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Moderators of treatment response in adults with ADHD treated with a vitamin–mineral supplement☆

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ABSTRACT

Background: To date there has been no research investigating moderators of response to micronutrient treatment of mental illness, specifically baseline nutrient levels.
Method: We conducted analyses of data from a randomized placebo-controlled trial (RCT) of 80 adults (≥16 years) with Attention-Deficit/Hyperactivity Disorder (ADHD), whereby participants were treated acutely (8 weeks) with micronutrients or placebo followed by an open-label (OL) phase of 8 weeks whereby all participants received micronutrients. To ensure that all participants had been exposed to the micronutrients for 8 weeks, only those 64 who had adhered to the treatment protocol and completed 8 weeks on nutrients were included in the data analysis: 34 from the group that had been randomized to the micronutrient arm, and 30 from the group that had been randomized to the placebo group and hence had only received nutrients in the OL phase. Six outcomes were examined: change in ADHD symptoms (self/clinician), ADHD responder, Clinical Global Impression-Improvement (CGI-I), change in mood, and change in Global Assessment of Functioning (GAF). Demographic, developmental and psychiatric history, current clinical characteristics, and baseline nutrient levels were all considered as putative predictors.
Results: There were significant changes in all outcome variables after 8 weeks exposure to the micronutrients. Among the nutrients recorded at baseline, substantial deficiencies (27%) were only observed for vitamin D. However, other than an association showing that higher iron at baseline was correlated with higher baseline depression scores, baseline nutrient levels were not correlated with baseline psychiatric variables/current clinical characteristics. Regression analyses revealed that *higher* baseline ferritin and *lower* baseline copper and vitamin D levels were associated with a better response to treatment for some but not all outcomes. None of the other nutrient levels was found to be associated with outcome, including zinc, vitamin B_{12}, iron, and folate. There were no childhood risk factors, demographic variables or clinical correlates that contraindicated micronutrient treatment; more severe symptoms at baseline and greater number of developmental risk factors predicted greater treatment response.
Conclusions: Further research looking at nutrients more broadly is required to confirm these initial observations about ferritin, vitamin D and copper; however, the results suggest that serum nutrient levels have limited value for identifying who will respond to treatment.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) in adulthood has become increasingly recognized as an important disorder to treat, with prevalence rates for adult ADHD estimated between 4 and 5% (Kessler et al., 2006) and poor long-term outcomes documented for those followed to adulthood (Klein et al., 2012). Predictors of treatment response are confined to medication trials with symptom severity, gender, co-occurring disorders, and academic achievement shown to influence outcome (Buitelaar et al., 2011; Torgersen et al., 2008). The most common risk factors studied are genetic; however, this emphasis has led to an overall neglect in considering the role that the environment

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; CAARS, Conners' Adult ADHD Rating Scales; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning; CGI-I, Clinical Global Impression-Improvement; NZSEI, New Zealand Socio-Economic Index; RCT, Randomized Controlled Trial; OL, Open Label; EMP, EMPowerplus; CAADID, Conners' Adult ADHD Diagnostic Interview for DSM-IV; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; DSM-IV, Diagnostic and Statistical Manual 4th Edition; SCID-I, Structured Clinical Interview for DSM-IV-TR Axis I Disorders; NIMH, National Institute of Mental Health; RdoC, Research Domain Criteria.

☆ Trial registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12609000308291.

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might play in the expression of the symptoms (Calarge et al., 2010). Although there has been a recent interest in the role that nutrients play in the expression and treatment of ADHD (Milte et al., 2012; Nigg et al., 2012), as well as studies showing associations between nutrient levels and ADHD behaviours (Arnold et al., 2005), to date no study on broad-based micronutrient supplementation has investigated whether nutrient levels can be useful at predicting treatment response.

Biochemical markers or biomarkers are becoming increasingly studied in attempts to identify those who might be at risk for ADHD as well as to identify possible areas for intervention (Scassellati et al., 2012). Some biomarkers are modifiable and thus may lead to targeted treatments. Individual nutrients have been the focus of studies attempting to determine the role that they may play in the expression of ADHD in children. The most studied candidates have been iron and zinc, with some positive and some negative results (Akhondzadeh et al., 2004; Arnold et al., 2011; Bilici et al., 2004; Cortese et al., 2009; Konofal et al., 2008; Oner and Oner, 2008; Oner et al., 2010; Sever et al., 1997; Uckardes et al., 2009). The rationale for supplementing with these nutrients includes the role that iron plays as a coenzyme of tyrosine hydroxylase, critical for dopamine synthesis (Oner and Oner, 2008), and the role that zinc plays in regulating the dopamine transporter, among its many functions (Lepping and Huber, 2010). There have been no studies looking at the impact of nutrient levels on the expression of ADHD in adults. Nutrient biomarkers seem a potentially profitable way forward to predict treatment responders, given that mechanisms by which nutrient treatments might work implicate nutrients working at the cellular level, either through improving mitochondrial functioning (Gardner and Boles, 2005), correcting in-born errors of metabolism (Kaplan et al., 2007), possibly addressing compromised gastrointestinal functioning (Jackson et al., 2012) or inflammation (Donev and Thome, 2010), or acting as cofactors for various metabolic activities in the body (Ames et al., 2002). Deficiencies in nutrients in particular may identify individuals who may benefit from micronutrient treatment.

This study presents the first investigation looking at whether nutrient biomarkers taken prior to a broad-based micronutrient treatment are useful for predicting treatment response in adults with ADHD. These predictors were explored alongside more common predictors such as demographic variables, developmental history, and clinical correlates (Buitelaar et al., 2011; Torgersen et al., 2008). This study aligns well with the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC), which encourages research that aims to uncover laboratory-based evaluations that can assist with prognosis and treatment (Insel et al., 2010).

