

**Study title:** Investigation into the effect of a micronutrient formula compared with placebo on stress of undergraduate University of Canterbury (UC) students.

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# Background

Stress is identified as a condition whereby one individual’s perception is one of not being able to cope with the demands of the situation (Lazarus, 1966). It is not only linked to a variety of physical health problems, such as the development of cardiovascular disease, atherosclerosis, oxidative stress, and inflammatory reactivity (Huang, Webb, Zourdos, & Acevedo, 2013), but can also be associated with poorer mental health, academic performance, and wellbeing (Myers et al., 2012). For example, in one study it was found that a greater amount of stress in university students was linked to increasing depression, hopelessness, and suicidal ideation (Ciarrochi, Deane, & Anderson, 2002). Various other researchers examined that stress among undergraduates is associated with lower academic achievement (Felsten & Wilcox, 1992; Pritchard & Wilson, 2003; Russell & Petrie, 1992). However, the adverse effects of stress on academic performance could not be established in other trials, where no relationship between stressful life-events and grades was found (Kemp, Helton, Richardson, Blampied, & Grimshaw, 2011; Petrie & Stoever, 1997).

The scientific literature suggests that stress is a highly prevalent phenomenon among students, including academic, social, and personal issues (Bayram & Bilgel, 2008; Misra, McKean, West, & Russo, 2000). Similarly, communication with Student Health Services at University of Canterbury (UC) and recent news media reports revealed that there are an increasing number of distressed students on UC campus. Generally, it is suggested that university students’ mental health is an internationally rising concern (Manthorpe, 2001), and evidence shows that college and university students represent an increased vulnerability to psychological distress and mental health issues (Manthorpe, 2001). This indicates that there is an urgent need for an intervention alleviating such psychological concerns. In Bursa, Turkey, a study examined moderate stress, anxiety and depression levels in approximately one-third (27.1%) to one-half of 1617 students (47.1%) (Bayram & Bilgel, 2008). In addition, a psychometric study of 1750 Norwegian first year undergraduate students showed that 21% of the students suffered from clinically elevated psychological stress (Nerdrum, Rustøen, & Rønnestad, 2006). Finding potential treatments that can reduce such stress levels is perceived as crucial for the prevention and reduction of other mental health problems (Gjerde, 1993).

Interventions should ideally be feasible and easy to implement, with a low likelihood of having adverse side effects. In Australia, interventions for work-related stress is based on stress management, particularly on teaching people relaxation techniques (Stough et al., 2011). However, studies show that the implementation of stress management techniques is not successful (Caulfield, Chang, Dollard, & Elshaug, 2004). Alternatively, prioritizing the prevention of stress by means of nutritional interventions might be a more successful approach (Stough et al., 2011). Scientific evidence of the past 20 years across a variety of countries, such as the UK, South Africa, and Australia, have indicated that the supplementation of B vitamins can increase resilience towards stress in the workplace, healthy individuals in the community, and university students (Long & Benton, 2013; Schlebusch et al., 2000; Stough et al., 2011; Young, Pipingas, White, Gauci, & Scholey, 2019). For optimal functioning of the brain, vitamins and minerals need to be sufficiently available as several physiological functions, such as the synthesis of neurotransmitter and receptor binding, glucose metabolism and cerebral blood supply, are dependent on multinutrients (Haller, 2005). Various B vitamins, including vitamin B9 (folate), vitamin B12, and vitamin B6, play a crucial role in the synthesis of the neurotransmitters dopamine and serotonin, which are involved in positive mood and therefore necessary for good mental health (Bottiglieri, 1996; Calderón-Guzmán et al., 2004; Stough et al., 2011). This might partly explain the beneficial impact of B vitamins on stress. One trial investigated the effects of a multinutrient supplement (Berocca) on stress in 80 healthy men, and found that taking the product for 28 days lead to significant positive effects on stress and anxiety (Carroll, Ring, Suter, & Willemsen, 2000). In addition, in a double-blind, placebo-controlled study with 300 participants, Schlebusch et al. (2000) examined that multivitamin supplementation lead to significant reduction in stress and anxiety (Schlebusch et al., 2000), which was supported by findings of several other studies (Haskell et al., 2010; Kennedy et al., 2010).

