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An Observational Preliminary Study on the Safety of Long-Term Consumption of Micronutrients for the Treatment of Psychiatric Symptoms

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Abstract

Objectives: There is an increasing body of literature documenting the efficacy of micronutrients (vitamins and minerals) interventions for the treatment of psychiatric problems in the short term; however, long-term safety is largely unexplored. The goal of this observational study was to investigate the safety of two commercially available broad-spectrum micronutrient formulas (EMPowerplus and Daily Essential Nutrients) given at doses above the Recommended Dietary Allowances for the long-term treatment of individuals with psychiatric symptoms.

Design: Participants on long-term treatment with micronutrients (medication-free) for psychiatric problems (attention-deficit hyperactivity disorder [ADHD, $n = 21$], anxiety/depression [$n = 13$]) were identified from ongoing research studies and the community through purchasing records. Seventeen children and 17 adults had blood tests to assess their full blood count, coagulation profile, liver and kidney function, fasting glucose, iron studies, key nutrients, and prolactin. Questionnaires assessed psychological/psychiatric functioning. Seventeen of the participants had completed the same measures pretreatment.

Results: The average length of consuming micronutrients was 2.66 years (standard deviation = 2.86). Excluding B_{12} (which was elevated for almost all participants), 94.6% of all blood test results were within the test reference ranges. One participant was diagnosed with hemochromatosis based on iron studies. No other clinically relevant adverse changes in blood results were identified pre- and post-treatment. No clinically significant adverse effects were reported. Post-treatment psychometrics identified that 85% of the participants were in nonclinical ranges for measures of ADHD, depression, anxiety, and stress.

Conclusions: We report preliminary evidence for the safety of long-term commercially available micronutrients, although questions remain. Overall, the substantial psychiatric benefits observed appear to outweigh the minimal observed risks in these participants. Screening for potential medical problems is recommended before initiating treatment. Long-term pharmacovigilance monitoring is required to ascertain any rare but significant adverse events.

Keywords: minerals, vitamins, safety, micronutrients, toxicity

Introduction

Vitamins and minerals (micronutrients) given in combination may provide an alternative to medication for the treatment of mental health issues with a growing body of literature supporting their efficacy.[1,2] Indeed, providing nutrients in combination appears to show some clinical benefit based on randomized placebo controlled trials (RCTs)[3–7]; however, there are little long-term data systematically investigating their safety. A study that has investigated safety within a mostly North American community setting showed a reassuring safety profile.[8] Other studies have established safety in short-term (10–12 weeks) RCTs.[3,4] Replication in other countries and for longer periods is essential to further

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examine the safety of long-term use of micronutrients, particularly where these are consumed at levels above the recommended dietary allowance (RDA).

The rationale for supplementing with micronutrient doses higher than the RDA is that some people may have higher nutritional needs than can be provided by food alone.[9] RDAs were developed to identify the minimum intake required to avoid a frank nutritional deficiency as opposed to a level that targets optimal brain functioning.[10] However, higher doses raise concerns about toxicity, particularly if the dose exceeds the upper limit (UL), a limit defined as the maximum daily intake at which no risk of adverse health effects has been identified. The risk of adverse reaction is likely to increase as intake exceeds the UL.

The principal aim of this study was to evaluate the safety (based on blood markers and reports of adverse events) of two nutrient combinations, commercially known as EMPowerplus (EMP) and Daily Essential Nutrients (DEN) (see Supplementary Table S1 for list of ingredients, maximum daily doses, RDA, and UL levels). These formulas were chosen because they have been examined in more than 35 published studies for treating various mental health conditions, have documented evidence of short-term safety and efficacy data,[3,4] and have been more extensively examined for the treatment of psychiatric conditions than any other multivitamin/multimineral formulas.[11] DEN is a modified version of EMP. Both formulations provide nutrients at levels above the RDA, and in some cases, above the UL. It is therefore essential that long-term supplementation (greater than 6 months) be evaluated for adverse effects through symptom report (adverse events) and blood markers. The secondary aim was to assess the longer term effectiveness of the formulas for the treatment of psychological symptoms.

Materials and Methods

Design

The study utilized an observational design to evaluate the health outcomes of individuals with psychological symptoms who took broad-spectrum micronutrients for at least 6 months. All participants were recruited either through ongoing research studies at the University of Canterbury (we have conducted two randomized controlled trials[3,4] in which we collected blood samples pretreatment, allowing for evaluation of change based on consumption of micronutrients) or through the New Zealand (NZ) distributor of the micronutrients, Straussherbs. EMP and DEN are not available through usual retail outlets meaning that all potential consumers can be contacted through the sole NZ distributor. The study was approved by the Human Ethics Committee at the University of Canterbury. All participants granted informed consent, and for participants younger than 16 years, their parents granted consent on their behalf with assent obtained from these children. Individual test results were shared with the participants and general practitioner (GP) with consent.

Participants and entry criteria

All participants were required to be taking a minimum of four pills per day continuously for a minimum of 6 months for the treatment of psychological symptoms. Four pills were chosen as they provide a micronutrient dose higher than typically consumed in a once daily multivitamin. Participants were also required to have no chronic pre-existing health condition nor to be taking any psychiatric medication.