2. Methods

2.1. Study design

The study received ethical approval from both the National Upper South A Health and Disability Ethics Committee and the Human Ethics Committee at the University of Canterbury. After describing the experimental nature of the trial and explaining the other treatment options available in the community, written informed consent was obtained from all participants. The trial was prospectively registered (ACTRN12609000308291).

Study details have been described previously (Rucklidge et al., in press). In brief, this was an 8 week double-blind (participants and investigators), parallel-group randomized controlled trial (RCT) designed to assess the efficacy and safety of a broad spectrum micronutrient formula (EMPowerplus (EMP)) compared with placebo followed by an 8 week open-label (OL) trial with EMP in medication-free men and women with ADHD, 16 years and older. Participants had to meet criteria for ADHD based on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID (Epstein et al., 2002)) or, for those under 18 years (n = 7), the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 1997). In addition, participants had to have an elevated level (T score > 65) on one or more of the three DSM-IV subscales of the Conners' Adult ADHD Rating Scales (CAARS (Conners et al., 2003)) on either the self or the observer versions. For participants under 18 years, the Conners' Rating Scales for youth and parents were completed (Conners, 1997). Comorbidity was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (SCID-I (First et al., 2002)). The SCID-I was also used to verify whether ADHD symptoms being reported were better attributed to another Axis I disorder. Information on historical symptoms was obtained for all participants either directly from the participants if possible or from reviewing past psychological assessments or report cards (if available) or interviewing family members for supporting information.

Participants took 5 capsules per day initially, divided into three doses to be taken with meals and water, increasing to 10 capsules per day after 3 days, divided into three doses. On the 7th day, the dose was further increased to 15 capsules per day, in 3 doses of 5 capsules. The placebo and EMP (see Table 1 for EMP ingredients) were identical in appearance, used the same coating, and the placebo included riboflavin in order to mimic the smell and change in urine colour associated with taking vitamins. Following the 8-week double-blind RCT phase, participants could chose to enter an 8-week OL phase using EMP (n = 69). The titration regimen used at the start of the RCT was used again for all participants at the beginning of the OL phase.

At baseline, trial completion and post-OL, laboratory blood screening tested thyroid functions, serum lipids, prolactin, fasting glucose, blood clotting, iron, zinc, vitamin D, vitamin B_{12} and copper levels. Urinalysis and urine drug screen were also undertaken. These data were reviewed by the study physician. Safety data including laboratory values and

Table 1
Ingredients of EMPowerplus™ with recommended daily allowances (RDA) for adults given in the same unit.

EMP ingredients	15 capsules	Male RDA	Female RDA
Vitamin A	5760 IU	3000	2333
Vitamin C	600 mg	90	75
Vitamin D	1440 IU	600	600[b]
Vitamin E	360 IU	22.5	22.5
Thiamin	18 mg	1.2	1.1
Riboflavin	13.5 mg	1.3	1.1
Niacin	90 mg	16	14
Vitamin B6	36 mg	1.3	1.3[b]
Folic acid	1440 μg	400	400
Vitamin B12	900 μg	2.4	2.4
Biotin	1080 μg	30	30[a]
Pantothenic acid	21.6 mg	5	5[a]
Calcium	1320 mg	1000	1000[b]
Iron	13.7 mg	8	18[b]
Phosphorus	840 mg	700	700
Iodine	204 μg	150	150
Magnesium	600 mg	400	310[b]
Zinc	48 mg	11	8
Selenium	204 μg	55	55
Copper	7.2 mg	0.9	0.9
Manganese	9.6 mg	2.3	1.8[a]
Chromium	624 μg	35	25[ab]
Molybdenum	144 μg	45	45
Potassium	240 mg	4700	4700[a]
Choline bitartrate	540 mg	550	425[a]
dl-Phenylalanine	360 mg	–	–
Citrus bioflavonoids	240 mg	–	–
Inositol	180 mg	–	–
Glutamine	180 mg	–	–
Methionine	60 mg	–	–
Grape seed	45 mg	–	–
Ginkgo biloba	36 mg	–	–
Germanium sesquioxide	20.7 mg	–	–
Boron	2400 μg	–	–
Vanadium	1194 μg	–	–
Nickel	29.4 μg	–	–

[a] Reference values are given as adequate intake as RDA not available.
[b] RDA varies with age.

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adverse events occurring during the RCT have been reported elsewhere (Rucklidge et al., in press).

2.2. Sample selection

To maximize the statistical power to detect associations with changes in outcome measures over eight weeks, we combined the data from the RCT and OL samples together. Data from the RCT phase for those randomized to EMP and data from the OL phase for those randomized to placebo during the RCT were used. Two participants who dropped out of the RCT phase while taking placebo were not included, as were those with treatment adherence in the RCT of less than 80% (n = 7). A further seven participants from the placebo group who did not complete the entire open-label phase of the trial were not included. These exclusions reduced our final sample to 64 participants (34 from RCT phase, 30 from OL phase). Due to laboratory omissions and disruptions caused by the on-going Canterbury earthquakes, some participants did not have either a baseline level done on a specific nutrient or a post-RCT nutrient level done. We used the post-RCT level (n = 7) as the baseline level for those randomized to the placebo phase, after establishing that there was no group change on these nutrient levels from baseline to post-RCT in the placebo phase. We used the 16 week level (n = 4) for the post RCT level for those who had been randomized to EMP.