Further epidemiological studies have found similar results (Rucklidge et al., 2012; Rucklidge & Blampied, 2011; Stough et al., 2011). Specifically, during the Christchurch earthquakes, the Mental Health and Nutrition Lab (Te Puna Toiora) at the University of Canterbury collected data on a multinutrient (vitamins and minerals) formula called EMPowerplus (EMP+), and findings showed that taking multinutrients resulted in improved health and faster recovery relative to affected individuals who did not take the multinutrients (Rucklidge & Blampied, 2011). Then, individuals who survived the February 2011 earthquakes in Christchurch (New Zealand) and who initially suffered from moderate-to-severe stress, anxiety, and low mood, and were treated with micronutrients, were more likely to recover and go into remission compared to a treatment-as-usual group (TAU) (Rucklidge et al., 2012). In particular, there was a decline from 65% to 19% for probable posttraumatic stress disorder (PTSD) rates in the multinutrient groups, whereas the TAU group did not shift from a rate of 48% PTSD.

Similarly, after a flood in Alberta in 2013, individuals who were experiencing severe depression, stress, and anxiety, and no previously reported mental disorders, displayed a significant large improvement in all areas of function (stress anxiety, low mood) after being treated with either a B-complex or broad-spectrum multinutrients (*d* > 0.8) (Kaplan, Rucklidge, Romijn, & Dolph, 2015), with significantly greater change than a group that only received vitamin D. Furthermore, Sole, Rucklidge and Blampied (2017) observed positive effects of multinutrients in children who experienced symptoms of anxiety and stress after an earthquake (Sole, Rucklidge, & Blampied, 2017). After taking capsules containing the EMP+ multinutrient formula over eight weeks, their anxiety and stress levels declined substantially, and the occurring side effects were mild.

The findings mentioned above indicate that multinutrient supplements are an effective treatment method for clinically elevated stress and anxiety. The Triage Theory by McCann and Ames (2009) illustrates that our body’s survival functions, such as the fight-or-flight response, is dependent on the availability of micronutrients (McCann & Ames, 2009). Particularly, short-term survival functions, as needed during an earthquake for example, require a great amount of the nutrients we receive from our diet. Further, nutritionally-dense foods are not always available after natural disasters, which increases the risk of malnutrition (Kuijer & Boyce, 2012). In addition, it was shown that affected individuals are likely to adhere to a poorer diet after experiencing a disaster (Kuijer & Boyce, 2012). All these factors might contribute to the observed beneficial effects of nutrient supplementation during stressful times.

Although the intake of multinutrients has been deemed safe (Rucklidge, Eggleston, Ealam, Beaglehole, & Mulder, 2019), a frequently concern is that the multinutrient doses are relatively high, that is higher than the Recommended Dietary Allowance (RDA) for some components of the formulation. Additionally, some people find the swallowing of capsules problematic.

Conveniently, a recent development in this field has been the introduction of a commercial product, the Lightning Stiks, which provides the nutrients in a dissolvable form at much lower doses relative to multinutrient capsules. This form of delivery has not been tested yet and represents the basis of the proposed study.

The Lightning Stiks are powdered candy straws that contain a blend of 36 vitamins, minerals and amino acids. It is absorbed sublingually, which means that there is no need for swallowing pills. It is wondered whether the dissolvable form allows for a lower dose to achieve the same effect as through gastrointestinal absorption. Further, although the ingredients are exactly the same as those used in previous studies (Rucklidge et al., 2012), the doses of all the ingredients are very much smaller. Particularly, *all doses are below RDA*, and there are no safety concerns associated with such low doses. Anecdotal reports suggest that the effects of the Stiks are similar to the capsule version, with many reporting feeling calmer, happier, more focused and less stressed; however, we do not have any clinical data to confirm these anecdotal observations.