Fourteen child and 3 adult participants from previous studies conducted at the University of Canterbury agreed to participate from a pool of 23 former participants identified as potentially eligible. For the Straussherbs participants, 117 customers deemed eligible by the company based on their purchasing history were contacted and informed about the research study. The purchasing history made it likely that a minimum number of pills were being consumed each day based on rate of ordering. Potential participants were invited to contact the PI (J.J.R.) if they were interested in participating. Their identities were not revealed to the researchers unless they chose to participate. A total of 34 customers indicated interest in the study. Following screening, 17 (14 adults and 3 children) were identified as eligible.

Procedures

Potential participants were sent a questionnaire to complete online (see the Psychological measures section below). Once that was completed and eligibility was confirmed, they were sent a blood form (see the following section, Safety measures). Study participants had been evaluated as part of routine long-term follow-up.

Safety measures

Participants were asked about adverse events over the period of consuming the micronutrients. Specific inquiry (yes/no) regarding common adverse symptoms, such as rash, dry mouth, insomnia, nausea, and change of appetite, was also made. For the University of Canterbury study participants, blood pressure, height, and weight were taken. All participants were required to complete a fasting blood test. Testing included full blood count, serum prolactin, urea and electrolytes, liver function, glucose, coagulation profile, iron, zinc, folate, vitamin D, vitamin B_{12}, and copper levels. All participants received a $10 petrol voucher to cover travel costs to a local blood laboratory, and they and their GP received a copy of the results. All blood test results were reviewed by the study physicians (M.J.F.E. and R.T.M.). Results falling outside the reference ranges were evaluated for clinical significance and repeated if necessary, with investigation as required. Any significant abnormality was also followed up with the participant and/or their GP.

Psychological measures

Although our primary focus was safety, the adult participants completed some psychological measures including the Depression Anxiety Stress Scale (DASS[12]) and the Conners Adult attention-deficit hyperactivity disorder (ADHD) Rating Scales (CAARS)–Self-Report: Screening Version[13] to inform effectiveness. For those participants younger than 18 years, parents completed the ADHD Rating Scale-IV,[14] the Screen for Child Anxiety Related Disorders (SCARED[15])–Parent Version, and the Child Mania Rating Scale–Parent Version (CMRS-P[16]) to assess the current psychological functioning of their children.

A score on the Clinical Global Impression–Improvement Scale (CGI-I[17]) was determined for all participants, either by the clinician, for those participants who had participated in previous research studies, or by the participants

themselves for the Straussherbs group. Clinicians or the participants were asked to indicate on a 7-point scale, which statement best applied, from a score of 1 (very much improved) to 7 (very much worse) to summarize change since consuming the micronutrients. A score of 1 or 2 (''much improved'' to ''very much improved'') identified a responder to the treatment.

Other areas assessed included dietary patterns using the brief diet intake questionnaire (modified from Baker et al.[18]) that assesses consumption of fruit and vegetables, breakfast, and fast foods. Demographic variables, including participant's ethnicity and parents'/adults' occupation, were also collected. The socioeconomic status of each participant's family was estimated using the New Zealand Socioeconomic Index of Occupational Status (NZSEI).[19]

Statistical analysis

Blood results were analyzed for percentage falling outside the normal references ranges. Means and standard deviations (SDs) were also calculated. For those 17 individuals where pretreatment data were available, change pre- to posttreatment in blood biomarkers and psychosocial variables was assessed using paired sample *t*-tests ($p < 0.05$ was considered significant), with effect sizes summarized using Cohen's *d*.

Results

The final sample consisted of 17 children and 17 adults. The children had been consuming the micronutrients for an average of 1.54 years (SD = 1.13), with a range of 0.65–5 years; 88% of the children were male, 88% were of European descent (the remainder were Māori). The ages of the children ranged from 9.2 to 14.6 years (average age of 10.9 years, SD = 1.5). All the children were taking DEN with an average dose of 10.53 pills (SD = 1.94), with a range of 8–15 pills per day. All 17 children were taking micronutrients for the treatment of ADHD.

The adults had been consuming the micronutrients for an average of 3.75 years (SD = 3.63), with a range of 0.83–12 years; 41% of the adults were male, all were of European decent, and ages ranged from 22.0 to 77.2 years (average age of 48.9 years, SD = 15.6). The average home income fell within the NZ$60–80,000 bracket with a mean NZSEI index of 53.38 (SD = 18.31). The average daily number of pills consumed by the adults was 9.88 (SD = 3.06), with a range from 4 to 15, with three participants taking EMP and the remainder taking DEN. Of the 17 adults, 4 were taking micronutrients for ADHD, the remainder ($n = 13$) for the treatment of symptoms associated with depression/anxiety.

The blood tests showed that one adult had evidence of iron overload (ferritin 1144 mcg/L; iron 33 μmol/L; % iron saturation 93%). Further testing confirmed a diagnosis of pre-existing hemochromatosis. This individual was advised to stop taking the nutrients given the inclusion of iron in the formula. One child with elevated copper (19.6 μmol/L) was sent for a repeat blood test and the second copper level came back within the normal range (13 μmol/L). Most results, excluding B_{12} and vitamin D, were just outside the reference range, and no other test result was considered by the psychiatrists providing oversight to require further evaluation. Dehydration was identified as a probable contributor to four abnormal results showing mildly elevated creatinine and hematocrit.

