Effects of Micronutrients as Treatment for Posttraumatic Stress Symptoms in Individuals Struggling with Anxiety and Depression; a Post-hoc Analysis of a Randomised Controlled Trial

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Abstract

Posttraumatic stress disorders often co-occur with depression and/or anxiety, leading to high levels of distress and low quality of life. Up to 70% of people with posttraumatic stress disorder do not achieve symptom remission from first-line pharmacological and psychotherapeutic interventions. Micronutrient interventions have demonstrated efficacy in treating acute posttraumatic stress and improving resilience after a disaster. This study investigated the efficacy of a micronutrient intervention for improving posttraumatic stress symptoms in people with functionally impairing anxiety and/or depression recruited to a 10-week randomised controlled trial (RCT) with 10-week open label (OL) phase. Seventy-two participants of 117 recruited endorsed a previous traumatic event and were included in the present study. There were no significant group differences on Impact of Event Scale – Revised between the micronutrient and placebo conditions at the end of RCT (between groups Effect Size (ES) *d* = 0.14, 95% CI [-0.53, 0.8]) nor at the end of OL (*d* = 0.27, 95% CIs [-0.35, 0.88]). Similar ESs were found for Depression, Anxiety and Stress Scale (DASS) total, depression and anxiety subscales, Patient Health Questionnaire–9 and Generalised Anxiety Disorder-7 Question Scale. The micronutrient group had larger ESs for DASS stress subscale at end of RCT and OL, and the end of OL Quality of Life Scale. Micronutrient expectation, treatment condition guess and past history of psychotropic medication were found to predict treatment response. This study found a 20-week micronutrient intervention was not superior in reducing chronic posttraumatic stress symptoms in people with co-occurring anxiety and depression over placebo. Future research may focus on predictors of treatment response including micronutrient expectation and past psychoactive medication use.

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Contents

Introduction

Many people experience potentially traumatic events in their lives, with estimates ranging from 50 to 80% of a population (Breslau, 2009; Kessler et al., 1995). The psychological distress we experience after a potentially traumatic event varies, and a large majority of us demonstrate resilience (Bonanno & Mancini, 2012). However, up to 30% of people experiencing a potentially traumatic event go on to develop traumatic stress disorders (National Institute for Health and Care Excellence, 2018). In Aotearoa New Zealand around 3% of the population each year experience one such disorder: posttraumatic stress disorder (PTSD) (Wells et al., 2006). A similar rate was found for a Christchurch birth cohort (Boden et al., 2015) after a series of earthquakes hit the city in 2010/2011, which is also where this study is being conducted.

A hallmark of posttraumatic stress disorders is the re-experiencing of the traumatic event, known as 'flashbacks'. These intrusive thoughts are considered a one of three key symptom groupings, along with avoidance and hyperarousal (Brewin et al., 2017; Horowitz, 2011). Intrusions or flashbacks are unwanted mental images related to any of the senses (for example, smell, sound, sight) that are typically related to the traumatic event. Intrusions tend to occur when the person experiencing them is in a relaxed state, triggering a fear response. Intrusions lead to hyperarousal, a high level of alertness and increased startle response. Hyperarousal stress responses can appear similar to anxiety, and include sudden bursts of alarm responses or panic attacks, or the stress responses may be experienced as a chronic state of anxiety. Ongoing stress responses can lead to fatigue, exhaustion and lack of sleep. Experiencing intrusions is unpleasant and can lead to the behavioural response of avoidance, for example avoiding reminders of the traumatic event, avoiding thinking about the trauma and attempts at avoiding or suppressing the emotional experiences associated with the stress response (Horowitz, 2011).

The strong emotions and hyperarousal states experienced from intrusions can lead to anticipatory anxiety about the intrusions occurring again and anxiety about one's own mental wellbeing given the apparently uncontrollable intrusions. Avoidance of reminders often leads to avoidance of social settings, and the use of drugs and alcohol to reduce intrusions (Ehlers & Clark, 2000). People experiencing a trauma response often report feeling numb, which along with the avoidance-type

symptoms, can appear as a lack of attention and focus (Horowitz, 2011). PTSD can also include alteration in cognitions and mood, amnesia for the traumatic event and may include dissociative symptoms and externalising symptoms such as aggression (American Psychiatric Association, 2013; Barbano et al., 2019; Brewin et al., 2017; Kessler et al., 1995; Price & van Stolk-Cooke, 2015).

The sequelae of intrusions, avoidance and hyperarousal along with anxiety and mood disturbance often lead to chronic dysfunction (Bonanno & Mancini, 2012), reduced quality of life (Balayan et al., 2014) and place a high economic burden on communities, including direct costs such as treatment and indirect costs such as absenteeism from work (von der Warth et al., 2020).

While PTSD has been recognised as a psychiatric disorder since the late 1970s (Horowitz, 2011), it is just one of many stress disorders. Due to the variety of clinical expressions of distress following an adverse event, the widely used *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association, 2013) has grouped a number of related disorders together under a separate category – trauma and stressor related disorders. Within the DSM-5 chapter on trauma, disorders relating to attachment as a result of social neglect in childhood are included, along with disorders relating to a specific stressor or traumatic event, adjustment disorder, acute stress disorder (ASD) and posttraumatic stress disorder (PTSD). ASD differs from PTSD in that symptoms are evident between three days and one month after the potentially traumatic event, whereas in PTSD, the symptoms are experienced more than one month after the event (American Psychiatric Association, 2013), and including more chronic presentations of posttraumatic stress.

An important part of the diagnostic criteria for ASD and PTSD is that the person experiencing stress meets a predetermined criterion for what is considered a traumatic event. The DSM 5 defines this as “exposure to actual or threatened death, serious injury or sexual violence” (page 271, (American Psychiatric Association, 2013) and lists a range of ways exposure may have occurred. This includes directly experiencing or witness the traumatic events, learning that the traumatic events occurred to a close friend or family member or through repeated exposure to the details of traumatic events, which includes people who may experience this through their work as police officers or first-responders. The criteria does not include repeated exposure through media unless this is the context of work.

Another diagnostic framework, the World Health Organisation’s International Classification of Diseases (ICD) uses a broader definition of a traumatic events - “Exposure to a stressful event or

situation of exceptionally threatening or horrific nature likely to cause pervasive distress in almost anyone" (World Health Organization, 2018). Furthermore, the ICD 11 includes Complex PTSD which reflects traumatic events of an ongoing nature where escape is difficult. The inclusion of a Complex PTSD diagnosis acknowledges that people exposed to many traumas over time, or prolonged traumatic events present differently to those who have experienced a single traumatic event or stressor. In complex cases, people experience symptoms of PTSD along with more entrenched difficulties in self-organisation, self-identity and/or personality (Brewin et al., 2017; Horowitz, 2011). In addition to PTSD symptoms, the ICD's Complex PTSD is characterized by ongoing difficulties in affect regulation, low self-worth and feelings of shame, guilt or failure related to the traumatic event and interpersonal difficulties (World Health Organization, 2018).

While it is useful to consider posttraumatic stress responses generally, the literature is largely focused on PTSD, where people experiencing these symptoms will have met diagnostic criteria for PTSD. Bonanno and Mancini (2012) argue that diagnostic cut offs are arbitrary and do not reflect the heterogeneity of responses to a potentially traumatic event. Further to this, Weiss (Weiss, 2004) argues that as time passes after a traumatic event symptom presentation will likely change so that the levels for clinical concern will change over time. Weiss also acknowledges that the type and severity of a traumatic event experienced will also lead to a different intensity of symptoms. (Weiss, 2004). Within this present study, post-traumatic stress responses will be considered more broadly than specific diagnoses, and will include the central features of a post-traumatic stress response – intrusions, avoidance and hyper-arousal.

Depression and Anxiety

Post-traumatic stress disorders often co-occur with anxiety and depression, and posttraumatic stress responses typically include depression, anxiety, grief and a range of psycho-social difficulties (American Psychiatric Association, 2013; Barbano et al., 2019; Horowitz, 2011; Kessler et al., 1995). Kessler and colleague's (1995) United States based co-morbidity study found PTSD co-occurred with major depressive episodes at around 48%, with phobias at around 30% and substance abuse disorders at a rate of around 28% for women and 51% for men.

The co-occurrence of PTSD, anxiety and/or depression highlights a group of people who likely have many symptoms that significantly impact on their lives. People experiencing PTSD and depression and/or anxiety report higher levels of distress than those experiencing depression and/or anxiety alone (Green et al., 2006; Nichter et al., 2019; Spinhoven et al., 2014). People with co-occurring major depressive disorder (MDD) and PTSD report lower quality of life and have higher rates of suicide ideation and attempts; and also respond to treatment, for example pharmacological treatment by citalopram, more slowly, if they respond at all (Steiner et al., 2017).

Depression and anxiety alone affect large numbers of people each year. For example, the life-time diagnosis rate of depression and/or anxiety in Aotearoa New Zealand for the 2017/2018 year was 20.9% with a 12 month anxiety prevalence of 14.8%, and 7.9% for mood disorders (Ministry of Health, 2018). Despite a 50% increase in mental health prescriptions over last 10 years (Health and Disability Commissioner, 2018) prevalence rates are increasing each year (Ministry of Health, 2018).