**Aims and Objectives**

Given the literature indicating the efficacy of micronutrient treatment for a range of psychological and psychiatric difficulties, and the rising number of students experiencing stress, it is important to scientifically examine the effectiveness of a new modality of multinutrients on stress.

The proposed study will be the first independent study to investigate the feasibility and effectiveness of Lightning Stiks as an intervention for stress and wellbeing. The research will also look at the relationship between stress and academic grades, and the effect of nutrients on academic grades. In addition, it will consider the impact of nutrients on stress associated with a pandemic (COVID19).

It is hypothesized that the Lightning Stiks will be found to be an acceptable and effective intervention to reduce stress in undergraduate UC students relative to a placebo. We also expect the intervention group to show lower stress after the intervention compared with a control group of individuals choosing treatment-as-usual (controls).

# Method

## Study design

This study will use the golden standard, recognised method for testing the benefits of micronutrients, namely a randomised, double-blind, placebo controlled trial (RCT). This series of individual cases will consist of three study periods:

*Study period 1:* On-line screening. Participants will be screened for eligibility by filling out a questionnaire supplying demographic information and various psychometric measures. Assuming they are eligible, they will meet with the study coordinator at Te Puna Toiora during the week before the intervention period starts. During that meeting, eligibility will be checked, questions about the research answered, consent obtained, and the participant will complete a baseline assessment. **In case we cannot meet our participants (e.g. due to COVID-19), meetings will be held and consent conducted over the phone or via Skype. Consent forms can be uploaded and emailed/mailed back to us. At the time of this application, the university continues to remain open, although prepared to modify research should it need to go online.**

Baseline data will be collected by means of an online survey including various psychometric measures. Participants will be supplied with sufficient Stiks - either as active or placebo formula – to cover consumption during the trial period. **If we cannot meet them, the randomized stiks will be mailed or delivered.**

*Study period 2:* A 4-week trial period, consuming either micronutrients or the placebo, with various psychometric questionnaires being completed on-line every two weeks. All participants in phase 1 will start and finish the active intervention or placebo Stiks on the same day.

*Study period 3:* This phase will commence as soon as the RCT is completed and will be a further 4-week open label trial. All participants will receive the Stiks active intervention and will fill out the same measures used in the first two study phases every two weeks.

As we are also interested in the effect of nutrients on academic grades and the relationship between stress and academic grades, we will ask for the participant’s permission to access their grades.

The study will be completed in two phases: one in semester 1 and one in semester 2. The study will have two phases, the first phase beginning in April 2020 and ending in June 2020, and the second phase starts in July 2020 and ending in November 2020. Each phase will involve the same sequence of recruitment, active vs. placebo consumption, and open-label trial. There will be a follow-up period starting three months from the last day of the open label trial, collecting data over two weeks.

The timetable for the phases has been designed so that the group recruited in Semester 2 will be a direct replication of the first semester trial, with events such as university examinations occurring at essentially the same time point in each semester trial. This attempts to control for changes in external stressors likely to be experienced by all participants in the course of a university semester (see timeline below).

The study will also include a follow-up period that starts three months from the end of the open label trial. Follow-up data will be collected mid-October 2020 for phase I participants and end of February 2021 for phase II participants.

Control group

In the proposed study, we will also be recruiting a control group of university students (all 16 years or older) who are either not eligible for the micronutrient study or have chosen not to participate. They will serve as a convenient treatment-as-usual control group. They will complete consent online and the same questionnaires as the intervention groups at baseline, four weeks, eight weeks, and five months. The questionnaires will include the same measures used in the intervention and placebo groups, including measures of stress, anxiety, depression, wellbeing, side effects, emotion regulation, substance use, and sleep. Again, we will ask for the student’s permission to access their grades.

#### **Participant recruitment**

Participants will be recruited through advertisement on Facebook (via the personal account and the University of Canterbury Student Association (UCSA) noticeboard), Instagram (personal account/Te Puna Toiora account), as well as through the UC residential halls. In addition, advertisement posters will be made and hung up on all the physical noticeboards around the UC campus after being stamped by the UCSA. Additionally, brochures will be printed.