Table 1 presents the overall blood test results for the entire sample after consumption of micronutrients. Among the 34 participants, 1003 blood tests were performed, of which 84 (8.4%) were either above or below the reference range. Twenty-eight of the 84 abnormal blood tests were due to elevated B_{12}. Excluding the elevated B_{12} levels (which were expected given the quantity of B_{12} consumed in a daily dose) and the abnormal results due to hemochromatosis, 5.4% of the blood tests were outside the reference range. Not including elevated B_{12} levels, 29 (85%) of the participants had at least one test outside the reference range.

Table 2 shows the pre- to post-blood results for those individuals who had participated in one of our research studies (14 children and 3 adults). The number of pills per day taken by this sample ranged from 6 to 15, with mean of 10.24 (SD = 2.14). They were all taking DEN. With the exception of B_{12}, none of the group means moved outside the reference range. Although seven group means changed statistically significantly pre- to post-treatment (hematocrit, potassium, urea, creatinine, B_{12}, folate, and vitamin D), individual differences were not identified by the study physicians as clinically significant. The significant changes in the nutrient levels were expected. There were no significant changes in body mass index, blood pressure, and pulse. Dietary patterns also did not change; the daily mean consumption of fruits and vegetables before the intervention was 5.07 (SD = 1.54) and 5.17 (SD = 1.72) post-treatment. Dose was not significantly correlated with the significant changes identified.

Table 3 summarizes the changes on the psychosocial measures for the ADHD subsample. The participants showed significant improvement in all measures of mood regulation, anxiety, and ADHD. Post-treatment means all fell in the normal nonclinical range.

The vast majority (85%) of individual post-treatment scores for the full sample fell within the normal nonclinical range. Based on the CGI-I scale, 31 of the 34 (91%) participants were identified by either self-ratings or, where available, clinician ratings as either much or very much improved. The remaining three (7%) were identified as being mildly improved.

In terms of reports of side effects, two parents of child participants and two adults reported stomachaches and headaches, but these were only present within the first month of consuming the micronutrients. No long-term adverse effects or serious adverse effects were reported.

Discussion

The long-term use of these two micronutrient formulas for the treatment of psychiatric symptoms was safe, well tolerated, and generally effective in our sample of 34 adults and children. Adverse effect profiles, post-treatment blood biomarkers, and pre- to post-assessment of these biomarkers confirmed that, for all but one participant, there was no evidence that the micronutrients caused any toxicity or detectable harm.

One participant was identified through testing as having pre-existing hemochromatosis. Although this disorder is rare,[20] it seems reasonable to recommend screening for

Table 1. Means (SD) for the Entire Sample Post-Treatment with Numbers Falling Below, Within, and Above the Reference Ranges

