



# Protocol for a randomised placebo-controlled trial investigating the efficacy and safety of a vitamin-mineral formula targeting dysregulated emotions in teenagers: The balancing emotions of adolescents with micronutrients (BEAM) study

Julia J. Rucklidge<sup>a,\*</sup>, F. Meredith Blampied<sup>a</sup>, Leona Manna<sup>a</sup>, Angela Sherwin<sup>a</sup>, Sue Bagshaw<sup>b</sup>, Roger T. Mulder<sup>b</sup>, Joseph Boden<sup>b</sup>

<sup>a</sup> School of Psychology, Speech and Hearing, University of Canterbury, New Zealand

<sup>b</sup> Psychological Medicine, University of Otago, New Zealand

## ARTICLE INFO

### Keywords:

Emotional dysregulation  
Minerals  
Vitamins  
Micronutrients  
Youth  
Irritability

## ABSTRACT

**Background:** Emotional dysregulation (ED) is a significant contributing factor to psychological distress in young people. ED is a transdiagnostic dimension characterized by an excessive reactivity to negative emotional stimuli with affective (anger) and behavioral (aggression) components, and is present across anxiety, mood and behavioral disorders. Due to early onset, high prevalence and persistence, ED in childhood is one of the most psychosocially impairing and cost-intensive mental health conditions, with not enough children improving with conventional treatments. Clinical trials have established preliminary efficacy of micronutrients (vitamins and minerals) in the treatment of ED. This project expands the research to examine micronutrient efficacy for teenagers with ED.

**Methods:** This study is the first double-blind (participant and investigators) 8 week randomized controlled trial (with 8 week open-label extension and one year follow-up) designed to explore the efficacy and safety of micronutrients compared with placebo in 150 medication-free emotionally dysregulated youth (12–17 years), referred via self-referral, delivered remotely throughout New Zealand, using a website for monitoring symptoms, with a psychologist available online via text, email and video for assessment and monitoring. The primary outcome measures will be the Clinical Global Impression (CGI-I), the reactivity subscale of the Emotion Dysregulation Inventory (EDI) and the Clinician Rated Temper and Irritability Scale (CL-ARI).

**Discussion:** Micronutrient intervention delivered alongside online assessment and monitoring has the potential to transform delivery of mental health care to young people who may not be willing or able to access traditional therapies. We also hope that this intervention shows acceptability across different ethnicities.

## 1. Introduction

Emotional dysregulation (ED) is often considered a central component of psychological distress in young people [1]. It is a transdiagnostic dimension characterized by an excessive reactivity to negative emotional stimuli with affective (anger) and behavioral (aggression) components and is present across anxiety, mood and behavioral disorders. Due to early onset, high prevalence and persistence, as well as developmental comorbidity, ED in childhood is one of the most psychosocially impairing and costly mental health symptom constellations

[1], with an insufficient number of children benefitting from conventional treatments [2,3].

Best evidence treatment for ED in children and adolescents advocates psychological therapies, although effect sizes are modest [4]. Even when psychotherapy is effective, it can be difficult to access due to a small number of practitioners and long waiting lists. Medications are often used despite poor efficacy data, with prescription rates for children and adolescents having increased over the last decade [5]. Fluoxetine is the only antidepressant that has shown superiority over placebo for the treatment of emotional dysregulation [6]; however, efficacy is modest

\* Corresponding author. University of Canterbury, Christchurch, New Zealand.  
E-mail address: [julia.rucklidge@canterbury.ac.nz](mailto:julia.rucklidge@canterbury.ac.nz) (J.J. Rucklidge).

<https://doi.org/10.1016/j.conctc.2022.101027>

Received 7 May 2022; Received in revised form 8 October 2022; Accepted 26 October 2022

Available online 27 October 2022

2451-8654/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and antidepressants can be associated with concerning side effects, in particular increased suicidal ideation being associated with rising antidepressant use in young people [7]. To contextualize the modest effect sizes of current treatments, it is estimated that between 30 and 50% of adolescents who receive any treatment will not respond [3], nor are there sufficient psychological resources to meet the demand [8]. There is a need for interventions that can directly target this underlying dysregulation, and are scalable and reachable to all communities, particularly those that are disadvantaged.

Research has identified that diet is a significant risk factor for the development of mental health issues in adolescents, in particular mood dysregulation [9,10]. Long-term studies suggest that early malnutrition is an important risk factor for behavioral problems [11]. Research has consistently shown that consuming nutrient dense food is critical to reduce the risk associated with the development of mood disorders in adolescents [10]. However, given the challenges associated with changing diet in adolescents, another method to improve mood is through supplementation with essential nutrients obtained from food, such as micronutrients (minerals and vitamins). The advantage of such an approach is that it is a relatively simple intervention to swallow pills at a time when motivation and ability to engage in major dietary changes can be severely compromised.

The biological rationale behind the importance of ingesting the full array of micronutrients for brain metabolic activity is well established: every neurotransmitter goes through many metabolic steps to ensure its synthesis, uptake, and breakdown. Every step requires enzymes, and every enzyme is dependent upon multiple co-enzymes (cofactors). A variety of vitamins and minerals are required as cofactors in most if not all of those steps [12]. There are a number of reasons why a nutritional intervention may be required over and above trying to improve dietary intake [13], including: 1) inborn metabolic dysfunction associated with slowed metabolic activity due to suboptimal availability of vitamin and mineral cofactors [14,15], 2) poor gut health and inflammation [16–18], and 3) mitochondrial dysfunction that may result in decreased production of cellular energy [19]. All of these individual factors may increase nutritional needs [14,15].

Over the last decade, clinical trials have established preliminary efficacy of broad-spectrum micronutrients in the treatment of a number of psychiatric/psychological disorders in children and young people [12]. Specifically, studies assessing micronutrients for the treatment of behavioral problems, ADHD, and autism have reported positive benefits with designs ranging from case reports [20] to open-label [21–24] to retrospective database analyses [25] to randomized placebo-controlled trials [26–29]. Micronutrients have also been shown to effectively improve aggression and emotional dysregulation in children [26,30,31], as well as reduce non-suicidal self-injury [32].

Publications on mechanism of action reveal that the effects of the nutrients are likely widespread, with evidence of potential modes of action detected across genetics [33], the microbiome [34], brain imaging [35], and nutrient serum levels [36]. Short and long-term safety have also been well established [24,26,37–40].

Based on overall findings, and specific symptoms that appear to benefit, directly targeting ED in youth with a broad array of nutrients is logical but requires testing to determine whether this age group can adhere to the treatment with relatively little oversight. This study intends to couple nutrient intervention with online monitoring. Research has identified that digital technology can be an effective and low-cost mode of mental health care delivery for young people [41,42].