#### **Baseline Assessment**

Demographic information will be collected including name, date of birth, contact details, home addresses, and ethnicity. During the baseline assessment, various psychometric questionnaires will also be administered by means of an online web-survey to assess baseline stress levels for undergraduate UC students. For full details of the measures to be used, please see the section “Assessment Tools” below. This information will determine what individualised measures will be used with each participant throughout the study (baseline, intervention period, open-label trial, and follow-up). A schedule of events can be found in the Appendices.

#### Inclusion Criteria:

1) Participants must be enrolled in an undergraduate degree at UC, 2) We do not want to discriminate based on age, hence participants who are 16 years of age are allowed to participate in the study, as long as they possess a level of understanding sufficient to complete the questionnaires and examinations required by the protocol and be considered reliable and compliant with the protocol (including the ingestion of 1 Lightning Stik/day), 3) Participants require English language competence sufficient to understand study materials and answer questionnaires, 4) Scores on the DASS-21 indicating at least mild levels of stress will be used as cut-offs for inclusion; specifically, participants will be eligible if they score 15 or above on the DASS-21 stress scale at screening (using adjusted scoring).

#### Exclusion criteria:

1) Potential participants must not have been taking psychotropic medications (e.g. antidepressants) in the prior 4 weeks nor for the trial period. 2) Any serious medical condition that might require hospitalization, 3) Any participant known to be allergic to the ingredients of the Stiks or placebo, 4) Pregnancy or breastfeeding, 5) Any medication with primarily central nervous system activity, including mood stabilizers, 6) Participation in study period 1 (semester 1) in either the active intervention or placebo group will exclude participation in study period 2 (semester 2). Participants won’t be excluded from taking any hormonal contraceptives.

#### Product and dosing:

The product that will be studied is called EMP Lightning Stiks and comes as a powdered candy straw that uses Direct-to-Mouth technology which means all the consumer has to do is put the powder directly in their mouth and let it dissolve under the tongue. The Stiks consist of a blend of 36 ingredients, including vitamins, minerals and amino acids. The matching placebo (provided for the purpose by the manufacturer of Stiks) is identical in appearance and taste but contains none of the active ingredients. The advantage of this mode of delivery is that the doses of the ingredients are much lower than those found in capsules and well below the RDA (as such no ingredient is given in a medicinal dose). Because the doses are all below RDA, there are no safety concerns for any of the proposed ingredients. All doses are well below the UL.

Participants are asked to take one pouch a day; however, as anecdotal reports have previously reported that as a consequence of taking the Lightning Stiks, individuals suffered from headaches in the first few days of taking them, our participants are advised to start with only ½ a pouch in this study for the first 2 days.

### Assessment Tools

An on-line survey created with Qualtrics will ask the participants from the active intervention, placebo and control group to complete measures of anxiety, depression, stress, wellbeing, emotion regulation, side effects, sleep, traumatic life events and alcohol and drug consumption. The measures that are proposed in this study are standard measures used in Te Puna Toiora: Mental Health and Nutrition Lab.

Qualtrics will present the participants with the following:

Primary outcome measures

*The* *Depression Anxiety and Stress Scale-21 (DASS)* is a 21-item, publically available questionnaire which assesses an individual’s current severity of symptoms relating to depression, anxiety and stress. Cut-offs have been provided to indicate normal, mild, moderate, severe, or extremely severe problems; anything below 10 (for depression), 8 (for anxiety) and 15 (for stress) is considered within the normal to mild range. If a potential participant scores 15 or above on the stress scale, they will be invited to participate in the study. Scores are adjusted based on using the short form.

*Modified Clinical Global Impressions Scale (CGI):* A self-administered scale that asks the participant to rate how much better/worse they feel since participation in the trial across mood, stress, anxiety, and energy. Each item has 7 answer possibilities from very much improved to very much worse.