Blood marker	*Reference range*	*Sample*	N	*Mean*	*SD*	*Minimum*	*Maximum*	N *(%) below*	N *(%) within reference*	N *(%) above*
Prolactin	50–550 mIU/L (F)	Children	16	175.81	65.26	43	303	1 (6)	15 (94)	0 (0)
	50–350 mIU/L (M)	Adults	17	211.29	98.18	75	399	0 (0)	17 (100)	0 (0)
		Total	33	194.09	84.50	43	399	1 (3)	32 (97)	0 (0)
Hemoglobin	115–145 g/L (children)	Children	16	133.25	7.08	126	151	0 (0)	14 (88)	2 (12)
	115–155 g/L (adults)	Adults	13	138.46	15.14	120	163	0 (0)	10 (77)	3 (23)
		Total	29	135.59	11.49	120	163	0 (0)	24 (83)	5 (17)
Hematocrit	0.35–0.43 (children)	Children	16	0.4	0.02	0.37	0.45	0 (0)	14 (89)	2 (11)
	0.35–0.46 (adults)	Adults	13	0.42	0.04	0.38	0.47	0 (0)	11 (85)	2 (15)
		Total	29	0.41	0.03	0.37	0.47	0 (0)	25 (86)	4 (14)
MCV	75–90 fL (children)	Children	16	83.43	3.44	77	89	0 (0)	16 (100)	0 (0)
	80–99 fL (adults)	Adults	13	91.10	2.80	86	94.2	0 (0)	13 (100)	0 (0)
		Total	29	86.86	4.97	77	94.2	0 (0)	29 (100)	0 (0)
MCH	24–30 pg (children)	Children	16	27.81	0.92	26	29	0 (0)	16 (100)	0 (0)
	23–33 pg (adults)	Adults	13	30.2	1.16	28	32	0 (0)	13 (100)	0 (0)
		Total	29	28.88	1.58	26	32	0 (0)	29 (100)	0 (0)
Platelets	150–425 × 10 (9)/L (children)	Children	16	300.81	47.06	233	423	0 (0)	16 (100)	0 (0)
	150–400 × 10 (9)/L (adults)	Adults	13	244.31	32.97	194	304	0 (0)	13 (100)	0 (0)
		Total	29	275.48	49.67	194	423	0 (0)	29 (100)	0 (0)
WBC	4.3–12.0 × 10 (9)/L (children)	Children	15	5.77	1.16	3.8	7.5	2 (13)	13 (87)	0 (0)
	4.0–11.0 × 10 (9)/L (adults)	Adults	13	5.66	1.46	3.5	8.7	2 (15)	11 (85)	0 (0)
		Total	28	5.72	1.29	3.5	8.7	4 (14)	24 (86)	0 (0)
Neutrophils	1.5–7.0 × 10 (9)/L (children)	Children	16	2.64	0.95	1.4	4.3	2 (13)	14 (87)	0 (0)
	1.9–7.5 × 10 (9)/L (adults)	Adults	13	3.11	1.32	1.2	6.2	3 (23)	10 (77)	0 (0)
		Total	29	2.85	1.14	1.2	6.2	5 (17)	24 (83)	0 (0)
Lymphocytes	1.4–4.5 × 10 (9)/L (children)	Children	16	2.38	0.35	1.9	3	0 (0)	16 (100)	0 (0)
	1.0–4.0 × 10 (9)/L (adults)	Adults	13	1.92	0.34	1.25	2.5	0 (0)	13 (100)	0 (0)
		Total	29	2.17	0.41	1.25	3	0 (0)	29 (100)	0 (0)
Monocytes	0.3–0.9 × 10 (9)/L (children)	Children	16	0.47	0.13	0.28	0.7	1 (6)	15 (94)	0 (0)
	0.2–1.0 × 10 (9)/L (adults)	Adults	13	0.44	0.11	0.3	0.7	0 (0)	13 (100)	0 (0)
		Total	29	0.46	0.12	0.28	0.7	1 (3)	28 (97)	0 (0)
Eosinophils	0.0–0.9 × 10 (9)/L (children)	Children	16	0.26	0.19	0.06	0.7	0 (0)	16 (100)	0 (0)
	0.0–0.5 × 10 (9)/L (adults)	Adults	13	0.14	0.12	0.02	0.43	0 (0)	13 (100)	0 (0)
		Total	29	0.21	0.17	0.02	0.7	0 (0)	29 (100)	0 (0)
Basophils	0.0–0.2 × 10 (9)/L	Children	12	0.048	0.03	0	0.1	0 (0)	12 (100)	0 (0)
		Adults	10	0.04	0.03	0	0.1	0 (0)	10 (100)	0 (0)
		Total	22	0.04	0.03	0	0.1	0 (0)	22 (100)	0 (0)
Sodium	125–145 mmol/L (children)	Children	17	139.53	1.42	136	142	0 (0)	17 (100)	0 (0)
	135–145 mmol/L (adults)	Adults	16	141.44	1.67	138	145	0 (0)	16 (100)	0 (0)
		Total	33	140.45	1.80	136	145	0 (0)	33 (100)	0 (0)
Potassium	3.5–5.2 mmol/L	Children	17	4.01	0.21	3.4	4.3	1 (6)	16 (94)	0 (0)
		Adults	13	4.22	0.57	3.6	5.7	0 (0)	12 (92)	1 (8)
		Total	30	4.10	0.41	3.4	5.7	1 (3)	28 (93)	1 (3)

(*continued*)

Table 1. (Continued)