A snapshot of the Waitaha Canterbury region after the exposure to a series of earthquakes in 2010-2011 based on a 35-year-old birth cohort suggests impairment due to depression and anxiety in Waitaha Canterbury region impacts many people. This study found similar rates of depression as the Aotearoa New Zealand prevalence (10.4% met DSM-V criteria for depression, 14.7% if sub-clinical presentation was included) and higher rates of anxiety disorders (13.3% of the sample met criteria for a DSM-5 diagnosis, and 26.7% met criteria for at least one symptom) (Fergusson et al., 2014) .

Depressive disorders are characterised by sad, empty or irritable mood and somatic and cognitive symptoms that impact the individual's ability to function. Symptoms often include diminished pleasure in activities, sleep disturbances, fatigue, inability to concentrate and suicidal ideation. The DSM-5 chapter on depressive disorders includes a range of distinct disorders that vary in the duration and timing of the symptoms, and include major depressive disorder (MDD), persistent depressive disorder (dysthymia) and premenstrual dysphoric disorder (PDD) (American Psychiatric Association, 2013).

Anxiety disorders include experiences of excessive fear and anxiety and are characterised by changes in behaviour, particularly avoidance, due to these fears and anxieties. Fear and anxiety are associated with the activation of 'fight or flight' responses (including the emotions of fear) and increased cautiousness and vigilance to threat (anxiety). The DSM-5 includes a range of anxiety

disorders that are differentiated by the objects or situations that elicit the fear or anxiety response and include generalised anxiety disorder (GAD), phobias and panic disorder (PD) (American Psychiatric Association, 2013).

Co-occurrence / co-morbidity (of PTSD)

The pattern of co-occurrence between PTSD and other disorders, particularly anxiety and depression has been explained in three ways. Firstly, that pre-existing mental health conditions, such as depression or anxiety make it more likely a person is exposed to trauma, or more susceptible to PTSD due to the vulnerabilities associated with their mental health status (Breslau, 2009). Secondly, that PTSD precedes other psychiatric disorders and has a causal link to depression and anxiety, for example a person's inability to recover from PTSD leads to depression (Bonanno & Mancini, 2012) , or that anxiety disorders like panic attacks develop through heightened interoceptive vigilance due to the existing trauma response (Shasha et al., 2018). The Cognitive Behavioural Therapy (CBT) model of depression, where early life experiences of stressors or trauma contribute to the formation of negative beliefs, leading to the cycle of depression, also supports this notion (Beck & Bredemeier, 2016).

The third explanation of the co-occurrence of PTSD and other mental health disorders is that the disorders share common risk factors, either genetic or environmental or both (Breslau, 2009). For example, Spinhoven et al. (2014) found that anxiety, depression and PTSD have shared risk factors, including female gender and childhood trauma.

The DSM-5 acknowledges the close relationship between stress-related disorders and other anxiety, obsessive compulsive and dissociative disorders. In earlier iterations of the DSM, PTSD was included in the anxiety disorder chapters (Brewin et al., 2017; Horowitz, 2011). It is also important to note that many of the criteria for PTSD as defined by the DSM and the World Health Organization's (2004) ICD-10 appear to overlap with the symptoms of both depression and anxiety, and it has been proposed the high rate of co-occurrence among PTSD, anxiety and depression reflects this diagnostic overlap (Barbano et al., 2019; Brewin et al., 2017; Kessler et al., 1995; Price & van Stolk-Cooke, 2015).

In response to what appeared to be a symptom overlap, the ICD-11 (World Health Organization, 2018) has utilised a diagnostic criteria for PTSD that includes only symptoms unique to PTSD, with the intention of reducing the diagnostic co-morbidity among PTSD, depression and anxiety

disorders. In 2019, prior to the ICD-11 being finalised, Barbano and colleagues compared co-morbidity rates with PTSD diagnoses from the ICD-10 criteria, which included PTSD non-specific symptom criteria, and the proposed ICD-11 PTSD-unique symptom diagnostic criteria. It was found that those who met the ICD-11 diagnostic criteria for PTSD had the same, if not higher rates of co-occurring depression or anxiety. This finding suggests that PTSD, depression and anxiety do not co-occur due to symptom overlap and that the three disorders are separate entities that often occur at the same time. Importantly, those with co-occurring depression and ICD-11 diagnosed PTSD experienced more severe PTSD and depression (Barbano et al., 2019).

By ascertaining if participants have had a traumatic experience and are experiencing posttraumatic stress responses, we are likely able to identify a subset of people experiencing anxiety and depression that also require treatment for their post-traumatic stress response, and based on Steiner et al. (2017)'s findings, may not respond to conventional anxiety and depression treatments. Additionally, by ascertaining if an individual is experiencing PTSD, this might provide a better explanation of the aetiology their symptoms than depression or anxiety alone and provide a treatment target that may prove more effective than treating depression and/or anxiety in isolation.

Stress responses

The potential posttraumatic stress sequelae can seriously impact wellbeing, and understanding our stress responses can assist us in understanding both the sequelae and possible interventions. Our bodies are hard-wired to respond to threat, and our physiological responses to stressors can explain trauma symptoms. There are many proposed mechanisms of action in the biology of PTSD, and neural circuitry involved in the anatomical responses seen in PTSD appear to be central (Kelmendi et al., 2017; Thomas & Stein, 2017). One possible model suggests that PTSD is a fear response that is learned during a traumatic event which is then not subsequently extinguished by exposure in safe situations. The hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system are both involved in this fear response, and release hormones such as cortisol to activate adaptive fear responses. Over-activation over a long period of time (in the case of chronic stress or PTSD) of these fear responses can have detrimental effects on other organs and parts of the brain (Thomas & Stein, 2017) likely as a result of inflammatory immune responses (Michopoulos et al., 2017).

The abnormal regulation of neurochemical systems is also implicated in PTSD neurobiology. Dopamine, noradrenaline, serotonin and opioid neurotransmitters are related to many PTSD symptoms, and work to increase activation in the case of noradrenaline and adrenaline, or to oppose the stress response in the case of endogenous opioids (Thomas & Stein, 2017). The role of glutamate in the stress response is also being researched. Glutamate is an excitatory transmitter and is released when the fear response is triggered. It is implicated in the learning of the fear response in various situations (Thomas & Stein, 2017).

We also have individual differences in our neural circuitry and neurotransmitter function as a result of our genetics or epigenetics which can alter our stress response. Epigenetics refers to how our genetic expression is altered by environmental factors (Klengel et al., 2014). A relevant example in the PTSD literature is the finding that the FKBP5 gene interacts with childhood abuse. The FKBP5 gene is associated with the regulation of glucocorticoid sensitivity and signalling which is important in stress reactions (Binder et al., 2008; Klengel et al., 2014). As such, when a developing child experiences abuse, the way this gene is expressed is altered by epigenetic mechanisms, leading to changes in the regulation of glucocorticoid and altered stress reactions. Additionally, Binder and colleagues found child abuse severity was a predictor of adulthood PTSD, and childhood adversity generally is a fairly consistent risk factor for PTSD (Brewin et al., 2000).

While these theories offer some understanding of PTSD, there remains considerable uncertainty around the mechanisms of PTSD, leading to uncertainty about what pharmacotherapies might work and why. What is clear is that there is likely a wide range of mechanisms contributing to the difficulties experienced with stress disorders.

PTSD treatment

Pharmacological

Selective Serotonin Reuptake Inhibitors (SSRIs) are the recommended first-line of pharmacological treatment for PTSD (Ipser & Stein, 2012; Ravindran & Stein, 2009; Starke & Stein, 2017) and the National Institute of Health and Care Excellence (NICE) recommends SSRIs for those seeking a pharmaceutical intervention (National Institute for Health and Care Excellence, 2018). SSRIs, an antidepressant commonly used to treat depression and anxiety-related disorders are thought to work because the neurotransmitter, serotonin is related to PTSD symptoms. Additionally, serotonin is

implicated in depression and anxiety disorders, so targeting serotonin could help with either co-occurring or overlapping symptoms of these disorders and PTSD. Unfortunately, side effects such as weight gain and sexual dysfunction limit the use of SSRIs for many people (Ipser & Stein, 2012), their effect size (ES) in treating PTSD relative to placebo is typically small (ES = 0.23, 95% CI[1], [0.12–0.33] (Thomas & Stein, 2017) and up to 70% of people do not achieve full remission of symptoms from SSRI medication for PTSD (Starke & Stein, 2017). It is difficult to draw general conclusions about the effectiveness of SSRIs. Different classes of SSRI have different rates of treatment effectiveness, with some demonstrating an over 40% placebo response rate in RCT and meta-analyses of the research have taken different approaches to study inclusion criteria (Hoskins et al., 2015).

Another reported side effect of pharmacological interventions, including SSRIs, is the common experience of withdrawal syndromes. Withdrawal syndromes can present as either the listed side effects of the medications, or what appears to be a rebound of psychiatric symptoms upon discontinuation of the medication (Chouinard & Chouinard, 2015). It is also proposed by Cosci and Chouinard (2020) that medications can produce persistent withdrawal disorder, which can last for more than 6 weeks and can be severe and irreversible. In some cases these withdrawal symptoms can continue for months and years (Cosci & Chouinard, 2020).