Secondary outcome measures

*Patient Health Questionnaire-9 (PHQ-9):* a self-administered measure of depression over the last 2 weeks, including 9 items that refer to potential problems that might have occurred. How often such problems have occurred can be scored on a 0 – 3 Likert scale. By means of a 10th item, the scale also asks as to how difficult potential problems have made it for the individual to work, to take care of things at home, or to socialize.

*Generalized Anxiety Disorder 7-item Scale* (GAD-7): a self-administered measure that assesses generalized anxiety disorder and screens for social anxiety, panic, and post-traumatic stress disorder (PTSD). It contains seven items, and each item can be scored from 0 - 3. The total score can range from 0 – 21, and scores of 5, 10, and 15 are used as the cut-off points for mild, moderate and severe anxiety.

*Perceived Stress Scale (PSS):* The PSS measures the perception of stress and asks about thoughts and feelings during the past 4 weeks. It assesses the degree to which situations in one's life are appraised as stressful (Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988). The PSS incorporates 10 items that can be scored on a 0 to 4 Likert Scale that refers to how often the individual feels in a certain way.

*Warwick-Edinburgh Mental Well-being Scale (WEMWBS):* A self-administered, 14 item, 1 to 5 Likert scale that measures hedonic and eudaimonic positive mental well-being over the past 2 weeks (Polak et al., 2015; Tennant et al., 2007).

*Abbreviated Profile of Mood States Questionnaire (POMS):* A 35-item scale with Likert items rated 0 – 4 that measures various aspects of mood and yields a total mood index, one positive mood index, and five negative indices (Grove & Prapavessis, 1992).

*The DSM-5 Level 2-Irritability-Affective Reactivity Index (ARI):* A concise, self- or parent-report scale for the dimensional measurement of irritability. It is an adapted version of the ARI and incorporates 7 items that ask about feelings of irritability during the past seven days, and how true a statement is can be scored on a 0-2 Likert scale. It has been shown to have good internal consistency and is considered an appropriate measure to assess irritability (Stringaris et al., 2012).

*The Side-Effect Checklist (SEC):* Based on the Antidepressant Side Effect Checklist (ASEC), this questionnaire has be modified in the lab to assess common side effects associated with taking pills. It includes 21 items that can be scored on a 0-3 Likert scale. In addition, it asks whether it is likely that those side effects are a consequence of the intervention.

*The Alcohol Use Disorders Identification Test (AUDIT-C):* The AUDIT-C is a 3-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence), with each 5 different answer possibilities. For the purposes of this study, we have changed one of the answer possibilities for question 2: As an answer to the question: how many standard drinks containing alcohol do you have on a typical day? - an individual can now choose ‘0’ (instead of “1” in the original).

*Drug Abuse Screening Test (DAST-10):* A 10-item screening tool to assess drug use asking about drug use during the past 12 months. Individuals can either choose ‘Yes’ or ‘No’ as an answer for each of the questions, and the total overall score is interpreted as the degree of problems related to drug abuse; a score of 0 = “no problems with drug use” (Skinner, 1982).

*Impact of Events Scale Revised (IES-R):* The IES-R (Weiss & Marmar, 1997) is a 22-item measure of commonly experienced symptoms following a distressing event. The IES-R subscales, intrusion (8 items), avoidance (8 items) and hyperarousal (6 items) correspond with the core diagnostic criteria in the DSM-IV for post-traumatic stress disorder (PTSD).

*The Minimal Insomnia Symptom Scale (MISS):* The MISS measures the quality of sleep by means of a 3-item, 0-4 Likert scale. Scores under a score of 6 are considered within the normal range (Broman, Smedje, Mallon, & Hetta, 2008).

*Dietary Screening Tool:* The Dietary Screening Tool (Bailey et al., 2009) is a measure of nutrition that assesses some daily food habits including frequency/regularity of eating breakfast, servings of fruit and vegetables, and fast food intake. It has 25 items with each having 2 to 5 answer possibilities either in form of a Likert scale or dichotomous (Yes/No) response. However, for the purposes of this study item 25, which refers to the use of nutritional supplements, will be removed from the measure.