Blood marker	*Reference range*	*Sample*	N	*Mean*	*SD*	*Minimum*	*Maximum*	N *(%) below*	N *(%) within reference*	N *(%) above*
Urea	1.4–5.7 mmol/L (children)	Children	17	4.38	0.95	2.3	6.3	0 (0)	16 (94)	1 (6)
	3.2–7.7 mmol/L (adults)	Adults	16	5.99	1.54	2.8	9	0 (0)	14 (88)	2 (12)
		Total	33	5.16	1.49	2.3	9	0 (0)	30 (91)	3 (9)
Creatinine	25–70 μmol/L (children)	Children	17	62.88	6.16	50	74	0 (0)	16 (94)	1 (6)
	45–110 μmol/L (adults)	Adults	17	81.65	20.48	18	114	1 (6)	15 (88)	1 (6)
		Total	34	72.26	17.68	18	114	1 (3)	31 (91)	2 (6)
Glucose	3.5–6.0 mmol/L	Children	17	4.96	0.63	3.4	5.8	1 (6)	16 (94)	0 (0)
		Adults	15	4.85	0.63	2.5	6.1	1 (7)	13 (86)	1 (7)
		Total	32	4.91	0.90	2.5	6.1	2 (6)	29 (91)	1 (3)
Calcium	2.2–2.6 mmol/L	Children	17	2.43	0.07	2.3	2.6	0 (0)	17 (100)	0 (0)
		Adults	16	2.43	0.07	2.3	2.6	0 (0)	16 (100)	0 (0)
		Total	33	2.38	0.07	2.3	2.5	0 (0)	33 (100)	0 (0)
Phosphate	1.0–2.0 mmol/L (children)	Children	17	1.38	0.15	1.1	1.6	0 (0)	17 (100)	0 (0)
	0.8–1.5 mmol/L (adults)	Adults	16	1.09	0.23	0.8	1.6	0 (0)	15 (94)	1 (6)
		Total	33	1.24	0.24	0.8	1.6	0 (0)	32 (97)	1 (3)
Magnesium	0.6–1.2 mmol/L	Children	17	0.83	0.069	0.7	0.9	0 (0)	17 (100)	0 (0)
		Adults	17	0.85	0.06	0.8	1	0 (0)	17 (100)	0 (0)
		Total	34	0.84	0.06	0.7	1	0 (0)	34 (100)	0 (0)
Albumin	32–48 g/L (children)	Children	7	40.29	1.50	38	42	0 (0)	7 (100)	0 (0)
	35–50 g/L (adults)	Adults	14	39.79	3.26	34	45	0 (0)	14 (100)	0 (0)
		Total	21	39.95	2.77	34	45	0 (0)	21 (100)	0 (0)
GGT	<30 U/L (children)	Children	17	13.71	7.54	9	42	0 (0)	16 (94)	1 (6)
	10–35 U/L (adults)	Adults	17	18.12	9.28	9	44	1 (6)	15 (88)	1 (6)
		Total	34	15.91	8.62	9	44	1 (3)	31 (91)	2 (6)
AST	10–50 U/L	Children	17	28	6.83	15	38	0 (0)	17 (100)	0 (0)
		Adults	17	22.88	8.11	12	42	0 (0)	17 (100)	0 (0)
		Total	34	25.44	7.83	12	42	0 (0)	34 (100)	0 (0)
ALT	0–40 U/L	Children	16	22.19	8.27	13	47	0 (0)	15 (94)	1 (6)
		Adults	17	23.29	10.19	10	41	0 (0)	15 (88)	2 (12)
		Total	33	22.76	9.18	10	47	0 (0)	30 (91)	3 (9)
Iron*	8–32 μmol/L (children)	Children	16	17.25	3.36	11	24	0 (0)	16 (100)	0 (0)
	10–30 μmol/L (adults)	Adults	14	17.86	8.32	5	40	1 (7)	12 (86)	1 (7)
		Total	30	17.53	6.08	5	40	1 (3)	28 (93)	1 (3)
Transferrin*	2.0–3.5 g/L	Children	16	2.65	0.28	2.2	3.2	0 (0)	16 (100)	0 (0)
		Adults	13	2.35	0.35	1.9	3.0	2 (15)	11 (84)	0 (0)
		Total	29	2.51	0.34	1.9	3.2	2 (7)	27 (93)	0 (0)
%Saturation*	16%–45%	Children	16	26.0	5.18	17	36	0 (0)	16 (100)	0 (0)
		Adults	13	29.15	11.42	9	53	1 (8)	10 (77)	2 (15)
		Total	29	27.41	8.53	9	53	1 (3)	26 (90)	2 (7)
Ferritin*	15–150 μg/L	Children	10	42.1	9.61	27	58	0 (0)	10 (100)	0 (0)
		Adults	5	105.00	45.20	53	174	0 (0)	4 (80)	1 (20)
		Total	15	63.07	39.81	27	174	0 (0)	14 (93)	1 (7)

(*continued*)

Table 1. (Continued)

Blood marker	*Reference range*	*Sample*	N	*Mean*	*SD*	*Minimum*	*Maximum*	N *(%) below*	N *(%) within reference*	N *(%) above*
Vitamin B_{12}	130–650 pmol/L	Children	17	1100.31	346.75	369	1476	0 (0)	1 (6)	16 (94)
		Adults	15	895.73	267.28	547	1392	0 (0)	3 (20)	12 (80)
		Total	32	1001.32	322.89	369	1476	0 (0)	4 (13)	28 (87)
Folate	>8 nmol/L	Children	17	38	3.60	28	43	0 (0)	17 (100)	0 (0)
		Adults	15	35.65	3.44	30	44.8	0 (0)	15 (100)	0 (0)
		Total	32	36.9	3.67	28	44.8	0 (0)	32 (100)	0 (0)
Vitamin D	50–150 nmol/L	Children	16	115.13	24.69	74	160	0 (0)	15 (94)	1 (6)
		Adults	15	111.6	27.74	79	164	0 (0)	14 (93)	1 (7)
		Total	31	113.42	25.83	74	164	0 (0)	29 (94)	2 (6)
Copper	12.6–19.0 μmol/L	Children	10	15.93	2.89	13	21.5	0 (0)	8 (80)	2 (20)
Zinc	10.0–17.0 μmol/L	Children	10	12.91	1.21	11.5	15.4	0 (0)	10 (100)	0 (0)
Cu:Zn ratio		Children	10	1.23	0.16	1.01	1.49			
INR	0.8–1.2	Children	12	1.08	0.06	1	1.2	0 (0)	12 (100)	0 (0)
		Adults	14	1.12	0.12	0.9	1.4	0 (0)	13 (93)	1 (7)
		Total	26	1.10	0.10	0.9	1.4	0 (0)	25 (96)	1 (4)
APTT	24–38 sec	Children	12	32.25	4.31	25	40	0 (0)	11 (92)	1 (8)
		Adults	15	30.53	5.04	22	38	1 (7)	14 (93)	0 (0)
		Total	27	31.3	4.72	22	40	1 (4)	25 (96)	1 (4)

*Removed case of hemochromatosis.