Antipsychotic drugs, particularly the off-label use of risperidone, are recommended in the NICE guidelines in conjunction with psychotherapies if people with PTSD have not responded to other interventions or have disabling hyperarousal of psychotic symptoms (National Institute for Health and Care Excellence, 2018). Bauer et al. (2014) report second generation antipsychotics are being used in the treatment of PTSD; however, there is no evidence for efficacy. Benzodiazepines are also found to have little evidence of efficacy with PTSD, despite still being prescribed regularly (Ipser & Stein, 2012). Baldwin et al. (2014) suggest pharmaceuticals are used to target specific PTSD symptoms, especially with treatment non-responders. There are many novel treatments being investigated; however, it remains unclear which pharmacotherapies work best and why. It is further proposed that individual differences in neurotransmitter function and epigenetic responses need further investigation as factors

[1] CI = Confidence Interval. Reporting of CIs, typically the 95% CI, specifies how confident we can be that the CI range includes the population parameter we are interested in Cumming (2012).

affecting the psychopharmacological treatment for PTSD (Lokshina & Liberzon, 2017; Thomas & Stein, 2017).

Psychotherapy

The use of psychotherapies such as CBT are often found at least as effective as pharmaceutical treatment in many cases, can be used as an adjunctive therapy (Kelmendi et al., 2017) and demonstrate long term efficacy over pharmaceutical interventions (Merz et al., 2019). CBT based psychotherapy is a NICE recommended treatment for children and adults experiencing PTSD (National Institute for Health and Care Excellence, 2018). CBT and cognitive therapy (CT) for PTSD involves assisting the individual to process traumatic events, learn relaxation techniques and through behavioural principles, extinguish fear responses in safe situations (Ehlers et al., 2005). Ehlers et al. (2005) review of CT for PTSD for 28 participants found the treatment was effective - the intent-to-treat effect sizes for the degree of change in PTSD symptoms from pre to post-treatment were Cohen's *d* = 2.70–2.82 (self-report), and 2.07 (assessor-rated). CT also had high acceptability and led to improvements in treatment participants' depression and anxiety symptoms.

In addition to CBT, the NICE guidelines report eye movement desensitization and reprocessing (EMDR) therapy has promising evidence in reducing PTSD symptoms (National Institute for Health and Care Excellence, 2018) and Seidler and Wagner's (2006) meta-analysis found EDMR to have similar efficacy as trauma-focused CBT. A 2013 Cochrane review of psychological therapies for chronic PTSD favoured trauma focused CBT and EDMR over waitlist and usual care for reduction in clinician-assessed PTSD symptoms (Bisson et al., 2013).

Hoskins and colleagues (2015) draw attention to typically large effect sizes for psychotherapies, as demonstrated by the Ehlers and colleagues' (2005) RCT, compared with effect sizes from pharmacotherapy trials. Hoskins and colleagues suggest methodological difficulties such as the inability to successfully blind participants in a psychotherapy condition make pharmacological trials intrinsically a tougher experimental test. A meta-analysis comparing trauma-focused psychotherapies and pharmacological therapies where only psychotherapy trials that used an active control were included found that trauma-focused psychotherapies were superior to medications and that the differences in efficacy became larger up to nine months post treatment (Lee et al., 2016). Lee also acknowledged that

despite the issues with blinding in psychotherapy trials, such studies were typically better designed, executed and reported on than pharmaceutical trials, and highlighted the high levels of bias observed in most medication trials including researchers being sponsored by the industry, selective data reporting and failure to disclose methods.

There is limited evidence of any benefit when pharmacological intervention is combined with psychotherapy, or of direct comparability (Baldwin et al., 2014; Hoskins et al., 2015). Studies often include participants using both pharmacological and psychotherapeutic interventions further hindering comparisons of the two treatment conditions (Hoskins et al., 2015). Nevertheless, while having established effectiveness, psychotherapy can be difficult for individuals to access due to costs and time commitment, and a lack of treatment provision, largely due to what Kazdin (2017) describes as "a treatment gap". To reach all those needing treatment for mental health, we need to develop new ways of delivering established, evidence-based treatment so that they are within easy reach of those in need, and are affordable (Kazdin, 2017). A further challenge is that because PTSD is often co-occurring, the other associated disorders may impact on treatment adherence, for example depression may reduce motivation to attend treatment sessions (Starke & Stein, 2017).

As noted above, some 70% of people seeking treatment for PTSD do not respond to either first line pharmacological or psychotherapeutic interventions (Starke & Stein, 2017). Starke and Stein define Treatment Resistant PTSD (TRPTSD) as PTSD that does not respond to evidence-based, symptom targeted recommended first line treatments. Their review article suggests extending and combining treatments for up to 24 months, with regular monitoring of symptoms until clinically meaningful remission is achieved, before introducing novel or emerging strategies such as yoga or new pharmacological interventions. The majority of drug and psychotherapy trials run for 8-12 weeks (for example Ehlers et al., (2005); Hoskins et al., (2015); Lee et al., (2016)) suggesting that for some, this may not be a sufficient length of time to achieve remission for people experiencing TRPTSD.

While pharmacological and psychotherapies are the most commonly used treatments for PTSD, anxiety and depression the increasing prevalence of mental health disorders and increasing reliance on pharmaceuticals in Aotearoa New Zealand (Health and Disability Commissioner, 2018) suggests this is not sufficiently reducing the burden of these disorders in our communities. Alarmingly, Kazdin (2017)

reports that world-wide, the majority of people experiencing mental health difficulties receive no treatment. This combination of lack of treatment effectiveness and lack of access to treatment around the world suggests we need to investigate alternative interventions to improve people's mental wellbeing. Given the high rates of co-occurrence (Price & van Stolk-Cooke, 2015; Starke & Stein, 2017), the complex temporal relationship between PTSD and depression (Steiner et al., 2017), and the known trauma sequelae with many psychiatric disorders (Spinhoven et al., 2014) it is of central importance we consider the presence of trauma when investigating treatment options for those experiencing all psychiatric disorders, especially anxiety and depression as this may be missed in regular medical consultations (Baldwin et al., 2014).

Nutritional Interventions

Given the difficulties providing treatment to everyone who needs help, and that existing treatments don't sufficiently alleviate posttraumatic stress symptoms for everyone, we need to consider alternative interventions that might be more accessible with fewer side effects. There is a long history documenting the important role of nutrition in mental well-being (Popper, 2014) and nutrition is increasingly being investigated as an intervention to improve mental wellbeing (Blampied et al., 2020). The literature supports claims that a highly processed 'Western diet' is linked with poorer mental wellbeing, likely due to poor availability of micronutrients, and the 'Mediterranean diet' is often associated with better mental wellbeing (Davison & Kaplan, 2012; Jacka et al., 2010; Popper, 2014). A recent meta-analysis found that dietary interventions significantly reduced depressive symptoms (Firth et al., 2019), and the Mediterranean diet was found to improve both depression and anxiety symptoms more effectively than the social support condition it was compared with (Jacka et al., 2017).

The role of nutrition in mental wellbeing is multi-faceted and complex. It is likely the mechanisms of action includes interactions among inflammation, epigenetics, mitochondrial dysfunction, the gut microbiota, tryptophan metabolism and the HPA axis (Marx et al., 2020). A good starting place is to consider the nutrients available to our brain for optimal neural functioning and wellbeing. In addition to macronutrients such as proteins, fats and carbohydrates fuelling our brains and bodies, many vitamins and minerals, collectively micronutrients, act as catalysts and co-enzymes in a range of important functions of neurotransmission and gene expression and are usually obtained

through our diet. To take just one example, the metabolism of serotonin (a neurotransmitter important in mood as noted above) synthesised from tryptophan, an amino acid derived from our diet, requires many co-factors in the form of vitamins and minerals (Russo et al., 2009).

Stress in general and post-traumatic stress responses in particular likely increase our nutritional needs, particularly for micronutrients. McCann and Ames (2009) propose that at times of high stress nutritional resources are directed towards survival functions rather than longer term biological functions. This idea about the allocation of nutrition resources is known as Triage Theory and builds on knowledge that our bodies prioritise the most important function and provide resources to it at the expense of other functions. Therefore, when our bodies are in 'fight or flight' mode, our bodies are programmed to direct our nutritional resources to that life-saving function over all other functions. Fight or flight responses are a natural and biologically advantageous response during a traumatic event and are activated when we experience PTSD symptoms such as hypervigilance, anxiety and flashbacks.

Many micronutrients have been associated with these fear, stress and anxiety responses. For example, vitamin B6 is an important co-factor in gamma-aminobutyric acid (GABA), serotonin and dopamine manufacture, all of which, as neurotransmitters, play important roles in the stress response. Vitamin B1 (thiamine) protects the adrenal gland which releases cortisol during times of stress thus protecting it from exhaustion (Head & Kelly, 2009). When our bodies are consistently responding to perceived threat, as is the case with PTSD, this creates a large nutritional demand for survival functions related to our physical and mental preparation for flight, fight or freezing. Our diets may not be able to provide the nutritional resources we require to maintain the stress response, and to also manufacture other neurotransmitters important in our wellbeing and recovery, particularly when the stressor and our response to it are chronic.

Epigenetics, the influence of environmental factors on how our genes are read is also influenced by our diet. A key process in how genes are read, is methylation. Methylation helps our DNA strands coil up, making the genes unreadable and therefore not expressed (Klengel & Binder, 2015; Klengel et al., 2014), which can therefore reduce the chances a genetic predisposition is expressed. Many nutrients are involved in methylation, and the availability of nutrients can affect methylation and therefore what genes are expressed or silenced. This process is powerfully illustrated by how the diet honeybee larvae is fed influences methylation and their genetic expression as adult bees. All social

honeybees are genetically the same, but those who are selectively fed royal jelly go on to develop into queen bees rather than worker or drone bees and demonstrate large differences in physiology, reproductive ability and life span (Maleszka, 2008).