*Health Anxiety Inventory (HAI) (short form):* The short form of the HAI comprises of 14 questions that have four answer possibilities each. We will be using the ‘week’ version of the HAI, asking participants about syptoms of health anxiety, attitudes and behaviour over the past week. For purposes of the proposed study, we have adapted the HAI to capture anxiety specific to COVID-19.

*COVID 19:* We will be asking questions about the participant’s current situation and stress regarding COVID-19. These questions are attached to the HDEC application.

## 

## Statistical Analysis

All statistical analyses will be carried out using the Statistical Package for Social Science (SPSS), Excel and Sigma Plot.

N = 120 participants will be sought for the study, split 60:60 as cohorts in S1 and S2. Of the 60 participants in each cohort, n=30 will receive the active intervention and n=30 the placebo. This number of participants is sufficient to detect a moderate effect size (.5), which is a reasonable expectation as a moderate effect size has previously been detected in similar studies that investigated the effect of micronutrients on stress (Rucklidge et al., 2012 & 2014). We cannot anticipate the size of the control group – however, their data will be compared to the other two groups using the same statistical methodology as those used to compare the two RCT groups.

Primary outcome measures

For the primary outcome measures (DASS-21 and Modified CGI), the repeated measures of the outcomes will be analysed using generalized linear mixed effects regression models. These models will permit the testing of differences between the micronutrient group and the placebo group over the course of the trial. The pooled mean scores (and standard deviations) throughout the trial on each of the outcomes will be used to compute estimates of effect size (Cohen’s d). For the Modified CGI, the groups will be compared at the end of the study treatment using t-tests.

Secondary outcome measures

For secondary outcomes, linear mixed effects models will also be used. For data from randomized trials, 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. The statistical test for differences between groups will be an F test.

## Anticipated costs

*Participant reimbursement*: The costs of this study are being funded by the University of Canterbury (funds provided to Master’s students) and the University of Canterbury Foundation. There are very few costs associated with the study. Mailing pills may become necessary due to changes in circumstances associated with COVID-19. These costs will not be more than a few hundred dollars. Any additional costs by funds donated to Te Puna Toiora. This funding will cover the costs of the $20 petrol vouchers that participants will receive upon completion of the study. This inducement is intended to increase adherence rates and supply of data.

*Control group:* Participants in the control group will receive a $20 petrol voucher as an insentive upon completion of the 4 questionnaires. This cost will be funded by the University of Canterbury (funds provided to Master’s students) and the University of Canterbury foundation.

## Resources

The product we are testing as well as the placebo is provided free of charge by the manufacturer (True Hope). They do not provide any financial support and are not involved in the study in any other way.

## Timetable

Study phase 1, semester 1 (recruit 60 participants):

|  |  |
| --- | --- |
| **Date** | **Event** |
| April 2020 | Begin recruiting and screening participants |
| May 2020 | Begin baseline measure and conduct consent  Intervention starts |
| June 2020 | Intervention ends  Open label trial starts |
| July 2020 | Open label trial ends |
| October 2020 | Follow-up period |

Study phase 2, semester 2 (recruit 60 participants):

|  |  |
| --- | --- |
| **Date** | **Event** |
| August 2020 | Begin recruiting and screening participants |
| Sept 2020 | Begin baseline measure and conduct consent  Intervention starts |
| October 2020 | Intervention ends  Open label trial starts |
| November 2020 | Open label trial ends |
| February 2021 | Follow-up period |

\*\*Please note we may need to adjust the timeline and starting times due to the changing environment associated with COVD19.

## Ethics

The overall safety of all involved in of the outmost importance. The following safety protocol outlines what safety measures have been put in place to ensure safety of researchers and participants at the University.