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; SD, standard deviation; WBC, white blood cells.

metabolic and electrolyte abnormalities before commencing treatment with micronutrients to prevent similar future occurrences and possible harm. Pretreatment screening should include a complete blood count, renal function, urea and electrolytes including calcium, phosphate, and magnesium, liver function tests, copper and ceruloplasmin, vitamin B_{12} and folate, and iron studies.

With regard to the specific blood test results, a number of results were outside the reference range. The majority (87%) B_{12} results were elevated suggesting good compliance with the treatment, which is important to establish given that the recruitment of the community participants was based on purchasing history. Excess B_{12} has not been deemed to be harmful, indeed, the Ministry of Health[21] has not set a UL for this vitamin given that it is water soluble and, other than a possible link with increased acne,[22] no serious adverse effects have been reported as a result of high levels of consumption.

We conducted more than 1000 blood tests. The reference range for the majority of the blood tests we undertook is the set of values 95% of the population is expected to fall within.[23] It is therefore predictable that ~5% of our blood tests lay outside the reference ranges. When the vitamin B_{12} results were excluded, the percentage of abnormal test results was 5.4%. Furthermore, most of the abnormal results were just outside the reference range.

The significant blood changes pre to post are worthy of some consideration. Although seven means changed in the pre to post comparisons, individual review of blood tests did not suggest clinical concern. The increases in the nutrient levels (vitamin D, vitamin B_{12}, and folate) were expected and have been previously reported.[3,4] The creatinine mean increased by ~5 μmol/L over the study period (indicating possible worsening of renal function). However, the mean value for urea decreased over the same period (suggesting the opposite). Overall, these results did not suggest deteriorating renal function while on micronutrients, although the small sample of this study means any conclusions are preliminary.

In keeping with a systematic review of the safety and tolerability of broad-spectrum micronutrient use,[8] as well as other reports,[24,25] the most common adverse effects reported were headaches and nausea. These effects were transient and resolved through advice to take micronutrients with food and water. Previous placebo-controlled trials evaluating micronutrients did not report group differences between placebo and active treatment in adverse effects.[3,4] It is therefore possible that the adverse effects reported in this group may relate to nonspecific effects associated with consuming capsules as opposed to specific effects secondary to the ingredients of the micronutrient formulation. While other surveys have revealed some common mild adverse events associated with vitamin/mineral supplements such as palpitations, abdominal pain, and nausea,[25] serious adverse events from consuming nutrient supplements are extremely rare.[26]

The micronutrient formulas contain ingredients that are above or greater than recommended daily intake levels. RDAs and ULs have been developed for guiding consumers as to the maximum dose that should be consumed of any single nutrient on a daily basis. These levels are often quoted when discussing optimal doses that should be consumed by the public.[27] However, it is important to consider that these levels were determined based on healthy populations. Given the relationship between poor nutrition and poor mental health,[28] it is possible that some individuals experiencing significant psychological symptoms may require micronutrients at levels above usual RDAs. We cannot therefore necessarily extrapolate data that have been collected from healthy populations and assume that they are

Table 2. Pre- and Post-Safety Biomarkers for Those Participants for Whom We Had Pretreatment Assessments