2.3. Outcome measures

All participants were monitored in face-to-face meetings by a clinical psychologist or senior clinical psychology graduate student under a psychologist's supervision. To capture the breadth of psychiatric symptoms monitored, six different outcome measures were considered: 1) change in total ADHD Conners' Adult ADHD Rating Scales (CAARS) score for self, 2) change in total ADHD CAARS score for clinician, 3) ADHD responder, 4) Clinical Global Impressions-Improvement (CGI-I), 5) change in Montgomery–Åsberg Depression Rating Scale (MADRS), and 6) change in Global Assessment of Functioning (GAF). These outcome measures were completed at baseline, end of RCT and end of OL and were assessed using the following procedures.

2.3.1. The CAARS

The CAARS (Conners et al., 2003) was completed by two raters based on observations of/by the participant over the previous 8 weeks: self (CAARS-S:L), and clinician (CAARS-O:SV). All raw scores are converted to T-scores based on age and gender. The score on the self-report was also used as a dichotomous outcome variable, ADHD responder, based on a ≥ 30% decrease in *either* attention or hyperactivity/impulsivity on self-report CAARS, a standard percentage change in ADHD ratings used in the ADHD literature (Wilens et al., 2005).

2.3.2. The CGI-I Scale

The CGI-I Scale (Guy, 1976) produces a score that ranges from 1 (very much improved) to 7 (very much worse) as compared with baseline functioning. The CGI-I was also used as an outcome variable to identify responders (either "much" to "very much" improved).

2.3.3. The MADRS

The MADRS (Montgomery and Åsberg, 1979), a 10 item scale administered by a trained clinician who assigns a severity rating for each symptom of depression based on a personal interview. Inter-rater reliability on a subset of these interviews (intra-class correlation coefficient) was estimated at 0.98.

2.3.4. The GAF

The GAF (American Psychiatric Association, 2000), a numeric scale (1 through 100) used by mental health clinicians to rate the general functioning of adults.

Change was computed as change over the 8 week period being assessed (i.e. either baseline to end of RCT or end of RCT to end of OL depending on whether the individual had been taking the micronutrients during the RCT phase).

2.4. Predictors

The following predictors were considered as potentially associated with treatment response: 1) exposure to EMP (RCT/OL), 2) demographic variables including age, gender, income, estimated IQ, education level, marital status (yes/no), 3) expectancy of treatment benefit, 4) dietary patterns assessed using a brief dietary intake questionnaire modified from Baker et al. (2003) to identify dietary patterns including consumption of fruit and vegetables, breakfast, consumption of fast foods, and eating when full producing a single total score with higher numbers indicative of healthier eating, 5) total positive responses within six CAADID developmental risk factor groups including gestational (e.g., mother ill, smoked, drank alcohol, used drugs), delivery (e.g., low birth weight, breech, foetal distress), developmental (e.g., slow to walk/talk), temperament (e.g., impulsive, fearful, irritable, colic), environmental (e.g., violence, abuse, neglect, family stress), and medical risk factors (e.g., allergies, asthma, meningitis), 6) presence of a current co-occurring psychiatric disorder and total current co-occurring disorders, 7) any history of comorbid psychiatric disorder and total number of past comorbid psychiatric disorders, 8) current cannabis user, 9) current alcohol abuser, 10) past psychotropic medication use, 11) enrolled in trial during the acute phases of the Christchurch earthquakes (February 22nd 2011 through to end of 2011), 12) baseline ADHD severity (rated by self/clinician), 13) baseline mood (MADRS), 14) baseline GAF, and 15) baseline nutrient levels (vitamin D, B_{12}, folate, zinc, copper, iron, and ferritin).

2.5. Statistical analyses

To provide an indication of the strength of the changes in the outcome measures and nutrient levels over eight weeks, the pre- and post-values were compared using paired t-tests.

The following statistical strategy was adopted to identify independent baseline moderators of response to EMP. T-tests, Pearson's correlation coefficients, and chi-square analyses as appropriate were used to determine the univariate associations between putative baseline predictors and treatment responses.

Hierarchical forward stepwise linear and logistic regression analyses were conducted for each outcome measure using any predictor that showed some association ($p < 0.10$) from the univariate analyses with a treatment response outcome. Whether EMP was taken during the RCT or OL phase was entered into the model regardless of whether its contribution was statistically significant. Predictors that entered into the model with a significant contribution of $p < 0.05$ were considered independently associated with treatment response.

3. Results

3.1. Patient characteristics

Baseline demographics, clinical features and nutrient levels are shown in Tables 2 and 3. Other than vitamin D, most participants entered the trial with serum nutrient levels within the normal reference ranges. Correlations between nutrient levels and baseline psychiatric variables (e.g., mood, ADHD scores, GAF) revealed only one significant association: baseline iron was significantly correlated with baseline MADRS ($r = 0.323$, $p = 0.009$), with higher baseline MADRS scores associated with higher iron levels. No relationship was observed between baseline ferritin and baseline mood.

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Table 2
Baseline demographic and clinical characteristics of study participants.