This study will be the first double-blind (participant and investigators), parallel-group RCT designed to explore the efficacy and safety of a broad-spectrum micronutrient formula compared with placebo in medication-free teenagers with dysregulated emotions in the community. We predict that participants given the micronutrients will have improved emotional regulation and better overall mental health functioning than participants given a placebo. We also predict there will be no group difference in adverse effects and emergence in suicidal

ideation. Measures of effectiveness will include standardised psychometrics and additional questions capturing general levels of anxiety, low mood and stress, alcohol intake, suicidality, non-suicidal self-injury and other measures of safety such as side effects and adverse events. Moderators will also be included such as socio-economic status, presence of personality difficulties, expectancy and gender. Cost effectiveness of micronutrient treatment will also be estimated through exploring rates of participants accessing medical treatment and days off sick across the two groups while participating in the study.

## 2. Methods

The trial will consist of five study periods: 1) Screening for eligibility, 2) a 2-week baseline monitoring period, 3) an 8-week period of randomized, placebo-controlled, double-blind acute treatment (RCT), 4) an 8-week open-label extension period (OL), and 5) a 1-year follow-up. The study has received ethics approval through the Health Disability Ethics Committee, approval through the Standing Committee of Therapeutic Trials (SCOTT) and has a data monitoring committee. It has also been prospectively registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov): ACTRN12621000399897.

### 2.1. Inclusion criteria

1) unmedicated adolescents between 12 and 17 years, 2) able to be compliant with protocol (including ingestion of as many as 12 capsules/day with food), 3) be attending primary, intermediate or high school, and 4) receive a minimum score of 10 on the Emotion Dysregulation Inventory-Reactivity subscale (parent report) at screening and moderately impaired as assessed by the Clinical Global Impression-Severity (CGI-S).

### 2.2. Exclusion criteria

1) metabolic conditions such as Wilson's disease (copper), haemochromatosis (iron), phenylketonuria (phenylalanine) and trimethylaminuria (choline), 2) known neurological disorders involving brain or other central function (e.g., previously diagnosed intellectual disability, autism spectrum disorder, epilepsy, MS, narcolepsy) or other major psychiatric condition requiring hospitalization (e.g., significant mood disorder with associated suicidality, substance dependence or psychosis), 3) pregnant or breastfeeding, 4) known allergies to the ingredients of the intervention or known or suspected allergy to any placebo excipient, and 5) any medications with primarily central nervous system activity, including psychotropic medication (e.g., SSRIs, tricyclics, benzodiazepines). Participants must have been off these medications for a minimum of four weeks prior to the trial. Participants will not be encouraged to come off a medication in order to participate.

### 2.3. Recruitment

Potential participants will present to either their GP or counsellor or can be family-referred via the website [www.taioratrial.net](http://www.taioratrial.net).

### 2.4. Study intervention (see Table 1 for a description of ingredients and doses)

Daily Essential Nutrients with added Vitamers (DEN), a micronutrient formula, was chosen as it (along with its predecessor EMPowerplus) is: 1) the most studied micronutrient formula (13 vitamins, 17 minerals, and 4 amino acids) for the treatment of psychiatric illnesses [43], 2) has resulted in medium between-group effect sizes for a range of psychological problems [26,27,38,44] and 3) the safety and tolerability of DEN is well documented [24,26,37–40].

## 2.5. Randomization

The randomization scheme will be generated by our trial statistician (JB) with the randomization sequence arranged in permuted blocks of 6. Participants will be stratified by gender. Neither the participants nor the study clinicians involved in the study will have access to the randomization list. A designated unblinded research assistant will be sent the randomization list and will prepare individual participant kits in advance, which will contain all required study pills for the 8-week RCT as well as a seven-day pill caddy. These kits will be sequentially numbered but identical. An administrator will mail the kits to individual participants based on the sequential numbering.

## 2.6. Trial administration

Trial monitoring will be via a website ([www.taioratrial.net](http://www.taioratrial.net)). Participants/families can complete all consent forms, intake assessments and weekly monitoring via the website through unique registration portals. Clinicians will be available throughout the trial via text/email and will provide phone/video conference call as required and/or if completion of questionnaires via website is proving problematic.

## 2.7. Screening phase

Once deemed potentially eligible based on screening, participants and/or primary caregivers will be contacted by phone/zoom by a psychologist who will further explain the study, gather informed consent and complete clinician measures to establish severity. One member of the team is a kaupapa (experienced in indigenous practices) Māori (indigenous New Zealander) clinical psychologist available to work with Māori referrals. For participants unable to consent, parental consent will be obtained as well as participant assent.

## 2.8. Baseline assessment

After receiving written consent/assent, participants and their families will be directed by the psychologist to access the website, create a unique log-in and complete baseline assessments. They will also complete a baseline assessment with the clinician. Both the participant and a parent will have their own unique login for the study. A second baseline will be repeated approximately two weeks later.

## 2.9. RCT phase

Participants will begin taking their assigned intervention after the two-week baseline phase. Interventions will be mailed to participants in order to arrive within two days of finishing baseline data collection. There will be clear instructions both on the intervention and on the website directing participants to take the intervention only when the baseline data collection phase has completely finished. Participants will initially take one capsule, three times each day. Every second day, the dose will increase by three capsules until a maximum dose of four capsules taken three times a day is achieved: a total dose of twelve capsules per day. Participants will continue to take the study interventions for eight weeks. Participants will be asked to estimate missed doses every week. They will also be asked to mail back any unused pills for a formal pill count.

Throughout the RCT phase, participants and their families will be asked to complete online questionnaires every week. At the conclusion of the RCT phase, participants and their parents will be asked to complete the same questionnaires as completed during the baseline assessment phase. The monitoring psychologist will contact participants at four weeks and at the end of the RCT phase to discuss progress and complete clinician monitoring questionnaires.

## 2.10. Open label (OL) phase

The OL phase, where all participants regardless of randomization are offered the micronutrient formula, will begin the week after participants have completed their eight-week RCT assessments. Titration of capsules will follow the same procedure as conducted in the RCT phase. Participants will be required to complete online questionnaires throughout OL. At the end of OL, study completers can independently access the micronutrients via a New Zealand distributor or via the company website. The monitoring psychologist will contact participants 4 weeks into OL and at the end of OL to discuss progress and confirm the one-year follow up.

## 2.11. One year follow up

At one year following the baseline monitoring period, participants will be contacted to complete the same online questionnaires they completed during the screening phase and to have a clinician review. This follow-up allows for assessment of the effectiveness of the micronutrients over time, evaluate any long-term side effects and naturalistically compare the micronutrients to other treatments families may have accessed over the follow up period.

## 2.12. Primary outcome measures

See [Table 2](#) for the primary outcome measures.

## 2.13. Secondary outcome measures

See [Table 3](#) for the secondary outcome measures.