According to Triage Theory, at times of high stress, or prolonged exposure to stress the nutritional resources available for methylation could be reduced leading to reduced methylation. Reduced methylation could result in genes making us vulnerable to mental health difficulties being expressed (Stevens et al., 2018). Good nutrition could therefore support us by providing all the vitamins and minerals needed in the methylation process, leading to the genes that makes us vulnerable to mental health difficulties remaining silent. An example of this phenomenon is the agouti gene expression in mice, which is influenced by the maternal diet during foetal development. Simply put, methylation of the gene reduces gene expression. When pregnant mice are fed a methyl-rich diet, hypermethylation occurs and agouti is not expressed, resulting in lean, less disease-prone offspring. When methylation does not occur in the specific genetic regions of the DNA coil, the agouti gene is expressed and mice have a yellow coat, are obese and at risk of cancer and diabetes (Stevens et al.,2018).

It is also possible that inborn errors of metabolism might impact our ability to utilise co-factors effectively (Ames, 2004). Errors of metabolism can lead to individuals requiring more of a particular nutrient than would be typically considered sufficient, and that by increasing the supply of that nutrient, the metabolic processes of the affected individual can be restored to expected levels. Our brains use a huge proportion of our daily intake of nutrition and many metabolic processes occur during normal brain function. Individual differences in metabolism or inborn errors means some individuals may require a greater nutritional intake than others to achieve normal function. For people with inborn errors, neurotransmission would be further impacted at times of high stress when nutrients are triaged in to life saving functions, potentially creating vulnerability to mental health difficulties.

Inflammation is a biological process that has recently been associated with both diet mental health difficulties. Inflammation is induced when our immune cells release cytokines as an innate part of our immune response to eliminate harmful agents and to protect and repair tissue. Because

inflammation affects cells, it can also affect cells of the brain. It is proposed that chronic inflammation in the brain leads to disruption of neurotransmission processes (Michopoulos et al., 2017). Increased inflammation has been associated with a number of psychiatric disorders including depression, anxiety and schizophrenia (Marx et al., 2020). The relationship between depression and inflammation appears to be bidirectional, in that depression increases inflammatory responses, and inflammation promotes depression, and that diet and lifestyle likely influence inflammation, which also influences depression (Bauer & Teixeira, 2019).

While the research is not conclusive, it is suggested PTSD is also associated with increased inflammation (Michopoulos et al., 2017), which Tursich et al. (2014) suggest is a result of chronic dysregulation of our physiological stress response system. The association between PTSD, anxiety, and depression, and inflammation suggests reducing inflammation is a potential intervention target (Firth et al., 2019; Marx et al., 2020; Michopoulos et al., 2017). Dietary interventions are therefore promising, by increasing vitamin and mineral intake in order to promote anti-inflammatory processes and to promote a diverse gut microbiota which is also thought to reduce inflammation (Marx et al., 2020).

Gavrieli et al. (2015) found that poorer diet was associated with early life adversity and PTSD symptoms; however, this correlation was no longer statistically significant when socioeconomic and education factors were taken into account, highlighting the interaction between nutrition and social factors. Other studies have found improvements in PTSD symptoms by reducing glutamate intake (Brandley et al., 2020), increasing anti-oxidant rich foods (Ebenezer et al., 2016) and increasing amino acid intake (Hoffman et al., 2015). The role of essential fatty acids has also been considered in the reduction of PTSD symptoms with little evidence of effectiveness (de Vries et al., 2016; Kagan et al., 2015; Matsumura et al., 2016).

Micronutrients

While the literature shows dietary improvement can improve mental health, dietary change is both complex and difficult to maintain, particularly in the context of mood difficulties (Leigh Gibson, 2006; Paans et al., 2019; Rothman et al., 2009; Rowe et al., 2011). Even when successful dietary change can be achieved, it has been argued that nutrient dense foods are more difficult to include in our diets due to changed farming practices and nutrient-depleted soils (Popper, 2014). Lack access to nutritious

and good quality food is unfortunately especially pertinent here is Aotearoa New Zealand with around 20% of people experiencing difficulty accessing food (Bowers et al., 2009). For these reasons, a growing number of researchers have been investigating the role that broad-spectrum micronutrient supplementation can play in the expression and treatment of mental illness (for example: Rucklidge and Kaplan (2013); Blampied et al. (2020); Retallick-Brown et al. (2020)).

Supplementation enables us to import nutrients that may not be available to us in our food supply, the consumption of which is highly beneficial. One example of this is women taking folic acid during pregnancy to improve foetal neural tube development. Broad-spectrum micronutrients are nutritional supplements containing a range of about 15 vitamins and 15 minerals which is considered preferable over single-nutrient formulas as nutrients do not function in isolation (Long & Benton, 2013; Rucklidge et al., 2012).

There is now a large body of research that has investigated the effect of micronutrients[2] on a variety of symptoms associated with mental illness, which has formed the basis of the current Nutrients for Mental Health, Anxiety and Depression (NoMAD) study (Blampied et al., 2018). M. Blampied and colleagues' (2020) review found that broad spectrum nutritional supplements were generally effective for the treatment of clinically significant depression, stress and anxiety. For the purposes of this introduction, only the studies directly relevant to the question 'Do nutrient supplements improve post-traumatic stress symptoms?' will be reviewed below.

Broad spectrum/complex vitamin B supplementation has an established evidence base in reducing stress (Kennedy et al., 2010; Stough et al., 2011) and is potentially beneficial in preventing stress (Blampied et al., 2020). A review and meta-analysis of RCTs found B vitamin supplementation was beneficial for stress (n = 958, SMD[3] = 0.23, 95% CI[0.02, 0.45], p = 0.03), but not mood or anxiety in healthy and 'at-risk' participants (Young et al., 2019).

Rucklidge and colleagues' (2012) found broad-spectrum nutritional supplements reduced stress and anxiety, avoidance and arousal compared with a non-randomised control group in the months

[2] The broad-spectrum micronutrient formulae used in in previous trials have included products commercially available as EMPowerplus and Daily Essential Nutrients, which have varied somewhat overtime due to a division of the company and updating of blends.

[3] Standardised Mean Difference (SMD) was used to detect overall effect in the meta-analytic review (Young et al., 2019).

following the 2010 and 2011 earthquakes in Christchurch. This trial recruited people experiencing stress and anxiety within 3 months following the severe earthquake aftershock in 2011, and included randomised groups taking either vitamin B complex, or two different doses of a broader based vitamin and mineral (micronutrient) supplement for 28 days. At baseline, 60% of the sample were found to have probable PTSD based on their scores on the Impact of Event Scale-Revised (IES-R; Weiss and Marmer (1997) Creamer et al. (2003)). While this rate was lower in the control group than the treatment groups (44% vs 65%), at 4 weeks, 48% of the control group had probable PTSD compare with 19% of the treatment groups (Rucklidge et al., 2012).

A similar response pattern was found in a replication trial after a Canadian flood event (Kaplan et al., 2015), and for survivors of the Christchurch mosque massacre in 2019 (Rucklidge et al., in press). The mosque massacre data was obtained through offering broad-spectrum micronutrient supplements to survivors as a clinical service based on translational science principles (Rucklidge et al., in press) and demonstrated improvements in depression, anxiety and stress, global functioning and again supported the use of micronutrient support after a disaster to reduce the risk of developing PTSD (with the risk estimate based on initial acute trauma after the traumatic event). These studies all reported a large (d_{av} >1) ES on trauma, depression and anxiety scores (Rucklidge et al., in press). Interestingly, the three disasters/traumatic events, where micronutrients supplementation has been found to be effective differ slightly: the earthquakes were a series of traumatic events over many months; the flood event lasted several days; and the massacre was a brief but highly concentrated traumatic event.

Participants in the earthquake study were followed up 12 months later and it was found both the treated and control groups improved significantly, with those who were in the treatment groups initially showing better long-term outcomes on most of the measures. Interestingly those who stayed on the supplements reported better functioning than those who did not, including participants who went on to medications for their difficulties (Rucklidge, Blampied, et al., 2014). Participants involved in a micronutrient study for adults with Attention-Deficit/Hyperactivity Disorder at the time of the Canterbury earthquakes were also found to have improved resilience to stress compared with those not receiving the micronutrient formula (Rucklidge & Blampied, 2011), suggesting taking a nutritional supplement that includes a complex vitamin B formula is beneficial at times of acute stress.

Research into the use of micronutrients has also established a pattern of reduction in hyperactivity and impulsivity (Gordon et al., 2015), aggressive behaviours and mood dysregulation (Rucklidge et al., 2018), and that micronutrients improve insomnia, which often co-occurs with other health and mental health disorders, (Lothian, Blampied, & Rucklidge, 2016) particularly PTSD. The Blampied et al. (2020) review also noted that the positive findings from the studies reviewed may be related to the inclusion of minerals as well as vitamins in the formulae researched.