Characteristic	Total sample (n = 64)	
Demographics	Mean ± SD or n (%)	Range within the sample
Age	35.2 ± 13.3	16.45–73.17
Male	42 (65.6)	
Estimated IQ[a]	113.9 ± 13.8	83–143
Socio-economic status[b]	44.6 ± 17.6	27–77
Married/common-law	28 (43.9)	
Dietary patterns[c]	32.3 ± 6.0	24–45
Expectancy of treatment effect[d]	4.7 ± 2.4	1–9
Developmental risk factors		
Gestation risk	0.6 ± 0.9	0–3
Delivery risk	0.4 ± 0.8	0–4
Temperament risk	3.9 ± 2.9	0–11
Developmental risk	0.4 ± 0.8	0–3
Environment risk	2.3 ± 2.3	0–8
Medical history risk	1.8 ± 1.4	0–5
Total comorbid psychiatric disorders—current	1.3 ± 1.4	0–5
Total comorbid psychiatric disorders—past	2.1 ± 2.0	0–7
Clinical characteristics		
ADHD type		
Inattentive	24 (37.5)	
Hyperactive/impulsive	4 (6.3)	
Combined	36 (56.3)	
Any comorbid psychiatric disorder		
Current	36 (56.3)	
Past	47 (73.4)	
Alcohol/substance abuse		
Current alcohol abuser	8 (12.5)	
Current cannabis user	7 (10.9)	
History of past psychiatric medications	33 (51.6)	
In earthquake	25 (39.1)	
Baseline outcome measures		
Self ADHD	74.8 ± 12.8	41–90
Observer ADHD	68.4 ± 11.6	41–90
Clinician ADHD	67.8 ± 10.8	44–90
MADRS	14.1 ± 7.5	2–33
GAF	61.8 ± 7.6	45–80

MADRS = Montgomery–Åsberg Depression Rating Scale.
GAF = Global Assessment of Functioning.
[a] Assessed using Block Design and Vocabulary subtests of the WAIS-III (Wechsler, 1997).
[b] Based on the NZSEI-96 which ranks occupations from 10 to 90 (Davis et al., 1997).
[c] Assessed using a brief dietary intake questionnaire modified from Baker et al. (2003) to identify dietary patterns including consumption of fruit and vegetables, breakfast, consumption of fast foods, and eating when full producing a total score with higher numbers indicative of healthier eating.
[d] Measured from 0 (not at all) to 3 (very much) across 4 variables (inattention, hyperactivity, impulsivity, mood).

3.2. Safety assessments

Full efficacy and safety of EMP have been reported elsewhere (Rucklidge et al., in press; Simpson et al., 2011); overall, EMP has a reassuring safety profile. For the trial period reported in this paper, among the 196 adverse events (AEs) reported in 48 participants; 190 (97%) of these were classified as mild (e.g., nausea, headache, sleep disruption, dry mouth) and 6 (3%) moderate (2 elevated prolactin, 2 elevated glucose, 1 elevated ALT and 1 glositis). It was unclear whether the 6 moderate AEs were related to the treatment.

3.3. Effectiveness

Pre- and post-treatment paired t-tests are illustrated in Table 4, showing significant ($p < 0.001$) changes in all outcome variables. Based on the CGI-I, 33 (51.6%) of the participants were identified as "much" to "very much" improved. Using ≥30% decrease in either attention or hyperactivity/impulsivity on self-report CAARS as an indicator of clinically significant change, 39 (60.9%) of participants were identified as ADHD responders. There were no cases of one rating decreasing by 30% while the other got worse.

3.4. Nutrients

Nutrient assays showed significant increases for vitamin D ($p < 0.001$), B_{12} ($p < 0.001$) and folate ($p < 0.001$) levels, but not for ferritin, iron, zinc and copper (Table 4). There was no change in reported eating patterns during the course of the trial.

3.5. Predictors of treatment outcome

Table 5 shows the p-values from the univariate analyses comparing the putative predictor baseline variables and the changes in the outcome measures. Any association that had a $p \leq 0.10$ (shown in bold) means that predictor was subsequently included in the hierarchical stepwise regression analysis for that outcome variable.

3.5.1. Self-reported ratings of ADHD

The predictor variables included for change in self-reported ADHD scores identified from the univariate analyses were past medication, developmental risk factors, current cannabis user, current alcohol abuser and baseline self-report ADHD. Only childhood developmental risk factors were independently associated with self-reported ADHD rating ($R^2_{adj} = 0.103, \beta = 0.303, p = 0.028$), with more developmental risk factors associated with greater change in self-reported ADHD symptoms.

Univariate predictors of the dichotomous ADHD responder variable, which was measured as ≥30% decrease on CAARS self-report from baseline, were developmental and environmental risk factors and baseline ferritin. Only baseline ferritin contributed significantly to the model ($R^2_{adj} = 0.126, \beta = 0.317, p = 0.027$).

To further explore the relationship between baseline ferritin levels and ADHD responder, chi square analyses were performed after dividing ferritin levels into tertiles. Based on these analyses, higher ferritin levels at baseline were significantly associated with ADHD response

Table 3
Baseline nutrient levels of study participants.

Baseline nutrient levels	Total sample (n = 64)			
	Mean ± SD	Range within the sample	Deficient (identified as below reference range): n (%)	Elevated (defined as above reference range): n (%)
Vitamin D (nmol/L): reference range: 50–150	65.2 ± 24.4	14–143	17 (26.6)	0
Vitamin B_{12} (pmol/L): reference range: 130–650	359.6 ± 122.3	223–706	0	3 (4.7)
Folate (nmol/L): reference range: 8.0–75	21.4 ± 8.9	6.5–41.0	1 (1.6)	0
Ferritin (μg/L): reference range: 20–200 (females) 20–500 (males)	110.1 ± 80.5	8–375	8 (12.5)	2 (3.2)
Iron (μmol/L): reference range: 10–30	18.9 ± 6.5	9–41	1 (1.5)	3 (4.7)
Zinc (μmol/L): reference range: 10–17	12.1 ± 1.6	9–16	7 (10.9)	0
Copper (μmol/L): reference range: 11–22 (females) 11–20 (males)	14.4 ± 3.3	8.6–28.2	5 (7.8)	3 (4.7)

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Table 4
Baseline and post 8-week exposure to nutrients on outcome measures and nutrient levels.