## Safety protocol related to visits at the University Lab:

The University of Canterbury has very clear Health and Safety procedures for all visitors. We have a dedicated Health and Safety Team at the University: <https://www.canterbury.ac.nz/about/health-and-safety/>. The Mental Health and Nutrition Lab is situated within the extensive facilities of the School of Psychology, Speech and Hearing, closely adjacent to clinics for audiology, clinical psychology, and speech therapy. All students and staff are trained to deal with emergency situations, such as evacuations, fire, and earthquakes. The Director of the Te Puna Toiora: Mental Health and Nutrition Lab is a First Aid Certificate holder and we are equipped with a First Aid Kit. All short-term visitors are briefed as to the Emergency evacuation procedures. All staff and students who work with individuals under the age of 18 obtain a police check. The Director of the lab (JR), Prof Neville Blampied, a research investigator involved in this study, and one of the current PhD students are registered psychologists such that in the event of any concerns for the wellbeing of participants, we have on hand trained professionals capable of dealing with such circumstances that may arise. In addition, within 20 meters of the lab there are a further 6 university staff who are registered psychologists available for consultation should the need arise.

Participant safety is the most important concern. Every potential participant will be screened to ensure that there are no physical/mental or metabolic (e.g. Wilson’s disease) conditions that may preclude participation. This clearance will be conducted by the study physician (Prof Roger Mulder). Safety of the intervention will be assessed every two weeks during the study period via a survey examining side effects and adverse events. When a serious adverse event is reported, it will be discussed with the study physician who will determine the appropriate course of action. In the case of worsening psychiatric symptoms or suicidal ideation with plan and intent, immediate contact will be made with appropriate mental health services.

Research participants will be informed if any new information regarding the products' safety is brought to our attention during the trial. If we feel that a student’s symptoms have increased to a clinically significant degree or that the product is causing any harm, we may discuss with participant the possibility of withdrawing them from the trial or may decide that they should discontinue their participation in the trial. Participants may be referred to their GP or emergency service until the condition associated with an adverse event has resolved or until it is stable. All adverse events will be documented. Serious adverse events would include events that result in hospitalization, life-threatening disability or death.

If a participant, for any reason, requires treatment with certain therapeutic agents (i.e. antibiotics), we note what they are taking and for how long. If a protocol exclusion violation has occurred (i.e., participant requires psychiatric medications), the participant’s involvement will be discontinued. If any participant is discontinued from the trial or decides to withdraw, we will carry out follow-ups to ensure participant well-being.

Potential side effects

In an RCT conducted at the University of Canterbury with adults (Rucklidge et al, 2014), the only recurring side effect of the formula was the aforementioned transitory gastrointestinal difficulties (loose stool, nausea or vomiting, if the product was taken on an empty stomach, contrary to recommendation) although this side effect did not occur more frequently in the active group as compared with the placebo group. It is important to note that this side effect typically lasts only a few days and can be addressed by staying hydrated. Additionally, we do not think that the mode of delivery used in the current trial will cause these gastrointestinal problems because the Stiks do not get absorbed via the gut.

As mentioned previously, anecdotal reports have reported that as a consequence of taking the Lightning Stiks, individuals suffered from headaches in the first few days of taking them. However, this could potentially be minimized by taking only half a Stik to start with, and increasing the doses over 2 days, which is the reason why our participants are advised to start with only ½ a pouch in this study for the first 2 days. Furthermore, the nutrients we are giving are in doses given for over the counter use, and so far, there have been no reported problems with such use. In addition, there have been 34 studies to date on the EMP micronutrient formula showing that no serious side effects or other effects have been noted. A recent safety study has just been published documenting its safety and tolerability: Rucklidge, J. J., Eggleston, M. J., Ealam, B., Beaglehole, B., & Mulder, R. T. (2019). An observational preliminary study on the safety of long-term consumption of micronutrients for the treatment of psychiatric symptoms. The Journal of Alternative and Complementary Medicine, 25(6), 613-622.

We have consulted with the Māori Research Advisory Group at the University of Canterbury regarding this type of research and the study has received approval to conduct nutritional research with Māori. The Ngai Tahu Consultation and Engagement Group (NTCEG) was consulted on February 11 2020 by means of the Māori Consultation form and they have approved the study process. No issues were identified, and further consultation with Māori is not required. The group is available for further consultation throughout the project.