Micronutrient interventions have been found to have few side effects or adverse events (Rucklidge et al., 2019; Simpson et al., 2011), making them preferable over many pharmaceutical interventions, and may be more accessible than psychotherapies for some (Blampied et al., 2020). Micronutrients can interact with medications, and the studies reported previously have been conducted with participants not concurrently taking pharmaceutical treatment for mental health difficulties. Popper (2014) lists possible interactions, citing the role of vitamins and minerals in many neural processes where medications are also active, and reports interactions can occur when taking nutrient interventions and having used a medication in the past that is associated with discontinuation syndrome. Discontinuation syndrome is another term for what was previously described as withdrawal syndrome, often presenting as a rebound of symptoms or medication side effects when someone stops taking a psychiatric medication (Cosci & Chouinard, 2020). In another study, micronutrients were used as an adjunct to regularly prescribed medications for people experiencing psychotic disorders and found that after six months patients required lower doses of medication, and had fewer symptoms after 15 months of adjunctive treatment when compared to medication-only patients (Mehl-Madrona & Mainguy, 2017). Note, however, that while many people experiencing posttraumatic stress difficulties and/or functionally impairing anxiety and depression will likely take medications for their difficulties, the use of micronutrients as an adjunctive treatment is beyond the scope of this study, and all participants were required to be free from psychoactive medications for 4 weeks prior to starting the study.

Given the effectiveness of micronutrient formulations on post-traumatic stress symptoms in the months immediately following a traumatic event, and the established acceptability of the intervention, participants reporting experiencing trauma in the NoMAD trial provide an opportunity to

test the efficacy of a micronutrient intervention on pre-existing post-traumatic stress responses, building on the existing support for micronutrient supplementation for acute stress responses.

This study investigated the relationship between the reported experience of an historic potentially traumatic event and mental wellbeing for the NoMAD trial participants. Participants were recruited to the NoMAD trial for functionally impairing anxiety and/or depression, were randomised to receive either a micronutrient or placebo intervention. Because people experiencing anxiety and/or depression and posttraumatic stress have been found to be a difficult to treat group, the data analysis undertaken also sought to describe the characteristics of micronutrient intervention responders in order to guide treatment decision-making.

It was hypothesised that participants in the NoMAD trial who met criteria for PTSD, would have more severe anxiety and/depression, and a lower quality of life than those who did not. Given the participants in the NoMAD trial were recruited based on self-reported functionally impairing anxiety and/or depression, participants regarded as having clinically concerning level of post-traumatic stress symptoms were predicted to respond to treatment more slowly than those without the same level of symptoms. It was also hypothesised that reductions in PTSD symptoms would occur alongside reductions in depression and anxiety, and improvements in quality of life.

It was hypothesised that the participants receiving the micronutrient supplements during the RCT phase of the trial would report fewer PTSD symptoms at the end of RCT than at baseline, and this reduction in PTSD symptoms would continue into the open label phase of the trial. It was also hypothesised that participants would have fewer PTSD symptoms at the end of the open label phase after receiving the micronutrient supplement for 20 weeks.

The study also aimed to increase Māori participation in the NoMAD trial. Te Tiriti o Waitangi is a guiding document in health research and Crown research guidelines require research to be responsive to Māori (Kukutai, 2004; Reid et al., 2017). Māori make up around 16% of the national population meaning a sample size reflective of the population leaves Māori as a minority (Ministry of Health, 2019)[4]. Increasing Māori participation in research strengthens the Māori voice in research and provides equal explanatory power for Māori and non- Māori (Reid et al., 2017). He kairangahau ākonga

[4] In the Waitaha Canterbury rohe, Māori make up 9% of the Canterbury District Health Board population (Ministry of Health, 2019)

Māori ahau, I am a Māori research student and as a post-positivist empiricist, recognise that cultural values interact with the research process, and this must be considered in the research process and the understanding of research findings.

It was hypothesised that there would be a small increase in Māori participation in the NoMAD study from November 2019 when we increased engagement with Māori communities.

Method

Study Design

NoMAD trial is a randomised, double blind, parallel-group, placebo-controlled trial of a micronutrient supplement intervention for people experiencing functionally impairing symptoms of anxiety and/or depression. Participants were recruited through General Practitioner (GP) and online referral from the Waitaha Canterbury region of Aotearoa New Zealand. After initial screening, participants were randomised to either receive a micronutrient formula (Daily Essential Nutrients – DEN) or a placebo (see Appendix 1 Pill Ingredients). The micronutrient intervention and the matching placebo were donated by Hardy Nutritionals. The randomised controlled trial (RCT) phase continued for 10 weeks and was followed by an open label (OL) phase for a further 10 weeks. A naturalistic follow up occurred 12 months from baseline (Blampied et al., 2018).

The trial was prospectively registered under the Australian and New Zealand Clinical Trials Registry (ANZCTR). Trial Identification = ACTRN12617001647325. Universal Trial Number (UTN) = U111111994026. Ethics approval was granted through the New Zealand Heath and Disability Ethics Committee 17/STH/131 on 14 November 2017 and the University of Canterbury Human Ethics Committee: HEC2017/108/LR, on 27 November 2017 (Blampied et al., 2018).

NoMAD Trial Inclusion and exclusion criteria

Participants in the NoMAD trial were required to be between 18 and 65 years old and live in the Waitaha Canterbury region. Regular access to the internet was a requirement in order to complete questionnaires. Additionally, they were required to be deemed competent to adhere to the trial protocols, including the ingestion of up to 12 capsules per day, and have written and spoken English

proficiency. All participants must have been experiencing functionally impairing symptoms of anxiety and/or depression.

Participants were excluded from the trial if they had a neurological disorder, other major psychiatric conditions requiring hospitalisations, active suicidality or other serious medical conditions. Participants were excluded if they were known to be allergic to any ingredients in the intervention formulae, if they were pregnant or if they were breastfeeding. Participants were excluded if they were taking medications with central nervous system activation, including psychiatric medications. Participants were required to have not taken these medications for a minimum of 4 weeks and were not encouraged to cease medication use in order to participate in the trial. Participants were also asked about dietary supplements they were taking and were asked to cease taking these for the duration of the trial.

Inclusion in this analysis

Participants from the NoMAD trial who endorsed experiencing a traumatic event as one of two trauma stem questions at baseline were included in this research project. The question "Have you ever experienced, witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? (e.g., serious accident, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, hold-up, fire, discovering a body, unexpected death, war, natural disaster…)" reflects a DSM 5 criteria for a PTSD diagnosis for experiencing a traumatic event. The second question asked "In the past month, have you experienced symptoms related to this traumatic event, including nightmares, flashbacks of the event, intense memories of the event or have you been avoiding places that remind you of the event?". Endorsing either stem question in the online questionnaire diverted the participant to the Impact of Events Scale- Revised (IES-R).

As this is a naturalistic post-hoc analysis of an existing study recruiting participants for functionally impairing anxiety and/or depression, the two randomisation streams were not based on the experience of trauma or otherwise. Participants who had completed the RCT phase prior to 3 December 2020 had their data included in this analysis.

Participant Recruitment

Participant recruitment occurred from June 2018 to October 2020. GPs were provided with information about the trial through presentations, posted information and advertising through GP networks. The study was also advertised on Facebook and through presentations to community groups. As recommended by Reid and colleagues (2018), our research group seeks to extend and develop relationships with the Māori communities in our local rohe, and to develop the Māori health research workforce. From November 2019, we developed bilingual/bicultural advertising and study documents (see Appendix 3 Bicultural /Te Reo Māori Resources), which were disseminated through Māori student and health workforce groups, both online and kanohi ki kanohi, face to face. The researchers visited kaupapa Māori health providers to initiate relationships with the intention of establishing mutually beneficial relationships and to share information about current studies that might be of interest to their communities.

Screening

Participants identified by their GPs to be experiencing functionally impairing symptoms of anxiety and/or depression were referred via the study website https://mmp.net.nz (see Appendix 2). The study website GP portal detailed the inclusion and exclusion criteria and details of the study. The electronic referral form required the GP to check a box confirming the participant was not taking anti-depressant medication and that they had reviewed the study criteria with the participant. Once a referral was received, potential participants were called by the principal investigator (PI) for a screening call, where the PI explained the study, gained informed verbal consent and arranged to collect written consent (Blampied et al., 2018).

In response to the March 2020 COVID19 level 4 lockdown and increased burden on primary health providers in Waitaha Canterbury, a change to the referral process was approved by the New Zealand Heath and Disability Ethics Committee (HDEC) and was operational from May 2020. Under the new pathway, potential participants completed a self-referral form, gave consent to contact their GP and were directed to complete a series of questionnaires, previously completed at the beginning of the baseline phase of the trial. On receipt of their self-referral and questionnaires, the participants were contacted by the PI to review eligibility, explain the study and arrange written consent. If any

information gathered suggested the participants were ineligible for the study, this was discussed with study co-PI and study physician. No participants required this. Participants' GPs were contacted after this phone screening to both inform them of their participation in the study and to allow for the GP to withdraw them from the study at the GP's discretion.

Written informed consent was granted by all participants before entry into this study. When deemed clinically or culturally appropriate a face-to-face appointment was offered with the PI and/or a Māori clinical psychologist. All participant information and consent forms are found in Appendix 4 and Appendix 5. All participant information was securely stored either locked files or on double password-protected web-based data collection system or the password protected University of Canterbury computer system at all times. Only the PI had clinical contact with participants, and no participant details were shared with other researchers to protect anonymity.