Variable	Total sample (n = 64)								
	Baseline		Post		Change from baseline	Confidence interval	t-Value	*p*	ES[a]
	Mean	SD	Mean	SD					
Self-report CAARS (T-scores)									
DSM combined	74.8	12.8	63.3	14.0	11.5	8.8 to 14.3	8.34	<0.001	1.04
DSM inattention	78.1	11.6	68.0	13.9	10.2	7.2 to 13.1	6.88	<0.001	0.86
DSM H/I	64.2	13.8	54.4	13.2	9.8	7.4 to 12.2	8.18	<0.001	1.02
Clinician CAARS (T-scores)									
DSM combined	67.8	10.8	60.7	10.9	7.1	4.6 to 9.7	5.65	<0.001	0.71
DSM inattention	68.6	10.1	62.3	11.4	6.2	3.5 to 9.0	4.49	<0.001	0.56
DSM H/I	62.4	12.9	55.7	11.45	6.7	4.4 to 9.0	5.84		0.73
MADRS total	14.1	7.4	9.2	7.8	4.8	3.1 to 6.6	5.57	<0.001	0.70
GAF	61.8	7.6	67.9	9.0	6.1	−7.9 to −4.2	−6.51	<0.001	0.81
Changes in nutrient levels									
Vitamin D (nmol/L)	66.7	25.3	80.6	22.04	14.0	7.6 to 20.3	−4.42	<0.001	0.63
Vitamin B_{12} (pmol/L)	366.1	127.3	739.9	262.7	373.9	312.8 to 435.0	−12.26	<0.001	1.64
Folate (nmol/L)	22.0	8.3	48.1	17.8	26.1	21.4 to 30.8	−11.13	<0.001	1.49
Ferritin (μg/L)	113.2	82.0	112.63	80.0	.6	−7.6 to −8.8	.145	0.885	0.02
Iron (μmol/L)	19.0	6.5	18.81	5.8	.2	−1.7 to −2.1	.238	0.813	0.03
Zinc (μmol/L)	12.1	1.6	12.1	1.5	.1	0.4 to 0.5	−.285	0.777	0.04
Copper (μmol/L)	14.6	3.4	14.9	3.3	.3	0.2 to 0.9	−1.25	0.215	0.16

CAARS = Conners Adult ADHD Rating Scale.
H/I = hyperactivity/impulsivity.
MADRS = Montgomery–Åsberg Depression Rating Scale.
GAF = Global Assessment of Functioning.
[a] Cohen's d measured as the mean change divided by the SD of the change.

(χ^2 (2) = 6.541, p = 0.038), with almost twice as many of those identified in the highest tertile for ferritin being classified as responders (81.8%) as compared with those identified in the lowest tertile of ferritin levels (45.5%). Due to the long history of research interest in zinc and iron levels in relation to ADHD behaviours, we also looked at zinc and iron levels divided into tertiles. There was no relationship between baseline zinc or iron levels and self-reported ADHD response (see Fig. 1).

3.5.2. Clinician ratings of ADHD

Univariate predictors of change in clinician-rated ADHD scores were total number of current psychiatric disorders, whether or not the participant was taking the micronutrients during the acute phase of the earthquakes, baseline MADRS and baseline clinician total ADHD score. Only baseline clinician-rated ADHD score contributed significantly to the model (R^2_{adj} = 0.193, β = 0.510, p = 0.001).

3.5.3. Clinical Global Impression-Improvement (CGI-I)

Predictors for the CGI-I included baseline vitamin D, baseline copper, and age. In the final model only baseline copper contributed significantly to the model (R^2_{adj} = 0.154, β = 0.359, p = 0.007).

To further explore the relationship between copper levels and CGI-I, chi square analyses were performed after dividing copper levels into tertiles and classifying participants as either responders ("much" to "very much" improved) or non-responders based on the CGI-I rating. A curvilinear relationship between copper levels and CGI-I was found (χ^2(2) = 6.546, p = 0.038). Among those in the highest tertile, only 35% were responders versus 76.5% in the middle tertile and 48.1% in the lowest tertile (see Fig. 2).

3.5.4. Depression ratings

Univariate predictors of change in MADRS from baseline to end of treatment included baseline MADRS scores, baseline GAF, baseline clinician-rated ADHD score, baseline vitamin D, baseline zinc, and baseline copper. The final model including three variables was significant (R^2_{adj} = 0.473, p < 0.001). Baseline MADRS (β = 0.614, p < 0.001), copper (β = −0.353, p = 0.002), and vitamin D (β = −0.274, p = 0.011) all contributed significantly to the model with higher baseline MADRS, lower vitamin D and lower copper levels leading to greater change in the MADRS.

Fig. 3 shows the relationship between improvement in MADRS scores and baseline vitamin D and copper levels divided into tertiles.

3.5.5. Global Assessment of Functioning (GAF)

Univariate predictors of change in GAF included developmental risk factors, total clinician ADHD score, MADRS, GAF, vitamin D, zinc, and iron. The final model was significant (R^2_{adj} = 0.272, p = 0.002), with baseline MADRS (β = 0.532, p < 0.001) and baseline vitamin D (β = −0.279, p = 0.045) identified as significant predictors. Lower baseline vitamin D and higher baseline MADRS were associated with greater change in GAF.