## 2.14. Further information

Demographic information will be collected at baseline, including socio-economic status, socio-economic deprivation, ethnicity, level of education and psychiatric family history. Ethnicities will be categorised in accordance with the Statistics New Zealand Ethnicity Standard Classification 2005 - v2 and New Zealand Ministry of Health Guidelines. The SES of each participant will be estimated using the New Zealand Socioeconomic Index of Occupational Status (NZSEI [45]) and deprivation will be assessed using the NZDep2013 [46]. Participants will also answer weekly questions on additional medication prescribed (e.g. antibiotics), visits to their GP, attendance at a hospital/afterhours clinic and reasons for their presentations (physical health, mental health), suicidal ideation, any adverse events (physical symptoms which may be attributed to the capsules), and an estimate of substances consumed during the week, including alcohol and nicotine/e-cigarettes/illicit drugs/vaping.

Standardized Assessment of Personality Abbreviated Scale Adolescent Version (SAPAS-AV) [47,48]: The SAPAS-AV is an eight-item questionnaire adapted from the adult version that requires a 'yes'/'no' answer from the participants when asked by clinicians. The scores on the SAPAS-AV range from 0 to 8. A score of  $\geq 3$  is indicative of personality difficulties and will be used as a moderator of treatment.

The Child and Adolescent Behavior Inventory: The CABI questionnaire consists of 75 questions completed by parents/caregivers at baseline [49,50]. These explore a wide range of problem areas ranging across anxiety, phobias, irritability, impulsivity, school performance and being bullied. This questionnaire can assist with classifying the sample.

Dietary Screening Tool (DST [51]): The DST is a 24 item self-report questionnaire that assesses dietary intake. Both the teen and the parent will complete it at baseline and switch points. The DST has a total score of 0–105 with higher scores indicating a healthier dietary pattern. The DST can identify individuals who are at a *nutritional risk* (total DST score  $< 60$ ), a *possible nutritional risk* (total DST score 60–75) and who are at *no*

**Table 1**

Ingredients: Daily essential nutrients and placebo.

Ingredients:	1 capsule	12 capsules
Vitamin A (as retinyl palmitate)	144 mcg	1728 mcg
Vitamin C (as ascorbic acid)	50 mg	600 mg
Vitamin D (as cholecalciferol)	6 mcg	72 mcg
Vitamin E (as d-alpha tocopheryl succinate & mixed tocopherols)	16.2 mg	194.4 mg
Vitamin K (75% as phyloquinone; 25% as menaquinone-7)	10 mcg	120 mcg
Thiamin (as thiamine hydrochloride)	5 mg	60 mg
Riboflavin	1.5 mg	18 mg
Niacin (as niacinamide & nicotinic acid)	12 mg	144 mg
Vitamin B6 (as pyridoxine hydrochloride & pyridoxal 5-phosphate)	5 mg	60 mg
Folate (as L5-methylfolate calcium & calcium folinate)	75 mcg	900 mcg
Vitamin B12 (as hydroxocobalamin acetate & methylcobalamin & adenosylcobalamin)	75 mcg	900 mcg
Biotin	90 mcg	1080 mcg
Pantothenic acid (as calcium D-pantothenate)	2.5 mg	30 mg
Choline	16 mg	192 mg
Calcium (as chelate)	110 mg	1320 mg
Iron (as chelate)	1.15 mg	13.8 mg
Phosphorus (as chelate)	70 mg	840 mg
Iodine (as Atlantic Kelp)	17 mcg	204 mcg
Magnesium (as chelate)	50 mg	600 mg
Zinc (as chelate)	4 mg	48 mg
Selenium (as chelate)	17 mcg	204 mcg
Copper (as chelate)	0.6 mg	7.2 mg
Manganese (as chelate)	0.8 mg	9.6 mg
Chromium (as chelate)	52 mcg	624 mcg
Molybdenum (as chelate)	12 mcg	144 mcg
Potassium (as chelate)	20 mg	240 mg
Proprietary blend ingredients: Great Salt Lake minerals, mixed tocopherols and mixed tocotrienols, Alpha-lipoic acid, Inositol, Acetylcarnitine (as acetyl-L-carnitine hydrochloride), Grape seed extract, Ginkgo biloba leaf extract, Methionine (as L-methionine hydrochloride), Cysteine (as N-acetyl-L-cysteine), Boron (as chelate), Vanadium (as chelate), Nickel (as chelate). Other ingredients: vegetarian capsule (hypromellose, titanium dioxide), microcrystalline cellulose, magnesium stearate, silicon dioxide		
<b>Ingredients: Placebo</b>		
Placebo Ingredients	Per capsule	12 capsules
Yellow corn masa flour	554.4 mg	6652.8 mg
White rice flour	45.25 mg	543 mg
Caramel colour powder (Class 1)	20.16 mg	241.92 mg
Magnesium stearate	4.25 mg	51 mg
Microcrystalline cellulose	4.25 mg	51 mg
Silicon Dioxide	1.58 mg	18.96 mg
Riboflavin	0.1 mg	1.2 mg
Hypromellose capsule, size '00' white (contains HPMC & titanium dioxide)	136 mg	1632 mg

risk (total DST score >75). The DST has been adapted to include New Zealand food products.

**Food Insecurity Assessment (FIA):** The FIA is an eight item self-report measure that assesses various aspects of food insecurity such as access to food, variety of food purchased and budgeting regarding food. Parents will complete this on behalf of the teen at baseline.

**Blinding question:** To measure the integrity of the blind, at week 8, the parent and teen will be asked whether they think the teen received active or placebo treatment. The monitoring psychologist will also record what group they thought the teen was in.

**Expectancy of a treatment effect.** At baseline, participants and parents will be asked how much they think the micronutrients will improve their current problems from 1 (not at all), to 4 (very much).

**2.15. Adverse event monitoring**

**Side effects:** The Side-Effect Checklist (ASEC [52]): Side effects and adverse events will be assessed at baseline and weekly during the RCT and open label phase using the ASEC which has been adapted by removing references to anti-depressants. The reason for assessing at

**Table 2**

Primary outcome measures used, including description and timepoint administered.

Measure	Description	Administered
<u>Clinical Global Impression (CGI-I)</u>	The CGI-I is widely and successfully used in clinical trials to measure change though consideration of all information gathered, including observations, self-report and questionnaire responses [54]. At each clinician meeting, the monitoring clinician will review the participants' outcome measures, talk to the families, and then make an estimation of improvement, on a 7-point scale from "very much improved" to "very much worse". Responders will be identified as those with a rating of "much" to "very much improved".	4, 5, 7, 8, 9
<u>The Clinician-rated Temper and Irritability Scale (CL-ARI)</u>	The CL-ARI will be used to methodically assess temper outburst and irritability [55]. This measure systematically evaluates the frequency, duration (ranging from mild to severe), and intensity of temper outbursts, irritable mood from mild to severe, and impairment associated with these behaviors and mood. Total score ranges from 0 to 100. Responses to this questionnaire, along with responses to questions related to the DSM-5 criteria, will assist the clinician to assess whether the child likely meets criteria for Disruptive Mood Dysregulation Disorder (DMDD).	1, 4, 5, 7, 8, 9
<u>The Emotion Dysregulation Inventory (EDI)</u>	The EDI [56] reactivity subscale will be used as a screening tool as well as for weekly monitoring. Each item is rated from 0 (not at all) to 4 (very severe). A score greater or equal to 10 (on a scale 0-28) on the EDI Reactivity subscale will be used to identify mildly to severely dysregulated kids. The scale is typically completed by an observer (parent).	1, 2, 3, 5, 6, 8, 9

Notes: 1 = Baseline, 2 = Baseline-2, 3 = RCT Weekly, 4 = RCT Week 4, 5 = End of RCT, 6 = OL Weekly, 7 = OL Week 4, 8 = End of OL, 9 = 1-year follow = up.

baseline is to assist with determining if the adverse event was present prior to consumption of the pills or is a treatment-emergent event. Should a participant indicate that they are experiencing a serious adverse event, the monitoring psychologist will contact the participant within 24 h. Any concerning adverse events will be discussed with the study physician. Some participants may need to titrate their dose more slowly and this will be discussed with the participant. In the case of a serious adverse event, the investigators will consider whether termination of the study is necessary.