Trial Procedures

After the receipt of their signed consent forms, participants were directed to the study website to create a unique log on and to complete baseline questionnaires. If any of their responses suggested they were not eligible for participation in the study this was discussed with the participant and was reviewed by the study supervisor and study physician. Both the intake questionnaires and the weekly progress monitoring questionnaires included a question monitoring risk. If a participant scored above a 2 on this scale, a pop-up box notification was set to be immediately delivered to the participant, instructing him/her to call their GP and giving information for crisis support services available. An automated email was also sent to the PI for further follow up within 24 hours. The protocol for this study outlined that participants who experience increased suicidality during the study would be considered on a case-by-case basis for their ongoing inclusion in the study.

Baseline Phase

Baseline questionnaires were completed at the start, mid-point and end of the two-week baseline phase. These questionnaires collected demographic information, history of the participant's depression and/or anxiety symptoms, treatment history, and expectations about the micronutrient intervention (see Appendix 6 Questionnaires). The primary measure of this present study, the Impact of Event Scale –Revised (IES-R), was only completed once at the start of baseline.

RCT phase

Randomisation

Participants were randomised to receive either a micronutrient formula DEN or the placebo. Randomisation was completed by a research assistant who had a purely administrative role and no participant contact. The randomisation sequence was arranged in permuted blocks of four using a programme based on the website randomization.com. The randomisation list was double coded and neither researchers nor participants had access to this. A pharmacist was sent the randomisation lists to prepare individual, identical, and sequentially numbered capsule kits which were then sent to individual participants by the research assistant. Individual sealed envelopes including individual randomisation conditions for each participant was securely stored to allow for unblinding of individual participants in the event of an emergency, but this action was never required.

The micronutrient and placebo capsules had no visible differences, and both products included riboflavin to ensure a change in urine colour occurred in both conditions. Micronutrient capsules have a strong odour, and both conditions had a vanilla sachet added to the capsule bottles to conceal any smell that might allow the participant to guess which condition they were in.

Treatment blinding was broken to allow for data analysis for this present study only as the NoMAD trial was not completed at that time. The PI remained blinded to treatment conditions and analysis outcomes and was not present in the lab as the data were analysed. The information shared with the researcher for this study only included participant ID numbers, demographics, outcome measure data and randomisation condition.

Intervention, titration, dosage

Upon completion of the baseline phase, participants were posted their capsules, as randomised. Clear titration instructions were provided to increase intake by three capsules per day every two days, starting at one capsule three times per day until a maximum dose of four capsules, three times per day (twelve capsules total each day) was achieved. Participants were supported by the PI if this titration needed to occur more slowly.

Open label

Upon completion of end of RCT data collection, participants were invited to participate in the OL phase of the trial for a further ten weeks. A re-titrating of capsules, identical to the protocol at the

start of RCT, was explained to participants. Participants were instructed to take a maximum of 12 micronutrient capsules per day.

Data Collection and Outcome Measures

During the NoMAD trial participants completed weekly questionnaires via their unique log on for the study website. At the start and end of baseline, end of RCT, end of OL and 12-month follow up all outcome measures were also administered, plus additional questions in Appendix 6 Questionnaires. Only data collected at baseline, and end of RCT and OL were included in this present analysis.

Participants were reminded by email, text message and/or phone calls to complete weekly questionnaires if they had not done so. If after 24 hours they had not completed the questionnaires another email was sent asking why they had stopped participating in the study and a variety of reasons were listed for selection. If their reason for stopping was related to adverse events or no response was given the participant was called by the PI for follow up.

Primary outcome measure

Impact of Event Scale- Revised (IES-R)

The IES-R (Weiss and Marmar (1997) in Creamer et.al. 2003) was administered as detailed above to participants in the NoMAD trial who endorsed either of the two stem questions at the start of baseline, end of RCT and end of OL phase. At baseline, participants were also prompted to provide a brief text description of the traumatic event they experienced.

The IES-R is a 22-item self-report measure that assesses subjective experiences of distress in relation to a self-identified traumatic event. The measure asks participants to indicate how distressed by the various difficulties listed in the questionnaire over the previous seven days. Items are rated on a five-point scale ranging from 0 (“not at all”) to 4 (“extremely”). The IES-R was developed to reflect the 3 aspects of the DSM criteria for PTSD and measures the general concept of traumatic stress as a two-factor structure of intrusion/hyperarousal and avoidance. It is a revised version of the 15-item, IES (Creamer et al., 2003; Sundin & Horowitz, 2018; Weiss, 2007). Internal consistency for the IES-R is reported as α =.95 (Creamer et al., 2003) and correlates well with other measures of PTSD, including the PTSD Check List (PCL). A total score cut off for probable PTSD of ≥33 has been suggested, and a score ≥24 is regarded as being of clinical concern (Creamer et al., 2003). The IES-R has three subscales –

"intrusion", "avoidance" and "hyperarousal", and subscale scores are calculated as mean score of the items in the scale (Weiss, 2004).

Secondary outcome measures

Clinical Global Impression – Improvement (CGI-I)

The Clinical Global Impression- Improvement (CGI-I; Guy (1976) Spearing et al. (1997)) is widely used in clinical trials to measure subjective change. It has been found to be associated with both patient-rated and psychometrically measured change (Leucht & Engel, 2006; Spearing et al., 1997; Zaider et al., 2003). Clinicians rate change in relation to the participants' outcome measures and comments made by the participant throughout the phases of the study. In this study the PI rated participants' clinical global improvements on a seven-point scale from 1("very much improved") to 7 ("very much worse") at the end of each phase of the trial (Spearing et al., 1997).

Depression Anxiety and Stress Scale (DASS 21)

The Depression Anxiety and Stress Scale (DASS 21; Lovibond and Lovibond (1995)) is a self-report questionnaire containing three 7-item scales measuring depression, anxiety and stress. Respondents rate statements using a 4-point scale of severity, with higher scores reflecting more severe experience of the items. It is well validated and has been used extensively in in community based research (Antony et al., 1998; Lovibond & Lovibond, 1995). The DASS 21 scores may be converted to DASS 42 equivalent scores by doubling each score, which has been found to have adequate construct validity and reliabilities. This allows for comparison with full DASS 42 scores, and the short considered more acceptable for participants (Henry & Crawford, 2005). Reliabilities were reported by Henry and Crawford as Cronbach's alpha (α); for the depression scale α = .88 (95% CI=.87–.89); for the anxiety scale, α =.82 (95% CI=.80–.83); for the stress scale, α = .90 (95% CI=.89–.91); and α =.93 (95% CI=.93–.94) for the Total scale. For the three subscales, cut off scores are routinely used. At least mild symptom levels are >9 for depression, >7 for anxiety, and >14 for stress; for moderate severity, these scores are >12, >9, and >18, respectively (see www.psy.unsw.edu.au/groups/dass).

Generalised Anxiety Disorder-7 Question Scale (GAD-7)

The Generalised Anxiety Disorder-7 Question Scale (GAD-7; Spitzer et al. (2006)) is a self-report questionnaire that measures the diagnostic criteria of Generalised Anxiety Disorder and is commonly

used to measure anxiety. The questionnaire consists of seven questions about the frequency of anxiety symptoms in the previous two weeks. Participants are asked to rate the frequency they experience from 0 (“not at all”) to 3 (“nearly every day”). A score above 10 on the GAD-7 is considered to indicate the presence of an anxiety disorder (Löwe et al., 2008). Internal consistency was reported as α =.89 (Löwe et al., 2008). It has also been found to be sensitive to change, and therefore a useful measure of treatment effectiveness (Hüsing et al., 2019).

Patient Health Questionairre-9 (PHQ-9)

The Patient Health Questionairre-9 (PHQ-9; Spitzer et al. (1999)) is a self-report questionnaire commonly used to screen for depression and to measure response to treatment (Cameron et al., 2008; Cameron et al., 2010). The PHQ-9 requires the participant to rate the frequency of nine symptoms of depression from 0 (“not at all”) to 3 (“nearly every day”). Internal consistency has been reported as α = 0.83 and 0.92 (baseline and end of treatment respectively) in a primary care study (Cameron et al., 2008). A meta-analysis suggested a cut of score of 12 provides reasonable specificity and sensitivity in clinical settings, however the cut off can vary based on the setting it is utilised in (Manea et al., 2012).

Quality of Life Scale (QOLS)

The Quality of Life Scale (QOLS; Flanagan (1982)) is a 16-item self-report questionnaire measuring five domains of quality of life - material and physical well-being, relationships with other people, social, community and civic activities, personal development and fulfilment, and recreation. Higher scores represent higher quality of life. Scores range from 16 to 112. The scale has been found to reliable and valid in measuring perceived quality of life for people with a range of chronic illness, has been validated in many cultures and is sensitive to change (Burckhardt & Anderson, 2003). The internal consistency was reported as α=.94 for a study of PTSD symptoms (Samuelson et al., 2017).