4. Discussion

This study investigated predictors of response to a micronutrient treatment for adults with ADHD, which produced significant changes in all outcome measures from pre- to post-supplementation. These findings are consistent with a large body of international literature showing the benefit of micronutrients as a treatment for psychiatric disorders (Rucklidge and Kaplan, 2013). Three baseline vitamin/nutrient levels showed an association with treatment response: ferritin, vitamin D, and copper. Greater ferritin at baseline predicted who would be classified as an ADHD responder, lower vitamin D at baseline predicted greater change on two outcome measures (MADRS and GAF), and lower copper levels also predictor greater response on two of the six outcome measures (MADRS and CGI-I). No other relationships between baseline nutrient levels and treatment response were identified.

Only baseline ferritin proved to be a predictor for changes in ADHD behaviours (with higher baseline values predicting better response), but only for one outcome variable (ADHD responder) and the amount of variance explained was small (12.6%). Why would *higher* baseline ferritin lead to greater response on ADHD symptoms? Serum ferritin reflects iron stores (Cook et al., 1974) so higher ferritin identifies those with healthy iron metabolism. Even with iron supplementation, it can take time to replenish the iron stores. It might be that those with low baseline ferritin take longer to respond to a treatment that includes iron supplementation than those who appear to metabolize iron normally, a hypothesis that could be verified with longer studies. Poor iron metabolism may contribute to slowed response given that people

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Table 5
Associations between the dependent variables and predictor variables measured as p-values.

	Δ Self ADHD total (T score)	Δ Clinician total ADHD (T score)	≥30% Δ ADHD self (yes/no)	CGI-I	Δ MADRS	Δ GAF
Demographic variables						
Married	0.506	0.720	0.628	0.940	0.607	0.925
Sex	0.820	0.852	0.827	0.543	0.539	0.869
Group (RCT/OL)	**0.064 (−)**	0.164	**0.042 (−)**	0.035	**0.049 (−)**	0.340
NZSEI	0.756	0.19	0.877	0.32	0.646	0.157
Education level	0.886	0.748	0.521	0.613	0.723	0.744
Estimated IQ	0.57	0.743	0.206	0.348	0.616	0.729
Age	0.784	0.153	0.702	0.029	0.134	0.168
Expectations/perceptions	0.790	0.253	0.259	0.221	0.602	0.470
Diet	0.859	0.267	0.645	0.423	0.635	0.560
Developmental risk factors						
Gestation risk	0.978	0.297	0.630	0.410	0.615	0.827
Delivery risk	0.757	0.424	0.247	0.443	0.886	0.184
Temperament risk	0.711	0.541	0.269	0.906	0.919	0.234
Developmental risk	**0.030**	0.385	**0.030**	0.496	0.460	0.059
Environment risk	0.507	0.473	**0.028 (−)**	0.901	0.222	0.918
Medical history risk	0.469	0.524	0.714	0.161	0.369	0.909
Clinical characteristics						
Total psychiatric—current	0.251	0.042	0.437	0.764	0.472	0.321
Total psychiatric—past	0.990	0.314	0.419	0.986	0.926	0.821
Any psychiatric—current	0.349	0.201	0.974	0.631	0.651	0.566
Any psychiatric—past	0.162	0.959	0.710	0.508	0.893	0.483
Past medication	**0.100 (−)**	0.847	0.210	0.275	0.948	0.377
Cannabis user	**0.086**	0.268	0.547	0.960	0.914	0.981
Alcohol abuser	**0.049**	0.853	0.383	0.940	0.925	0.788
In earthquake	0.839	**0.033 (−)**	0.688	0.558	0.421	0.415
Baseline outcome variables						
CAARS Self ADHD	**0.018**	0.262	0.945	0.738	0.293	0.199
CAARS Clinician ADHD	0.135	**0.001**	0.751	0.644	**0.084**	**0.044**
MADRS	0.330	**0.004**	0.774	0.302	**0.002**	**0.001**
GAF	0.512	0.139	0.476	0.177	**0.034 (−)**	**0.012 (−)**
Nutrient levels						
Vitamin B_{12}	0.189	0.646	0.735	0.134	0.545	0.373
Folate	0.308	0.654	0.858	0.481	0.812	0.670
Vitamin D	0.592	0.734	0.326	**0.040**	**0.008 (−)**	**0.048 (−)**
Ferritin	0.350	0.698	**0.011**	0.825	0.896	0.540
Copper	0.969	0.996	0.927	**0.004**	**0.064 (−)**	0.207
Zinc	0.865	0.795	0.699	0.684	**0.058**	**0.072**
Iron	0.426	0.227	0.519	0.266	0.145	**0.034**

CAARS = Conners Adult ADHD Rating Scale, MADRS = Montgomery–Åsberg Depression Rating Scale, GAF = Global Assessment of Functioning, CGI-I = Clinical Global Impression-Improvement (lower score indicates greater improvement), NZSEI = New Zealand Socio-Economic Index, RCT = Randomized Controlled Trial, OL = Open Label.
(−) indicates a negative association between the baseline factor or level and outcome.

with higher ferritin levels at baseline were more likely to be ADHD responders. Longitudinal research has shown that even when iron stores are replenished, the effects of the depletion continue to reflect in poor educational outcomes 10 years later (Lozoff et al., 2000).