	N	*Pretreatment mean*	*Pretreatment SD*	*Number of cases outside reference range*	*Post-treatment mean*	*Post-treatment SD*	*Number of cases outside reference range*	*Paired t-test*	p	*Effect size (ES)*
Prolactin	15	160.67	80.75	2	174.93	61.45	1	–0.569	0.578	0.15
Hemoglobin	16	133.13	8.25	0	136.63	10.68	3	–1.807	0.091	0.47
Hematocrit	16	0.39	0.02	0	0.41	0.03	2	–2.835	**0.013**	0.8
MCV	16	83.38	4.06	0	84.80	4.32	0	–2.119	0.051	0.53
MCH	15	27.93	1.53	0	28.21	1.14	0	–1.027	0.322	0.28
Platelets	16	291.44	60.62	0	291.88	53.82	0	–0.036	0.972	0.00
WBC	15	5.43	2.09	3	5.75	1.16	1	–0.603	0.556	0.17
Neutrophils	16	2.98	2.69	2	2.81	0.94	3	0.255	0.802	0.07
Lymphocytes	16	2.35	0.96	1	2.21	0.42	0	0.744	0.468	0.24
Monocytes	16	0.45	0.19	3	0.44	0.12	1	0.035	0.973	0.01
Eosinophils	16	0.27	0.16	0	0.27	0.20	0	–0.070	0.945	0.01
Sodium	13	139.69	1.38	0	139.31	1.49	0	0.959	0.356	0.27
Potassium	13	3.97	0.15	0	4.09	0.12	0	–3.807	**0.002**	1.09
Urea	13	5.05	0.92	3	4.36	1.06	2	2.485	**0.029**	0.69
Creatinine	17	64.18	18.97	1	69.00	17.87	1	–2.308	**0.035**	0.56
Glucose	17	4.99	0.45	0	5.01	0.82	1	–0.088	0.931	0.02
Calcium	17	2.45	0.07	0	2.42	0.04	0	1.768	0.096	0.46
Phosphate	17	1.38	0.17	0	1.37	0.20	0	0.324	0.750	0.08
Magnesium	17	0.84	0.08	0	0.83	0.07	0	0.324	0.750	0.08
GGT	17	13.53	4.98	0	15.35	9.15	1	–1.580	0.134	0.76
AST	17	25.88	5.27	0	27.41	5.71	0	–1.245	0.231	0.30
ALT	16	19.00	6.99	0	23.38	9.01	1	–1.813	0.090	0.46
Iron	17	18.76	5.54	1	17.24	3.35	0	1.042	0.313	0.26
Transferrin	13	2.72	0.35	0	2.62	0.26	0	1.288	0.222	0.37
%Saturation	13	28.92	10.24	1	25.23	4.95	0	1.467	0.168	0.47
Ferritin	12	38.67	19.03	0	49.00	22.46	0	–2.144	0.055	0.63
Vitamin B_{12}	16	419.31	185.98	2	1084.94	326.03	15	–9.490	**<0.001**	2.63
Folate	16	27.85	10.17	0	37.50	3.10	0	–3.712	**0.002**	1.07
Vitamin D	13	65.15	24.40	3	109.77	21.45	0	–6.855	**<0.001**	1.91
Copper	11	14.59	1.53	2	15.66	2.88	2	–1.968	0.077	0.84
Zinc	11	12.45	1.38	1	12.64	1.46	1	–0.463	0.653	0.14
Cu:Zn ratio	11	1.18	0.12		1.24	0.15		–0.979	0.350	0.30
Body mass index	14	19.54	3.40		19.92	3.90		–0.838	0.424	0.28
Blood pressure (systolic)	10	110	15.77		105.8	10.99		0.854	0.415	0.28
Blood pressure (diastolic)	10	65.8	21.67		62.5	8.1		0.54	0.602	0.21
Pulse	10	83.7	10.86		81.2	13.14		0.533	0.607	0.17
Diet	14	36.5	5.74		34.7	6.07		1.151	0.271	0.31

p-Values in bold are considered significant, missing data due to laboratory errors.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; SD, standard deviation; WBC, white blood cells.

Table 3. Pretreatment and Post-Treatment Score on the Psychosocial Measures for Those Participants Observed Over Time

	N	*Pretreatment mean*	*Pretreatment SD*	*Post-treatment mean*	*Post-treatment SD*	*t*	p	*Effect size (ES)*
CMRS total	14	25.43	12.61	5.64	4.01	6.77	**<0.001**	2.51
CGAS/GAF	17	49.82	7.80	73.35	11.30	–9.318	**<0.001**	2.36
CGI-S global	17	5.18	1.07	1.88	0.86	12.294	**<0.001**	3.03
SCARED (parent rated) total	17	21.86	16.7	10.86	11.94	2.762	**0.016**	0.77
ADHD inattentive (raw score)	17	20.82	5.78	9.24	4.70	8.988	**<0.001**	2.21
ADHD hyperactive/impulsive (raw score)	17	19.53	5.76	7.41	4.54	9.26	**<0.001**	2.29
ADHD total (raw score)	17	40.29	10.42	16.65	8.75	10.321	**<0.001**	2.53
ADHD inattentive (T score)	17	73.47	10.48	54.29	7.95	9.031	**<0.001**	2.27
ADHD hyperactive/impulsive (T score)	17	78.18	12.14	56.59	9.78	8.89	**<0.001**	2.21
ADHD total (T score)	17	77.71	10.58	55.82	8.84	10.963	**<0.001**	2.71

p-Values in bold are considered significant.
ADHD, attention-deficit hyperactivity disorder; CGI-S, Clinical Global Impression–Severity–Global; CMRS, Child Mania Rating Scale; SCARED, Screen for Child Anxiety Related Disorders–Parent Version; SD, standard deviation.

relevant to all those who are symptomatic. It is possible that the nutritional requirements of individuals who respond to micronutrients may be greater than the healthy general population. Nevertheless, given that magnesium and zinc are provided at doses above the UL, tracking possible adverse events associated with these nutrients (such as gastrointestinal distress and lethargy)[29] would be advised.

It is important to note that RDAs and ULs are established based on consuming a single nutrient. It is possible that RDAs and ULs are less relevant when nutrients are consumed in combination with other nutrients. It also needs to be acknowledged that ULs can be arbitrary and vary across different countries; for example, ULs for children are derived through downward extrapolation from adult ULs.[29] Dietary treatments with single ingredients can create deficiencies in other nutrients. For example, taking folate without vitamin B_{12} can contribute to masking a B_{12} deficiency,[30] and taking zinc without copper can affect copper metabolism.