Members of all cultures will be encouraged to participate in the study. Respect for Māori customs and traditions will be of the highest priority in order to ensure that cultural factors do not impede their desire and willingness to participate.

The Mental Health and Nutrition Research lab, Te Puna Toiora, has been focusing over the last year on increasing Te Reo used within the lab, which is reflected in being gifted a Māori name, translating words within the lab into Māori, and having bilingual business cards. We will ensure that Te Reo is used within the information sheet as well to ensure that the research is perceived as welcoming for Māori.

We have a cultural advisor and clinical psychologist Leona Manna available for consultation to any participant who needs cultural support. We have also consulted her on the design of our previous projects and the design of this one is modelled on that of others that have received her input. Further, participants have the option to discuss with the research team any queries or worries that they may have at any time. These options will be clearly communicated via the information sheet, which individuals are advised to read before commencing participation.

## Research site

Te Puna Toiora: Mental Health and Nutrition Laboratory; Room 465

School of Psychology, Speech and Hearing

University of Canterbury

Private Bag 4800

Christchurch 8140

New Zealand

## Investigators

*Prof Julia Rucklidge*: Primary Investigator/supervisor. Prof Rucklidge will oversee the running of the study and provide support and supervision to researchers on the project, being available at all times should any difficulties arise.

*Nurina Katta:* Coordinator/Investigator. Nurina Katta will be the participant’s primary person to contact in case of questions or concerns. The proposed study is part of a Master’s of Science (MSc) degree in Psychology.

*Prof Neville Blampied:*  Co-Investigator. Prof Blampied will provide support and supervision to researchers on the project with specific expertise in case study design.

*Prof Roger Mulder*: consulting psychiatrist to the team.

## Risk Management

As the principal investigator and as someone located on site for data collection, the responsibility for risk management (such as managing psychological symptoms) of the project will be undertaken by Prof Rucklidge (registered clinical psychologist). Prof. Rucklidge will be consulted on all aspects of the project and will therefore be aware of any foreseeable risks which can then be reviewed and cleared with the study physician Prof Roger Mulder. Any serious adverse effects will be reported to the ethics committees (HDEC and Human Ethics Committee at University of Canterbury), and the trial will be terminated if serious adverse effects known to be caused by the nutrients occur.

## Data ownership

All data associated with the study and all reports resulting from the same will be owned by the authors.

## Conflicts of interest

There is no conflict of interest in the proposed study. The supplements used in this trial will be donated by the manufacturers. Study investigators have no financial affiliations with the manufacturer of the product.

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**Appendices**

## Appendix A: Lightning Stiks active intervention ingredient list – this table shows the comparison in dose between EMP (used previously) and the dose of the Sticks (used in this study). As is evident, the dose of all ingredients is about 10 times lower and all below RDA. As such, they are being provided in OTC doses, not medicinal doses.



**Appendix B: Lightning Stiks placebo ingredient list**

Erythritol, Natural Flavors, Malic Acid

**Appendix C: Schedule of Events**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Baseline | Wk 2 RCT | Wk 4 RCT | Wk 6 open label | Wk 8 open label | Follow-up |
| DASS | x | x | x | x | x | x |
| PHQ-9 | x |  | x |  | x |  |
| GAD-7 | x |  | x |  | x |  |
| PSS | x |  | x |  | x |  |
| WEMWBS | x | x | x | x | x | x |
| POMS | x |  | x |  | x |  |
| ARI | x |  | x |  | x |  |
| SEC | x | x | x | x | x | x |
| AUDIT-C | x |  | x |  | x |  |
| DAST-10 | x |  |  |  |  |  |
| IES-R | x |  | x |  | x |  |
| MISS | x | x | x | x | x | x |
| Modified CGI |  |  | x |  | x | x |
| Dietary Screening Tool | x |  | x |  | x |  |
| HAI | x |  | x |  | x | x |