**Non-suicidal self-injury and suicidal ideation:** Deliberate self-harm (frequency, intensity, duration and onset) will be assessed at every clinical review. The clinician will meet individually with the teen and ask about suicidal ideation and self-harm. If there is concern of risk, then confidentiality may be breached in order to develop a safety plan with the parent. In addition, the teen will be asked weekly about suicidal ideation and to what extent they had thoughts in the last week from: 0 (I don't have any thoughts of killing myself) to 3 (I would kill myself if I had the chance). Intervention to ameliorate risk will be delivered if participants' response is a 2 or above.

**Table 3**  
Secondary outcome measures used, including description, timepoint administered and completed by whom.

Measure	Description	Administered
<i>Participant-rated measures:</i>		
<u>The Kessler psychological distress scale (K10)</u>	The K10 comprises ten questions about psychological distress and has been successfully used with children and adolescents [57,58]. Each of the 10 questions is scored 1 (none of the time) to 5 (all of the time) and scores are summed to provide a total K10 score. Scores range from 10 to 50. A cut off of 25 identifies moderate distress.	1, 5, 8, 9
<u>Generalised Anxiety Disorder 7-Question Scale (GAD-7):</u>	The GAD-7 [59] is a seven-item self-report questionnaire that measures the key diagnostic components of Generalised Anxiety Disorder and has been successfully used in high school students to assess anxiety [60]. It asks the teen to indicate whether specific feelings associated with anxiety have been present over the last week ranging from "Not at all" to "Nearly every day". Scores range from 0 to 21.	1, 2, 3, 5, 6, 8, 9
<u>Brief Resilience Scale (BRS):</u>	The BRS measures one's ability to bounce back or recover from stress [61] and is a 6-item scale with statements designed to assess resilience such as: "I tend to bounce back quickly after hard times" and "I usually come through difficult times with little trouble." Scoring is measured on a 5-point scale (strongly disagree (1) to strongly agree (5)), adding the responses on all six statements with possible ranges from 6 to 30.	1, 5, 8, 9
<u>The paediatric quality of life enjoyment and satisfaction questionnaire (PS-LES-Q):</u>	The PQ-LES-Q is a quality of life self-report measure designed for use in children and adolescents 12–17, covering 15 areas (e.g., peer and family relationships, energy, getting things done) and ratings are made on a five point scale from "very poor" to "very good" [62].	1, 5, 8, 9
<u>The Perceived Stress Scale (PSS):</u>	This self-report scale measures the degree to which one experiences psychological stress [63]. It has been used successfully to measure stress in adolescents [64]. Items assess feelings of being overwhelmed and being unable to control or predict events in one's life during the last month from "never" to "very often".	1, 5, 8, 9
<i>Participant and Parent-rated measures:</i>		
<u>The Affective Reactivity Index (ARI):</u>	The ARI will be used as a weekly tool for monitoring irritability [65,66]. The scale contains 6 items and participants and parents are asked to rate each item from not true to certainly true on items assessing feelings and behaviors specific to irritability and 1 item related to impairment. Scores range from 0 to 12.	1, 2, 3, 5, 6, 8, 9
<u>Modified Participant Global Impression (PGI-I):</u>	Participants and parents will be asked to rate how much they thought the teen's mood, anxiety, stress, energy and overall functioning has changed since they started the trial. The PGI-I	2, 3, 5, 6, 8, 9

**Table 3 (continued)**

Measure	Description	Administered
	uses a 7-point scale from 1 (very much improved) to 7 (very much worse). This measure allows participants and parents to give a subjective rating of perceived change.	
<u>Strengths and Difficulties Questionnaire (SDQ):</u>	The SDQ has a parent and youth form (11–17) and assesses positive and negative psychological attributes measuring both problem behaviors and competencies [67]. The 25-item questionnaire assesses across a number of areas of functioning, including emotional, behaviors, peer problems, prosocial behaviors, hyperactivity and conduct problems [68]. Participants are asked to rate each item from "not true" to "certainly true." A Total Difficulties Score ranging from 0 to 13 falls within the normal range, 14–16 within the borderline range, and 17–40 in the abnormal range. The SDQ also provides an Impact score showing how much a participant's present difficulties are interfering with life.	1, 5, 8, 9
<u>Clinician-rated measures: Parent Target Problem (PTP):</u>	During the clinician interview, the parent and teen will identify and nominate two of the teen's biggest problems, and reports frequency, duration, impairment, and provide examples. At each follow up interview, those same problems will be revisited and rated from 1 (problem resolved or extremely improved) to 9 (extremely worse) as compared to how those behaviors were at baseline.	1, 4, 5, 7, 8, 9
<u>Columbia Impairment Scale (CIS)</u>	The Columbia Impairment Scale (CIS) is a 13-item scale administered by the clinician to provide a global measure of impairment and validated for use with children and adolescents [69, 70]. The items tap 4 major areas of functioning: interpersonal relations, broad psychopathological domains, functioning in job or schoolwork, and use of leisure time. Items are scored on a spectrum ranging from 0 "no problem" to 4 "a very big problem."	1, 5, 8, 9
<u>Children's Global Assessment Scale (CGAS):</u>	The CGAS [71] is used by the clinician to assess the overall severity of disturbance in the participants based on all the information gathered at the clinical interview. It is a single numerical scale from 1 (most impaired) – 100 (healthiest). Those who score $\geq 70$ are considered to be within the normal range.	1, 4, 5, 7, 8, 9
<u>Clinical Global Impressions Severity Scale (CGI-S):</u>	The CGI-S is a single-item rating of the clinician's assessment of the severity of symptoms from "Normal not ill" to "among the most extremely ill patients" [72].	1, 5, 8, 9
<u>ADHD Rating Scale-5, home version, Adolescent:</u>	The ADHD Rating Scale-5 [73] assesses ADHD symptoms in	1, 5, 8, 9

(continued on next page)

Table 3 (continued)