Demographics

At the start of baseline demographic information was collected (Appendix 6 Questionnaires) including gender, ethnicity, occupation, level of education, income, mental health difficulties and previous treatment. Participants could self-identify as multiple ethnicities and the data collection website utilised the New Zealand Department of Statistics question format (Stats NZ, 2020). Self-reported ethnicities were then grouped into ‘Pakeha/NZ European’, ‘NZ Māori’ (the indigenous people of Aotearoa New Zealand), people who identified as both ‘NZ Māori and Pakeha/NZ European’, and

'Other', which included those identifying as ethnicities such as Australian, Chinese, British or Latin American. Kukutai (2004) suggests recognising those who identify as being only Māori as a different group of people to those identifying as both Māori and another ethnicity, however in this study only one participant identified as solely Māori, and both groups have been combined. Ethnicity data was missing for 8 participants due to a website error.

Occupation data was collected and used to assign a New Zealand socio-economic index (NZSEI) (Fahy et al., 2017). Participants who reported being students, stay at home parents, or unemployed/sickness beneficiaries, or who did not report an occupation, were assigned a score based on 'occupational potential', based on age and highest education qualification (Fahy et.al., 2017, table A5). Participants who reported being retired were assigned an NZSEI score based on their previous employment if reported or their occupational potential. Four participants (two in each randomised group) did not provide sufficient demographic data to estimate this score and were excluded from the group NZSEI analysis.

Data Analysis

The clinical and demographic characteristics of the participants endorsing a past traumatic experience at baseline were compared to those of the participants who did not endorse a past traumatic experience, using Jamovi (version 1.2) (R Core Team, 2019; The Jamovi Project, 2020). Cohen's *d* Effect Sizes (ES)and their 95% Confidence Intervals (CIs), number of cases (*n*) mean scores and standard deviations (SD) were calculated for pre-to-post data using software provided by (Cumming, 2011). Conventional ES size guidelines of a small *d* = 0.2 to 0.5, a medium *d* – 0.5 to 0.8 and large *d* – 0.8 were used (Lakens, 2013). A second ES, the Percent Superiority (PS, also known as the Common Language ES) was also calculated using software provided by Lakens (2013). This provides the likelihood, expressed as a percentage, that any randomly selected participant will have a clinically improved score at the end of the RCT or OL phases compared with their baseline score (Lakens, 2013).

Modified Brinley plots (mBP) (Blampied, 2017) were constructed for IES-R and DASS data to show individual changes within groups, between baseline and end of RCT, and baseline and end of OL. These plots are a form of scatterplot with each participant's scores at two time periods plotted against

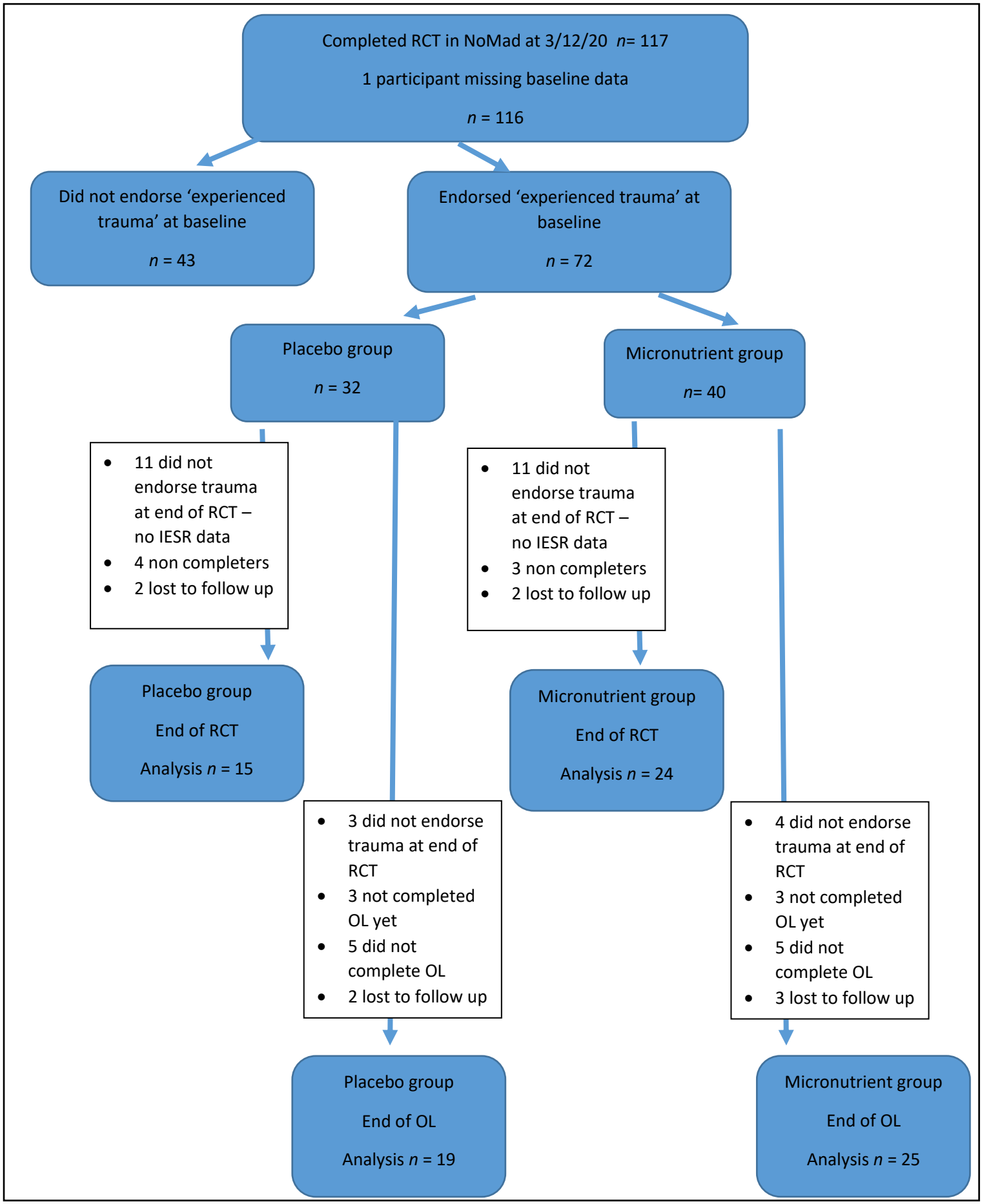
each other and show change over time with regard to clinical cut off and the Reliable Change Index (RCI).

All participants in this analysis had endorsed experiencing a traumatic event at baseline and completed the IES-R. Subsequent repeated administration of the IES-R was dependant on participants further endorsing the traumatic event or symptom item at each later time point in the trial. Twenty-two cases (eleven in each randomised group) did not endorse trauma at the end of the RCT phase and seven did not at the end of OL (three from the placebo group, 4 from the micronutrient group), resulting in them not having IES-R scores at one or both of these time points. This is outlined in the study flow diagram (**Figure 1**). As this analysis was conducted post-hoc, the missing data at the end of the phases resulted in fewer cases in each group than had a pre and a post treatment score. Initial analyses were conducted using only cases with paired pre- and post-treatment scores.

In an attempt to reduce the case attrition resulting from the lack of complete IES-R scores across time, the reasons for the non-endorsement of trauma at a later time point were considered based on interactions between the PI and the participant. Several reasons were identified that might have led to non-endorsement of trauma experiences. This could be a result of the participant considering their trauma resolved; avoidance of completing the questions due to their difficult nature or other unknown reasons. In order to increase the number of cases in each group, estimated scores were generated for those endorsing experiencing trauma at baseline, but not at another time point. An end of RCT and/or end of OL an IES-R score was assigned based on the participant's respective CGI-I at the same time point. An IES-R score of "0" (reflecting that their traumatic symptoms were resolved) was assigned if the CGI-I rated them as 'much improved' or 'very much improved' (a score of 2 or below). A score in the form of the last score carried forward was assigned at the later time points if the CGI-I rated them as 'minimally improved', 'not changed' or any category of worse (scores of 3 and above). For the RCT score estimation, this resulted in five participants in the placebo condition having "0" scores added in, and five in the micronutrient group. Four participants had a score carried forward in the placebo group, and five in the micronutrient group. Additionally, two participants in the placebo group were found to have a score at both baseline and end of open label. Based on their assigned CGI-I, an IES-R score was assigned that reflected their OL score based on their end of RCT CGI-I. A similar process was

Figure 1

Study Flow Diagram of Participant Inclusion in this Analysis



completed for the OL scores and three scores were carried forward in the placebo condition and four in the micronutrient group, along with one score being estimated as a "0".

The intervention was also evaluated by identifying treatment responders. Treatment response was calculated three ways. Firstly, the suggested IES-R cut off score of 33 for probable PTSD (Creamer et al., 2003) was used to identify participants who had scored above 33 at baseline, and who's scores had reduced to below 33 at end of RCT and/or OL. Treatment response was also considered by using a criterion of a 50% reduction in IES-R scores pre to post treatment, and in this analysis only those with baseline scores above 24, the suggested cut off for clinical concern, were included. This method is consistent with that used in trials of anti-depressant medications (Furukawa et al., 2016), and reflected criticism by Weiss (2004) of the use of cut off scores, especially in cases of historical exposure to a traumatic event. He suggests the use of the lower scores of 24. The third criteria for determining treatment response involved determining participants who had been rated as a 'much improved' or 'very much improved' (a score of 2 or below) on the CGI-I, which is also consistent with methods used in anti-depressant medication trials (Furikawa et al. 2016), and calculations included all trauma endorsing participants regardless of missing IES-R scores or completion status. In all these calculations, treatment non-completers were considered as non-responders.