Another possibility is that because high ferritin can reflect inflammation (Kalantar-Zadeh et al., 2004), perhaps the micronutrients improved inflammation and thereby indirectly improving ADHD symptoms (Donev and Thome, 2010). There is a growing body of literature linking ADHD to atopic eczema and other diseases involving inflammation (Buske-Kirschbaum et al., 2013; Chen et al., 2013) such that the idea that inflammation may contribute to ADHD symptoms is a research pathway worthy of further exploration. Future research would need to measure inflammatory markers in combination with nutrients in order to verify such a causal hypothesis.

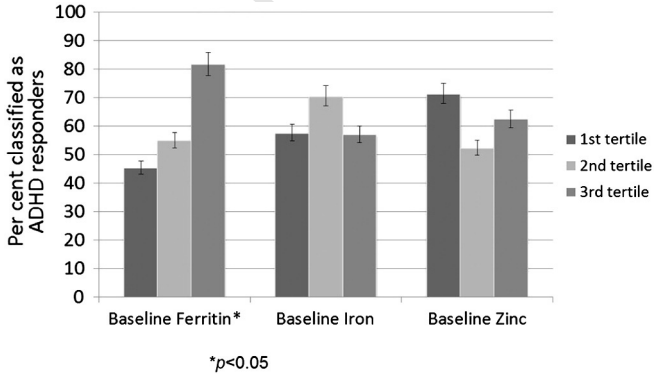

Fig. 1. Baseline nutrient levels converted to tertiles (1st tertile is the lowest) and compared with per cent ADHD responders, bars represent standard errors with percentage.

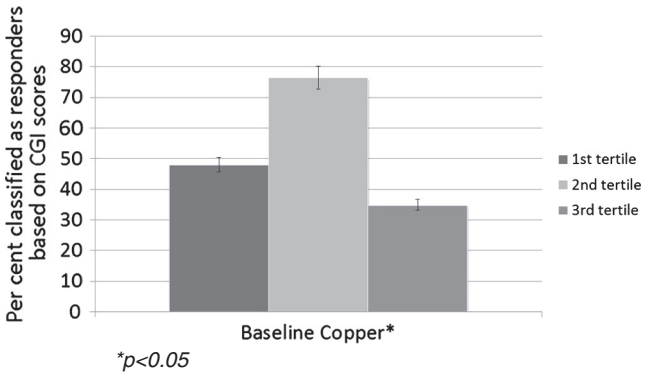

Fig. 2. Baseline nutrient levels converted to tertiles (1st tertile is the lowest) and compared with per cent CGI responders, bars represent standard errors with percentage.

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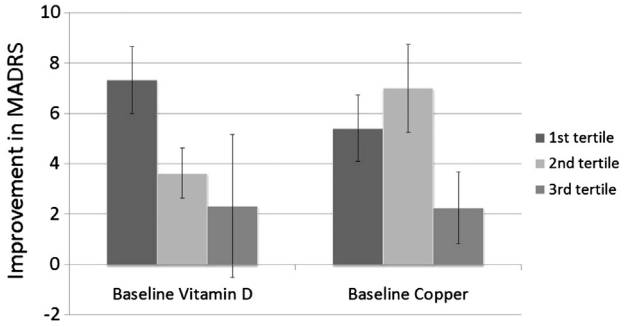

Fig. 3. Baseline nutrient levels converted to tertiles (1st tertile is the lowest) and compared with improvement in MADRS scores, bars represent standard errors.

Contrary to many child studies on ADHD (Arnold et al., 2005; Konofal et al., 2004), but not all (Donfrancesco et al., 2013), we did not observe significant correlations between nutrient levels such as zinc, iron and ferritin and ADHD behaviours at baseline. Possibly by adulthood, the risk factors for ADHD are so heterogeneous that the likelihood of finding significant correlations with nutrients diminishes substantially. Further, some researchers have challenged the use of serum markers for ADHD. For example, Donfrancesco et al. (2013), who ran the largest trial looking at serum ferritin in ADHD children and controls, found no association between serum ferritin and ADHD behaviours, and challenged the field to move beyond serum markers, raising the concern that serum ferritin is only a marker of peripheral iron status, not brain iron status and therefore may not correlate well with brain iron levels.

Unlike other research (Stewart and Hirani, 2010), we did not see significant associations at baseline between vitamin D levels and mood ratings even though a substantial percentage of our sample was vitamin D deficient at baseline (27%), a rate of vitamin D deficiency consistent with other research (Parker and Brotchie, 2011). Most of our participants did not enter the trial in a depressed state, which worked against finding an association between vitamin D and mood. However, we observed that those who did enter the trial with low vitamin D showed greater change in mood over the trial as compared with those who entered the trial with higher vitamin D, consistent with other studies showing that supplementing with vitamin D is an effective treatment for mood symptoms (Lansdowne and Provost, 1998).

The curvilinear relationship between CGI-I ratings and copper suggests that there may be a delicately balanced optimal level for copper. Note that copper levels mostly fell in the "normal" reference range and therefore we were not identifying anyone with copper deficiencies per se. The concern related to copper is typically copper toxicity, not copper deficiency (Nahar et al., 2010). Also, excess serum copper can reflect zinc deficiency (Wapnir, 1998) and therefore, those with higher serum copper may require them longer to benefit from the treatment as their zinc stores first need to be replenished. This hypothesis needs to be tested with longer exposure to nutrients and larger sample sizes. Copper levels are also highly influenced by other trace elements (Nahar et al., 2010) and therefore the observations made for copper need to consider the relative intake of other trace elements in the micronutrient formula.