These positive studies of micronutrients sit alongside large studies that identify health risks associated with the consumption of single or few nutrients. For example, risk of lung cancer has been identified as increasing with the use of B_6 and B_{12} from individual supplement sources (but not from multivitamins) for men only (with increased risk associated with being a smoker),[31] and risk of prostate cancer is reported to increase with individual supplementation with folic acid.[32] However, not all studies report these risks[33–35] and others show a potential protective role.[36] We do not know if these risks–benefits exist with the consumption of nutrients in combination. Further research is needed to examine these possible negative associations and consumers need to be informed that at this stage, the long-term risks of micronutrient supplementation contain some uncertainty and continue to be evaluated. Although the risks are low, it is also important for future research to evaluate any possible harms associated with the elevations outside the reference range in nutrients we did observe in some people (such as vitamin D in 2 of 31 participants and high vitamin B_{12} in 28 of 32 participants). Larger studies could also usefully investigate whether genetic differences are associated with specific adverse effects.

There are a number of limitations associated with a naturalistic observational study like this one. One important limitation is that the participants in this study were all people who have chosen to take micronutrients over the long term and are thus likely to be representative of individuals who both perceive ongoing benefit from micronutrients and tolerate their ongoing consumption. Those who stopped taking the micronutrients are not represented in this study. Further systematic evaluation of this group could add insight into the potential negative side effects of long-term consumption. Two longer term studies suggest that those who stop consuming the nutrients have poorer psychological outcomes than those who remain on them.[37,38] These studies also reported that the reasons for stopping these formulations related to the number of pills and cost, rather than adverse effects or lack of efficacy.[37,38]

Another limitation is that the size of our sample was small and the majority of participants were of NZ European ethnicity and of average SES. We did not have any pregnant or breastfeeding women in the study and caution is advised using nutrients with these populations, although current research in our laboratory is evaluating safety in these populations. People who have specific medical problems, such as renal and liver problems or thyroid dysfunction, may need special monitoring. Future research would therefore benefit from evaluating larger more diverse samples to identify less common and idiosyncratic adverse events. However, as long as micronutrients are self-funded, it is unlikely that evaluations in a wider ethnic and diverse socioeconomic group are possible. Only through larger sampling and post-marketing surveillance is it possible to identify less common adverse effects associated with a treatment.

The sample consisted of people who were not taking psychiatric medications to treat their mental health problems; as a consequence, this sample is not representative of clients treated by specialist mental health services. Previous studies have noted that patients treated with psychiatric medication can lower their medication dose after

micronutrients are added and dose reductions are recommended to avoid toxicity.[39,40] The mechanism through which psychiatric medications interact with micronutrients is not yet known, but it is possible that this is at least partially mediated via the cytochrome p450 system.[41] It is also well documented that some medications prescribed for physical health problems, such as proton pump inhibitors, diuretics, epilepsy drugs, cholesterol drugs, and cardiac and hypertensive drugs, can induce subclinical and clinical micronutrient deficiencies as well as impair metabolism of vitamins and minerals.[42]

The evaluation of two different products complicates interpretation of the data. There are some differences in doses across the two products, as well as differences in a small number of ingredients, although overall there are more similarities than differences. Furthermore, there have been minor modifications of the formulas over time, which has resulted in some changes in ingredients as well as the recommended daily dose (from 15 to 12 for DEN and from 15 to 8 for EMP). Also, the dose that participants were taking varied between 4 and 15 pills; however, the lack of a relationship between change in blood markers and dose provides some confidence that the higher doses were not driving the identified changes in urea, potassium, and creatinine. More controlled trials in the future with consistent ingredients and doses would be desirable.

Not all abnormal blood tests were repeated unless it was deemed clinically necessary. However, it is possible that abnormal results were early indicators of developing problems. This seems unlikely given the long-term nature of the study. Patients and GPs were made aware of abnormal results, and longer term follow-up may be informative regarding this possibility.

We did not have a control group in this study. Change over time in both the blood biomarkers and psychosocial functioning may also be the results of many other factors. We assessed change in diet and that does not appear to be a contributor. Indeed, fruit and vegetable consumption for the children minimally decreased over the time evaluated. Regression to the mean, maturity, positive expectancy, and improvement in social circumstances are just some examples of variables that could all contribute to the positive changes in psychosocial functioning observed. The CGI-I was completed in some cases by the participants rather than a trained clinician. This limits somewhat the interpretation of the CGI-I results. Nevertheless, the positive benefits observed align with many studies conducted investigating efficacy of these formulations.[3,4] Finally, our range of laboratory tests is not exhaustive and it is possible that aspects we did not investigate were adversely affected by micronutrients. However, the very low level of adverse effects reported by participants is somewhat reassuring in this regard.

Conclusions

Overall, this study provides support that these formulations appear to be a safe, tolerable, and useful long-term treatment for ADHD, depression, and anxiety, although large-scale inclusive studies are still required. The benefit-to-risk ratio is very favorable in this sample. Routine screening for metabolic and electrolyte abnormalities before commencing treatment and intermittently during follow-up is recommended to detect and mitigate any adverse effects. Our study also suggests that those who have a positive response to micronutrients may sustain these benefits over the longer term.

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Authors' Contributions

All authors were involved in the conception and design, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the submitted version.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1

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