Measure	Description	Administered
	children and adolescents. Raw scores are converted to percentiles depending on age and gender. Containing 18 items that assess each item from 0 (never/rarely) to 3 (very often), the scale is linked directly to DSM-5 diagnostic criteria for ADHD. Alongside administering the scale, clinical questions covering the DSM-5 criteria will be asked in order to assess the likelihood the child has ADHD and ODD.	
<u>Children's Revised Impact of Events Scale (CRIES):</u>	The Children's Revised Impact of Event Scale (CRIES-13) is a brief measure designed to screen children 8 to 17 at risk for Post-Traumatic Stress Disorder (PTSD) [74]. There are 8 items that are scored on a four point scale: "Not at all" to "Often". There are three sub-scales: Intrusion, avoidance, and arousal. A cutoff score of 30 identifies those who likely have PTSD. It will be administered by clinicians only to participants self-identifying a current trauma that is interfering with functioning.	1, 5, 8, 9

Notes: 1 = Baseline, 2 = Baseline-2, 3 = RCT Weekly, 4 = RCT Clinician Week 4 check-in, 5 = End of RCT, 6 = OL Weekly, 7 = OL Clinician Week 4 check-in, 8 = End of OL, 9 = 1-year follow = up.

### 2.16. Sample size and power calculations

Based on previous studies that examined the treatment of emotional dysregulation using broad-spectrum micronutrients compared with placebo in children with ADHD [26] ( $d = 0.66$ ), an effect size of  $d = 0.5$  was chosen. As such, the total number of participants required would be 126 (63 in each group). Allowing for a 20% attrition rate, the adjusted number-per-treatment condition would be 75 and total sample size required would be 150 randomized 1:1 to the two conditions.

### 2.17. Data analysis plan

All data will be analysed on an intent-to-treat and per-protocol populations. All continuous measures will be analysed using generalised linear mixed-effect regression models. This modelling procedure allows the researcher to fit individual-specific slopes and intercept terms, which can account for individual variability in treatment response more precisely than methods based on Analysis of Variance. Possible moderators of treatment will also be included such as presence of personality difficulties, SES, age, gender, diet, and expectancies. The statistical test for differences between groups will be an F test. Baseline scores on the primary outcome measures will be used as covariate factors, as well as measures of demographic characteristics. The pooled mean scores (and standard deviations) over the course of the trial on each of the primary outcomes will be used to compute estimates of effect size (Cohen's  $d$ ). The CGI-I will also be reported as responder/non-responder by group using chi-square analyses/odds ratios. A score of 1 or 2 (very much improved and much improved) will be used to identify responders. All tests will be two tailed and any p values less than 0.05 will be considered statistically significant. Clinically significant outcomes will be determined by calculating the Reliable Change Index. Changes must exceed the relevant RCI before clinical significance of the outcome is addressed.

The intention to treat (ITT) population for the primary analyses of outcomes will include all randomised participants. For the ITT

population, if there is no exit effectiveness evaluation then the last evaluation will be used, this may be the baseline assessment in some circumstances. For the ITT analyses, participants are analysed according to their randomly allocated treatment group irrespective of the actual treatment received.

The per-protocol (PP) population for each efficacy measure will include all participants who take at least 75% of the allocated pills, have no significant protocol deviations and have all appropriate assessments relevant to the outcome.

Demographic characteristics will be compared across the treatment groups using independent samples  $t$ -tests in order to test for potential failures of randomization. For purposes of group statistical inference, data will be analysed first on an intention-to-treat basis using the last observation carried forward method and second on a per-protocol analysis that includes those who complied with and completed the protocol.

The safety population, which will be used for all safety analyses, will include all participants who have taken at least one dose of study product. Treatment-emergent adverse events and risk events from the double-blind phase will be individually listed by randomized group, indicating the preferred term, date of onset, date resolved, severity, relatedness, frequency, action taken in relation to study medication and whether the adverse event is serious. The incidence of more common adverse events (greater than 5%) or adverse events of special interest may also be summarized for each randomized group.

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final study publication.

## 3. Discussion

The BEAM trial is unique and significantly extends the current research base. The focus on a constellation of symptoms rather than a diagnostic category aligns with the recognition that many symptoms are transdiagnostic and it is the symptoms that are impairing the individual, not the diagnosis [53]. Providing the intervention entirely online means that the intervention is scalable and reachable, particularly to rural and disadvantaged communities. The demand for mental health services is too large for services to continue to address the mental health crisis with labour intensive 1:1 approaches. Further, these approaches are not always considered acceptable methods for addressing the mental health of young people, particularly indigenous populations. A nutritional intervention, if successful, can be administered simply, with little oversight. Indeed, micronutrient intervention delivered alongside online assessment through a website has the potential to transform delivery of mental health care to young people who may not be willing or able to access traditional therapies. By working directly with primary care providers in the community for referrals, we hope to facilitate physicians becoming educated on this intervention such that if it is proven to be efficacious, they can easily translate the findings into their own clinical practice. It could also be relevant to food labelling and ensuring that micronutrient content of foods is clearly labelled in the nutritional facts of a food. As this study has been developed alongside Māori health providers, it fits within a Tikanga Māori framework (a legal necessity in Aotearoa New Zealand), working closely with the participant, their family, and health providers to assist in improving mental health outcomes.

This study has potential limitations, including the ingestion of up to 12 pills a day, which can be difficult for some people. However, previous research has indicated that it is possible to support individuals to improve daily compliance with the regime. There is no third party rater (i.e. a teacher) so we will not know if the intervention is making a notable difference in the classroom setting. However, the COVID

restrictions, lockdowns, and the ongoing self-isolation requirements make it virtually impossible to gather these data. Although diet is being assessed, it will not be a focus of the study and therefore it will be difficult to reliably assess change over the 8 weeks RCT. However, previous research suggest that diet does not typically change quickly, and as such, it is expected that dietary patterns will remain relatively stable. Teenagers with ED are at risk for non-suicidal self-injury but protocols are in place to help manage these behaviors. Given that dysregulated teens are often excluded from participation in research we felt that it was important to include them so the findings will be more generalizable to teens engaging in NSSI. Micronutrients alongside remote monitoring present as a viable way to reach youth struggling with mental health problems easily and safely.

### Declaration of competing interest

The authors declare they have no competing interests.

### Acknowledgements

This work is supported by an Health Research Council (HRC) Explorer Grant, UC Foundation and the School of Psychology, Speech and Hearing. The micronutrients and matching placebo are being supplied for free by Hardy Nutritionals.