In contrast, no associations were observed between baseline folate and vitamin B_{12} levels with any of the psychiatric variables at baseline as well as outcome variables, despite some research suggesting that low folate and low vitamin B_{12} are associated with depression (Levitt and Joffe, 1993; Seppala et al., 2013). Some research suggests that assessing vitamin B_{12} deficiency may be better determined from assays of cerebral spinal fluid than by blood serum (Prousky, 2010). We did note a modest correlation between baseline iron and baseline mood with higher iron levels being correlated with greater depression. Too much or too little serum iron can be related to fatigue, poor concentration and moodiness although research findings are mixed (Hunt and Penland, 1999) and serum level may not be a good reflection of absorption of iron in the brain. Further research is required to explore this unexpected finding.

Although blood nutrient levels significantly increased over the 8 week treatment period (vitamin D, B_{12} and folic acid), only B_{12} levels were raised beyond "normal" reference levels. As no adverse effects have ever been associated with a high B_{12} intake from either food or supplements (National Health and Medical Research Council, 2006), these increased levels are unlikely to be of concern. It is possible that significant changes in circulating levels of key vitamins including folate, vitamin B_{12} and vitamin D contributed to the positive effects we observed with micronutrient supplementation given their known role in the regulation of mood (Taylor et al., 2004; Wilkins et al., 2006), homocysteine metabolism (Huskisson et al., 2007), and synthesis of neurotransmitters (Bottiglieri et al., 2000).

The results also indicated that there are no specific demographic variables (age, socio-economic status, gender, marital status, education) that would contraindicate micronutrient treatment for ADHD in adults. The only developmental variable that was identified as a significant predictor of response was developmental history (e.g., slow to talk, walk, read, toilet train) with a greater number of risk factors associated with greater change in self-reported ADHD symptoms. People with a history of developmental risk factors may prove to benefit even more from this treatment than those without, perhaps because early malnutrition may have played a role in the developmental delays reported (Galler et al., 2012). Similar to literature on other studies investigating predictors for ADHD treatment response, we found that psychiatric history as well as history of alcohol and drug abuse did not predict treatment response (Buitelaar et al., 2011). Current psychiatric status also did not predict outcome, indicating that initiating this treatment with individuals who have psychiatric problems in addition to ADHD would not be contraindicated. In fact, several participants who reported alcohol or drug use at baseline reported a reduction or cessation of these behaviours during the trial (Harrison et al., 2013).

4.1. Limitations

While this is the first study examining predictors of response to micronutrient treatment in ADHD, it has some limitations including the small sample size, the fact that half the participants knew what they were taking (i.e., open label) which may have influenced their self-report ratings, rudimentary assessment of dietary patterns, and the reliance on self recall to assess childhood risk factors. Additionally, a large number of analyses have been undertaken and therefore, there is a likelihood that the significant associations identified represent type I errors rather than genuine associations. As such, results remain exploratory and require validation in future research.

Despite the notable improvement in ADHD and mood symptoms following 8 weeks of micronutrient treatment, supplementing individuals with nutrients could contribute to unknown risks. For example, due to genetic polymorphisms, some individuals cannot metabolize iron and as a consequence, excessive iron intake can result in serious medical concerns, including hemosiderosis. It is expected that such individuals at risk would experience significant side effects and voluntarily stop the treatment; however, it is a risk to monitor. In that there are controversial findings linking folic acid intake and cancer (Figueiredo et al., 2009; Roswall et al., 2013; Zhang et al., 2008), the increased folate levels observed (while remaining in the normal range) need to be considered when weighing the risks and benefits associated with this micronutrient treatment (Reynolds, 2002). Whether these identified risks hold when nutrients are given in combination is still unknown.

5. Conclusions

This is the first study to investigate the associations among serum nutrient levels and other presenting features with treatment response to a micronutrient intervention for ADHD in adults. The aim of identifying

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the factors that predict better treatment response is to target therapy to those who may benefit from the treatment. Those included in the analyses were largely a compliant group who we felt confident had been exposed to nutrients for an 8 week period, and even under these ideal conditions, only a few significant associations were identified, highlighting the complexity associated with identifying specific nutrient biomarkers and other predictors of outcome. Future research would need larger sample sizes to verify these initial positive observations and whether baseline ferritin, copper and vitamin D prove to be important serum nutrient levels to assist with predicting who might respond to this type of intervention. It is important, however, to consider that for two of the three nutrients identified as possible predictors of outcome, the majority of participants had "normal" levels at baseline, questioning using reference ranges for these nutrients to identify individuals who may benefit from nutrient therapy.

While the study was unable to highlight many significant associations between baseline measures and outcomes, it should not be surprising that this was the main finding. ADHD is a complex multifactorial disorder that has multiple risk factors of which nutrient deficiency may be only one of them. No single risk factor is likely necessary or sufficient to explain the disorder (Scassellati et al., 2012). Some have argued that peripheral changes in biochemical measures in blood serum may not be useful in determining what is occurring at a subcellular level of a metabolically active brain. Measuring individual serum levels may not be the best way to investigate mechanisms of action of a broad-based micronutrient treatment as each nutrient may impact on absorption and serum levels of other nutrients (Rucklidge et al., 2013).

To date, no biomarker for ADHD has achieved the status of clinical utility as a diagnostic tool or as a predictor of treatment outcome (Scassellati et al., 2012). We also know very little about how specific these biomarkers are to ADHD. Despite the overall low number of associations between the baseline features and outcome, the treatment was effective for over half of the participants and so we are left wondering what mechanisms are at play. Perhaps investigating the interaction between genes and nutrients, in the form of metabolomics, or measuring nutrient levels in other ways, such as through hair analysis or directly in the brain using magnetic field correlation imaging, or in combination with other biomarkers such as markers of inflammation, would be more fruitful.

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