD, Indika et al. (2023) cite that while some supplements have been studied in RCTs as monotherapy, few studies have used multinutrient supplements or studied the effectiveness of their combination in ASD. They propose that using a combination of vitamins may have advantages over monotherapy, including higher bioavailability, synergistic action and reduced adverse effects due to high doses. In that regard, our study adds to the few others that have used multiple nutrients over single nutrient treatment and also shows its safety and tolerability. Identifying a treatment biomarker to target with specific micronutrients may also improve statistical significance.

In interpreting the findings of this study, several limitations should be acknowledged. Firstly, the limited sample size (N=11) has indeed constrained the statistical power of the analysis and, therefore, it affects the generalizability of the results.

A larger sample size would provide more insights into the effects of micronutrient supplementation on clinical outcomes in individuals with ASD. Secondly, the absence of a control group prevents direct comparisons between treated participants and untreated individuals, limiting our ability to isolate the effects of the micronutrient supplement from other confounding factors.

A well-matched control group would have allowed for a more comprehensive evaluation of treatment efficacy. Finally, we do not have information regarding the types of diets the participants were on, especially if they were on any special or limited diets, which could have influenced their response to the micronutrient supplementation.

5. Conclusion

Despite these limitations, this study contributes valuable insights into the potential benefits of micronutrient supplements in individuals with ASD. It is one of the few studies that examined micronutrient supplementation in this population and showed trends towards improvement in clinical outcomes and the safety and tolerability of the treatment in this population. The small sample size and absence of a control group certainly warrant caution in the interpretation of the results but also highlight the need for future research with a larger number of participants and appropriate control groups. By addressing these limitations, subsequent studies may achieve a better understanding of the effects of micronutrient supplementation on clinical outcomes in ASD, further enhancing the potential for targeted and effective interventions for this population. Acknowledgements: We would like to thank JS Foundation for funding this study. We are also grateful to TrueHope Nutritional Support Ltd. for supplying the micronutrient supplements.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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