### References

- [1] M. Döpfner, J. Katzmann, C. Hanisch, J.M. Fegert, M. Kölsch, A. Ritschel, A.-K. Treier, M. Hellmich, V. Roessner, U. Ravens-Sieberer, T. Banaschewski, A. Götz-Korten, A. Consortium, Affective dysregulation in childhood - optimizing prevention and treatment: protocol of three randomized controlled trials in the ADOPT study, *BMC Psychiatr.* 19 (1) (2019), 264–264.
- [2] R. Mulder, J. Rucklidge, S. Wilkinson, Why has increased provision of psychiatric treatment not reduced the prevalence of mental disorder? *Aust. N. Z. J. Psychiatr.* 51 (12) (2017) 1176–1177.
- [3] F.F. Liu, M.C. Adrian, Is treatment working? Detecting real change in the treatment of Child and adolescent depression, *J. Am. Acad. Child Adolesc. Psychiatry* (2019).
- [4] J.R. Weisz, S. Kuppens, M.Y. Ng, D. Eckshtain, A.M. Ugueto, R. Vaughn-Coaxum, A. Jensen-Doss, K.M. Hawley, L.S. Krumholz Marchette, B.C. Chu, V. Robin Weersing, S.R. Fordwood, What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice, *Am. Psychol.* 72 (2) (2017) 79–117.
- [5] Z.A. Barczyk, J.J. Rucklidge, M. Eggleston, R.T. Mulder, Psychotropic medication prescription rates and trends for New Zealand children and adolescents 2008–2016, *J. Child Adolesc. Psychopharmacol.* (2019).
- [6] A. Cipriani, X. Zhou, C. Del Giovane, S.E. Hetrick, B. Qin, C. Whittington, D. Coghill, Y. Zhang, P. Hazell, S. Leucht, P. Cuijpers, J. Pu, D. Cohen, A. V. Ravindran, Y. Liu, K.D. Michael, L. Yang, L. Liu, P. Xie, Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis, *Lancet* 388 (10047) (2016) 881–890.
- [7] D.A. Brent, Antidepressants and suicidality, *Psychiatr. Clin.* 39 (3) (2016) 503–512.
- [8] J.J. Rucklidge, K.A. Darling, R.T. Mulder, Addressing the treatment gap in New Zealand with more therapists-is it practical and will it work? *N. Z. Med. J.* 131 (1487) (2018) 8–11.
- [9] F.N. Jacka, P.J. Kremer, M. Berk, A.M. de Silva-Sanigorski, M. Moodie, E.R. Leslie, J.A. Pasco, B.A. Swinburn, A prospective study of diet quality and mental health in adolescents, *PLoS One* 6 (9) (2011), e24805.
- [10] F.N. Jacka, P.J. Kremer, E.R. Leslie, M. Berk, G.C. Patton, J.W. Toumbourou, J. W. Williams, Associations between diet quality and depressed mood in adolescents: results from the Australian Healthy Neighbourhoods Study, *Aust. N. Z. J. Psychiatr.* 44 (5) (2010) 435–442.
- [11] J.R. Galler, C.P. Bryce, M.L. Zichlin, G. Fitzmaurice, G.D. Eaglesfield, D.P. Waber, Infant malnutrition is associated with persisting attention deficits in middle adulthood, *J. Nutr.* 142 (4) (2012) 788–794.
- [12] J.J. Rucklidge, J.M. Johnstone, B.J. Kaplan, Nutrition provides the essential foundation for optimizing mental health, *Evidence-Based Practice in Child and Adolescent Mental Health* 6 (1) (2021) 131–154.
- [13] M.R. Taylor, C. Chuang, K.D. Carrasco, S. Nagatomo, J.J. Rucklidge, Dietary and micronutrient treatments for children with neurodevelopment disorders, *Current Developmental Disorders Reports* 5 (4) (2018) 243–252.
- [14] B.N. Ames, I. Elson-Schwab, E. Silver, High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): relevance to genetic disease and polymorphisms, *Am. J. Clin. Nutr.* 75 (2002) 616–658.
- [15] B.J. Kaplan, S.G. Crawford, C.J. Field, J.S. Simpson, Vitamins, minerals, and mood, *Psychol. Bull.* 133 (5) (2007) 747–760.
- [16] E. Aarts, T.H.A. Ederveen, J. Naaijen, M.P. Zwiers, J. Boekhorst, H.M. Timmerman, S.P. Smekens, M.G. Netea, J.K. Buitelaar, B. Franke, S.A.F.T. van Hijum, A. Arias Vasquez, Gut microbiome in ADHD and its relation to neural reward anticipation, *PLoS One* 12 (9) (2017), e0183509.
- [17] X. Ming, N. Chen, C. Ray, G. Brewer, J. Kornitzer, R.A. Steer, A gut feeling: a hypothesis of the role of the microbiome in attention-deficit/hyperactivity disorders, *Child Neurol Open* 5 (2018), 2329048x18786799.
- [18] W.H. Oddy, K.L. Allen, G.S.A. Trapp, G.L. Ambrosini, L.J. Black, R.C. Huang, P. Rzehak, K.C. Runions, F. Pan, L.J. Bellin, T.A. Mori, Dietary patterns, body mass index and inflammation: pathways to depression and mental health problems in adolescents, *Brain Behav. Immun.* 69 (2018) 428–439.
- [19] L. Toker, G. Agam, Mitochondrial dysfunction in psychiatric morbidity: current evidence and therapeutic prospects, *Neuropsychiatric Dis. Treat.* 11 (2015) 2441–2447.
- [20] J.J. Rucklidge, R. Harrison, Successful treatment of Bipolar Disorder II and ADHD with a micronutrient formula: a case study, *CNS Spectr.* 15 (5) (2010) 289–295.
- [21] K. Patel, L.T. Curtis, Comprehensive approach to treating autism and attention-deficit hyperactivity disorder: a pre-pilot study, *J. Alternative Compl. Med.* 13 (10) (2007) 1091–1097.
- [22] B.J. Kaplan, J.E. Fisher, S.G. Crawford, C.J. Field, B. Kolb, Improved mood and behavior during treatment with a mineral-vitamin supplement: an open-label case series of children, *J. Child Adolesc. Psychopharmacol.* 14 (1) (2004) 115–122.
- [23] J.J. Rucklidge, M. Taylor, K. Whitehead, Effect of micronutrients on behavior and mood in adults with ADHD: evidence from an 8-week open label trial with natural extension, *J. Atten. Disord.* 15 (1) (2011) 79–91.
- [24] H.A. Gordon, J.J. Rucklidge, N.M. Blampied, J.M. Johnstone, Clinically significant symptom reduction in children with attention-deficit/hyperactivity disorder treated with micronutrients: an open-label reversal design study, *J. Child Adolesc. Psychopharmacol.* 25 (10) (2015) 783–798.
- [25] J.J. Rucklidge, D. Gately, B.J. Kaplan, Database analysis of children and adolescents with bipolar disorder consuming a multinutrient formula, *BMC Psychiatr.* 74 (10) (2010), <https://doi.org/10.1186/1471-244X-10-74>.
- [26] J.J. Rucklidge, M.J.F. Eggleston, J.M. Johnstone, K. Darling, C.M. Frampton, Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial, *JCPP (J. Child Psychol. Psychiatry)* 59 (3) (2018) 232–246.
- [27] J.M. Johnstone, I. Hatsu, G. Tost, P. Srikanth, L.P. Eiterman, A.M. Bruton, H.K. Ast, L.M. Robinette, M.M. Stern, E.G. Millington, B.L. Gracious, A.J. Hughes, B.M. Y. Leung, L.E. Arnold, Micronutrients for attention-deficit/hyperactivity disorder in youths: a placebo-controlled randomized clinical trial, *J. Am. Acad. Child Adolesc. Psychiatry* (2021).
- [28] J.B. Adams, T. Audhya, E. Geis, E. Gehn, V. Fimbres, E. Pollard, J. Mitchell, J. Ingram, R. Hellmers, D. Laake, J. Matthews, K. Li, J. Naviaux, R. Naviaux, R. Adams, D. Coleman, D. Quig, Comprehensive nutritional and dietary intervention for autism spectrum disorder—a randomized, controlled 12-month trial, *Nutrients* 10 (3) (2018) 369.
- [29] J.B. Adams, T. Audhya, S. McDonough-Means, R.A. Rubin, D. Quig, E. Geis, E. Gehn, M. Loresto, J. Mitchell, S. Atwood, S. Barnhouse, W. Lee, Effect of a vitamin/mineral supplement on children and adults with autism, *BMC Pediatr.* 11 (2011) 111.
- [30] S. Schoenthaler, S. Amos, W. Doraz, M.-A. Kelly, G. Muedeking, J. Wakefield, The effect of randomized vitamin-mineral supplementation on violent and non-violent antisocial behavior among incarcerated juveniles, *J. Nutr. Environ. Med.* 7 (1997) 343–352.
- [31] S. Schoenthaler, I. Bier, The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial, *J. Alternative Compl. Med.* 6 (1) (2000) 7–17.
- [32] L. Mehl-Madrona, B. Leung, C. Kennedy, S. Paul, B.J. Kaplan, Micronutrients versus standard medication management in autism: a naturalistic case-control study, *J. Child Adolesc. Psychopharmacol.* 20 (2) (2010) 95–103.
- [33] A.J. Stevens, J.J. Rucklidge, K.A. Darling, M.J. Eggleston, J.F. Pearson, M. A. Kennedy, Methylomic changes in response to micronutrient supplementation and MTHFR genotype, *Epigenomics* 10 (9) (2018) 1201–1214.
- [34] A.J. Stevens, R.V. Purcell, K.A. Darling, M.J.F. Eggleston, M.A. Kennedy, J. J. Rucklidge, Human gut microbiome changes during a 10 week Randomised Control Trial for micronutrient supplementation in children with attention deficit hyperactivity disorder, *Sci. Rep.* 9 (1) (2019), 10128.
- [35] N. Borlase, T.R. Melzer, M.J.F. Eggleston, K.A. Darling, J.J. Rucklidge, Resting-state networks and neurometabolites in children with ADHD after 10 weeks of treatment with micronutrients: results of a randomised placebo-controlled trial, *Nutr. Neurosci.* (2019) 1–11.
- [36] J.J. Rucklidge, M.J.F. Eggleston, K.A. Darling, A.J. Stevens, M.A. Kennedy, C. M. Frampton, Can we predict treatment response in children with ADHD to a vitamin-mineral supplement? An investigation into pre-treatment nutrient serum levels, MTHFR status, clinical correlates and demographic variables, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 89 (2019) 181–192.
- [37] J.J. Rucklidge, M.J.F. Eggleston, B. Ealam, B. Beaglehole, R.T. Mulder, An observational preliminary study on the safety of long-term consumption of micronutrients for the treatment of psychiatric symptoms, *J. Alternative Compl. Med.* (2019).
- [38] J.J. Rucklidge, C.M. Frampton, B. Gorman, A. Boggis, Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial, *Br. J. Psychiatry* 204 (4) (2014) 306–315.
- [39] K.A. Darling, M.J.F. Eggleston, H. Retallick-Brown, J.J. Rucklidge, Mineral-vitamin treatment associated with remission in attention-deficit/hyperactivity disorder symptoms and related problems: 1-year naturalistic outcomes of a 10-week randomized placebo-controlled trial, *J. Child Adolesc. Psychopharmacol.* 29 (9) (2019) 688–704.

- [40] S. Simpson, S. Crawford, E. Goldstein, C. Field, E. Burgess, B. Kaplan, Systematic review of safety and tolerability of a complex micronutrient formula used in mental health, *BMC Psychiatr.* 11 (2011) 62.
- [41] S. Moor, J. Williman, S. Drummond, C. Fulton, W. Mayes, N. Ward, E. Dovenberg, C. Whitaker, K. Stasiak, 'E' therapy in the community: examination of the uptake and effectiveness of BRAVE (a self-help computer programme for anxiety in children and adolescents) in primary care, *Internet Interventions* (2019), 100249.
- [42] S.N. Merry, K. Stasiak, M. Shepherd, C. Frampton, T. Fleming, M.F. Lucassen, The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial, *BMJ* 344 (2012) e2598.
- [43] C. Popper, B.J. Kaplan, J.J. Rucklidge, Single and broad-spectrum micronutrient treatments in psychiatry practice, in: P.L. Gerbarg, P.R. Muskin, R.P. Brown (Eds.), *Complementary and Integrative Treatments in Psychiatric Practice*, American Psychiatric Association Publishing, Arlington, VA, 2017, pp. 75–104.
- [44] J.J. Rucklidge, R. Andridge, B. Gorman, N. Blampied, H. Gordon, A. Boggis, Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses, *Hum. Psychopharmacol.* 27 (5) (2012) 440–454.
- [45] K.M. Fahy, A. Lee, B.J. Milne, in: S.N. Zealand (Ed.), *New Zealand Socio-Economic Index 2013, 2017*. Wellington.
- [46] J. Atkinson, C. Salmund, P. Crampton, in: U.o. Otago (Ed.), *NZDep2013 Index of Deprivation, 2014*. Wellington.
- [47] M. Kongerslev, P. Moran, S. Bo, E. Simonsen, Screening for personality disorder in incarcerated adolescent boys: preliminary validation of an adolescent version of the standardised assessment of personality – abbreviated scale (SAPAS-AV), *BMC Psychiatr.* 12 (1) (2012) 94.
- [48] P. Moran, M. Leese, T. Lee, P. Walters, G. Thornicroft, A. Mann, Standardised Assessment of Personality–Abbreviated Scale (SAPAS): preliminary validation of a brief screen for personality disorder, *Br. J. Psychiatr.* 183 (3) (2003) 228–232.
- [49] C. Cianchetti, M. Pasculli, A. Piattau, M.G. Campus, V. Carta, R. Littarru, G. S. Fancello, A. Zuddas, M.G. Ledda, Child and adolescent behavior inventory (CABI): standardization for age 6-17 Years and first clinical application, clinical practice and epidemiology in mental health, *CP & EMH* 13 (2017) 20–26.
- [50] C. Cianchetti, N. Faedda, M. Pasculli, M.G. Ledda, G. Diaz, A. Pescechera, F. Craig, F. Morelli, U. Balottin, V. Guidetti, A. Zuddas, L. Margari, Predictive validity for the clinical diagnosis of a new parent questionnaire, the CABI, compared with CBCL, *Clin. Child Psychol. Psychiatr.* 25 (2) (2020) 507–519.
- [51] R.L. Bailey, P.E. Miller, D.C. Mitchell, T.J. Hartman, F.R. Lawrence, C.T. Sempos, H. Smiciklas-Wright, Dietary screening tool identifies nutritional risk in older adults, *Am. J. Clin. Nutr.* 90 (1) (2009) 177–183.
- [52] R. Uher, A. Farmer, N. Henigsberg, M. Rietschel, O. Mors, W. Maier, D. Kozel, J. Hauser, D. Souery, A. Placentino, J. Strohmaier, N. Perroud, A. Zobel, A. Rajewska-Rager, M.Z. Dernovsek, E.R. Larsen, P. Kalember, C. Giovannini, M. Barreto, P. McGuffin, K.J. Aitchison, Adverse reactions to antidepressants, *Br. J. Psychiatr.* 195 (3) (2009) 202.
- [53] P. Fusar-Poli, M. Solmi, N. Brondino, C. Davies, C. Chae, P. Politi, S. Borgwardt, S. M. Lawrie, J. Parnas, P. McGuire, Transdiagnostic psychiatry: a systematic review, *World Psychiatr.* 18 (2) (2019) 192–207.
- [54] M.K. Spearing, R.M. Post, G.S. Leverich, D. Brandt, W. Nolen, Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP, *Psychiatr. Res.* 73 (3) (1997) 159–171.
- [55] S.P. Haller, K. Kircanski, A. Stringaris, M. Clayton, H. Bui, C. Agorsor, S. I. Cardenas, K.E. Towbin, D.S. Pine, E. Leibenluft, M.A. Brotman, The clinician affective reactivity index: validity and reliability of a clinician-rated assessment of irritability, *Behav. Ther.* 51 (2) (2020) 283–293.
- [56] C.A. Mazefsky, L. Yu, P.A. Pilkonis, Psychometric properties of the emotion dysregulation inventory in a nationally representative sample of youth, *J. Clin. Child Adolesc. Psychol.* (2020) 1–13.
- [57] M.F. Smout, The factor structure and predictive validity of the Kessler Psychological Distress Scale (K10) in children and adolescents, *Aust. Psychol.* 54 (2) (2019) 102–113.
- [58] R.C. Kessler, P.R. Barker, L.J. Colpe, J.F. Epstein, J.C. Gfroerer, E. Hiripi, M. J. Howes, S.-L.T. Normand, R.W. Manderscheid, E.E. Walters, A.M. Zaslavsky, Screening for serious mental illness in the general population, *Arch. Gen. Psychiatr.* 60 (2) (2003) 184–189.
- [59] R.L. Spitzer, K. Kroenke, J.B. Williams, B. Lowe, A brief measure for assessing generalized anxiety disorder: the GAD-7, *Arch. Intern. Med.* 166 (10) (2006) 1092–1097.
- [60] R. Alharbi, K. Alsuhabani, A. Almarshad, A. Alyahya, Depression and anxiety among high school student at Qassim Region, *J. Fam. Med. Prim. Care* 8 (2) (2019) 504–510.
- [61] B.W. Smith, J. Dalen, K. Wiggins, E. Tooley, P. Christopher, J. Bernard, The brief resilience scale: assessing the ability to bounce back, *Int. J. Behav. Med.* 15 (3) (2008) 194–200.
- [62] J. Endicott, J. Nee, R. Yang, C. Wohlberg, Pediatric quality of life enjoyment and satisfaction questionnaire (PQ-LES-Q): reliability and validity, *J. Am. Acad. Child Adolesc. Psychiatry* 45 (4) (2006) 401–407.
- [63] J.W. Roberti, L.N. Harrington, E.A. Storch, Further psychometric support for the 10-item version of the perceived stress scale, *J. Coll. Counsel.* 9 (2) (2006) 135–147.
- [64] X. Liu, Y. Zhao, J. Li, J. Dai, X. Wang, S. Wang, Factor structure of the 10-item perceived stress scale and measurement invariance across genders among Chinese adolescents, *Front. Psychol.* 11 (2020), 537–537.
- [65] A. Stringaris, Irritability in children and adolescents: a challenge for DSM-5, *Eur. Child Adolesc. Psychiatr.* 20 (2) (2011) 61–66.
- [66] A. Stringaris, R. Goodman, S. Ferdinando, V. Razdan, E. Muhrer, E. Leibenluft, M. A. Brotman, The Affective Reactivity Index: a concise irritability scale for clinical and research settings, *J. Child Psychol. Psychiatry Allied Discip.* 53 (11) (2012) 1109–1117.
- [67] L. Stone, R. Otten, R. Engels, A. Vermulst, J. Janssens, Psychometric properties of the parent and teacher versions of the strengths and difficulties questionnaire for 4- to 12-year-olds: a review, *Clin. Child Fam. Psychol. Rev.* 13 (3) (2010) 254–274.
- [68] R. Goodman, Psychometric properties of the strengths and difficulties questionnaire, *J. Am. Acad. Child Adolesc. Psychiatry* 40 (11) (2001) 1337–1345.
- [69] H.R. Bird, D. Shaffer, P. Fisher, M.S. Gould, et al., The Columbia Impairment Scale (CIS): pilot findings on a measure of global impairment for children and adolescents, *Int. J. Methods Psychiatr. Res.* 3 (3) (1993) 167–176.
- [70] B.K. Attell, C. Cappelli, B. Manteuffel, H. Li, Measuring functional impairment in children and adolescents: psychometric properties of the columbia impairment scale (CIS), *Eval. Health Prof.* 43 (1) (2020) 3–15.
- [71] D. Shaffer, M.S. Gould, J. Brasic, P. Ambrosini, P. Fisher, H. Bird, S. Aluwahlia, A children's global assessment scale (CGAS), *Arch. Gen. Psychiatr.* 40 (11) (1983) 1228–1231.
- [72] W. Guy, P.A. Clearly, J.H. Close, C.K. Conners, L. Covi, ECDEU Assessment Manual for Psychopharmacology. DHEW Publication (ADM) 76-338, US Department of Health, Education, and Welfare, Washington (DC), 1976.
- [73] G.J. DuPaul, T.J. Power, A.D. Anastopoulos, R. Reid, *ADHD Rating Scale—5 for Children and Adolescents. Checklists, Norms, and Clinical Interpretation*, The Guilford Press, New York, 2016.
- [74] S. Perrin, R. Meiser-Stedman, P. Smith, The children's revised impact of event scale (CRIES): validity as a screening instrument for PTSD, *Behav. Cognit. Psychother.* 33 (4) (2005) 487–498.