Change scores were calculated by subtracting the end of phase (RCT or OL) score from the baseline score of the same measure. Percent change scores were then computed and are the change score as a percent of the original baseline score.

Independent sample t-tests, Chi-square tests of independence, ANOVA, ANCOVA and regression analysis were performed using Jamovi (version 1.2) software (Fox & Weisberg, 2020; Lenth, 2020; Meyer et al., 2017; R Core Team, 2019; The Jamovi Project, 2020). Statistical significance was determined as $p < .05$.

Results

Study Sample

This post-hoc analysis included participants recruited for the NoMad trial from June 2018 to 3 December 2020 who had completed the RCT phase of the trial. One hundred and seventeen participants had completed the RCT phase, seventy-two (62%) of whom reported having experienced a traumatic event at baseline. One participant did not complete baseline questionnaires due to an online

questionnaire error and was excluded from analysis. Participants were randomised upon entry to the trial, and of those who had experienced a traumatic event, 32 were randomised to receive placebo, and 40 to micronutrient treatment (see **Figure 1**).

Four participants (12%) of the placebo group dropped out before completing the 10-week RCT phase, which was a similar rate to the micronutrient group where 6 dropped out (15%). Reasons for non-completion included inability to swallow pills, increased symptom severity, using a medication that precluded participation and being lost to follow up. Three participants (9%) of the placebo group compared to one participant (2%) of the micronutrient group completed a shorter RCT phase prior to entering the OL phase by negotiation with the PI, and due to increased symptom severity or intolerance of the blinding to treatment condition. These differences were not found to be statistically significant in a Chi-square test of independence (X^2 (2, n = 72) = 1.63, p = .44).

Characteristics of Trauma-endorsing Participants

Of the 72 participants who reported having experienced a traumatic event in the baseline questionnaire anxiety as measured by the DASS was the only significantly different clinical characteristic between those who had experienced past trauma and those who had not (see **Table *1***). Participants with past trauma had higher anxiety scores than those who did not.

Presenting anxiety and depression symptom duration was reported at baseline as 1 = less than 12 months, 2 = 12 months to 2 years, 3 = 2 to 5 years or 4 = 5 or more years. The mean symptom duration for those reporting trauma was 3.61, and for those not reporting a traumatic event, 3.49, meaning both groups had an average duration of 2 to 5 years of symptoms which was not statistically significantly different (p = .463). Ninety-three percent of all participants, both those reporting past trauma and those not-endorsing past trauma had received treatment in the past for anxiety and/or depression. Sixteen percent of the trauma endorsing group reported having received successful treatment for their anxiety and/or depression in the past, compared with 3% of the group who did not report past trauma. Twenty-one percent of the trauma endorsing group and 22% of the non-endorsing group reported past treatment had not been successful and 63% of the trauma endorsing group reported partial treatment success, compared with 75% of the trauma non-endorsing group. There was no significant difference

Table 1

Clinical Characteristics of the Sample Comparing Participants Reporting a Past Traumatic Event and Those That Did Not at Baseline

Variable Mean (SD)	**Trauma** *n* = 72	**No trauma** *n* = 43	**Mean difference**	**Effect size Cohen's *d***	**95% Confidence Intervals**	***P* value**
DASS 21[1]						
Total	51.8 (24.9)	45.3 (17.8)	6.42	-0.299*	(-0.67, 0.1)	.108
Dep	19.6 (11.2)	18.8 (9.13)	.8	-0.08	(-0.45, 0.3)	.69
Anx	11.9 (8.84)	8.42 (6.07)	3.44	-0.43	(-0.82, -0.04)	.03
Stress	20.3 (9.02)	18 (7)	2.23	-0.27	(-0.65, 0.12)	.17
GAD 7	10.8 (5.93)	9.67 (4.15)	1.16	-0.217*	(-0.6, 0.17)	.227
PHQ 9	14.4 (5.33)	13.2 (5)	1.235	-0.237	(-0.62, 0.15)	.221
QOLS	69.6 (13.7)	70.1 (14.2)	1.46	0.097	(-0.37, 0.56)	.687

Note. * Welch's t used due to collinearity.
[1] DASS 21 scores converted to DASS 42 equivalent scores
Dep – DASS 21 depression subscale, Anx – DASS 21 anxiety subscale, Stress – DASS 21 stress subscale

between those reporting trauma and those not reporting trauma in the reported success of past treatment ($X^2(2, n = 88) = 3.48, p = .176$).

Ninety-three percent of all participants, both those reporting past trauma and those not-endorsing past trauma had received treatment in the past for anxiety and/or depression. Sixteen percent of the trauma endorsing group reported having received successful treatment for their anxiety and/or depression in the past, compared with 3% of the group who did not report past trauma. Twenty-one percent of the trauma endorsing group and 22% of the non-endorsing group reported past treatment had not been successful and 63% of the trauma endorsing group reported partial treatment success, compared with 75% of the trauma non-endorsing group. There was no significant difference between those reporting trauma and those not reporting trauma in the reported success of past treatment ($X^2(2, n = 88) = 3.48, p = .176$).

The types of trauma experienced by participants is summarised in **Table *2***. Participants disclosing earthquakes, bushfires and terror attacks were grouped as 'disaster'. 'Witnessing traumatic

event' included witnessing medical events, accidents, assaults and work-related exposure. 'Loss' included death of loved ones through suicide, accident and still-birth; and 'assault' included physical and sexual assaults. 'Relationship abuse' was separated from other forms of assault due to its ongoing nature, as was the grouping of 'childhood abuse'. Of the participants who disclosed their traumatic event, 20 (28%) reported experiencing an additional traumatic event or events. When more than one traumatic event was disclosed, the most serious or earliest (for example childhood abuse) event was included in the table below. Nine of those reporting more than one traumatic event endorsed experiencing childhood abuse, of whom, 56% reported later traumatic events.

Table 2

Type of Traumatic Experience Disclosed by Trauma Endorsing Participants

Trauma type	*n*	% of trauma sample
Disaster	17	24%
Childhood abuse	16	22%
Witnessing traumatic event	8	11%
Loss	4	6%
Relationship abuse	4	6%
Assault	4	6%
Accident	3	4%
Medical event	1	1%
Not described	15	21%
Total	72	

Trauma type was grouped further as a likely single event trauma, including disaster, witnessing a traumatic event, loss, assault, accident, and medical event, or as a likely ongoing series of traumatic events, which included childhood abuse and relationship abuse. An independent samples t-test was conducted to explore the impact of the type of trauma that was reported (and treated as the primary trauma in this analysis) on the IES-R scores. IES-R scores were found to differ significantly based on type of trauma with those reporting a likely ongoing series of traumatic events having a mean IES-R score of 37.6 (SD = 20.1) compared with those reporting what was likely a single one off type of trauma having a mean IES-R score of 18.7 (SD = 18.4), $t(53) = -3.55$, $p = <.001$. This is presented in Figure 2.

Pearson product-moment correlation coefficients were computed to investigate the relationship between baseline IES-R scores and baseline secondary outcome measures for those endorsing trauma, see Table 3. Baseline IES-R scores were found to be positively moderately correlated

with baseline DASS anxiety and stress subscale scores and the total DASS score. There were moderate correlations between the DASS depression subscale, GAD-7 and the PHQ-9. There was a small but non-significant negative correlation between the IES-R and QOLS.

Figure 2

Baseline IES-R Score, Grouped by Recurring or Single Event Trauma Exposure

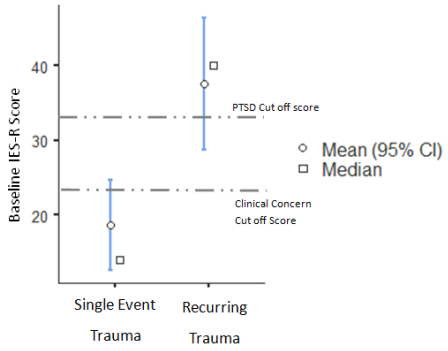


Table 3

*Correlations (Pearson's r) for Baseline Variables (Statistically Significant Values in **Bold**)*

	IES-R	DASS Depression	DASS Anxiety	DASS Stress	DASS total	GAD-7	PHQ-9	QOLS
IES-R	—							
DASS Depression	**0.353**	—						
DASS Anxiety	**0.658**	**0.458**	—					
DASS Stress	**0.513**	**0.677**	**0.693**	—				
DASS total	**0.577**	**0.855**	**0.810**	**0.911**	—			
GAD-7	**0.415**	**0.441**	**0.661**	**0.756**	**0.705**	—		
PHQ-9	**0.369**	**0.658**	**0.541**	**0.642**	**0.719**	**0.679**	—	
QOLS	-0.054	**-0.520**	-0.155	**-0.286**	**-0.390**	-0.123	**-0.297**	—

Randomised Groups Characteristics

Baseline demographic information is shown in **Table *4*** and the two treatment conditions were comparable. Both treatment conditions in the trauma sample had similar percentages of Pakeha / NZ European participants; however, differed in the composition of Māori and other groupings, largely due to people identifying as being from outside of Aotearoa New Zealand.

A research objective for this study was to increase the recruitment of Māori participants. Ten percent of the entire sample (from June 2018 including those who had completed RCT by 3 December 2020) identified as Māori. The rate was the same before and after increased efforts to engage with Māori communities started in December 2019.

A Chi-square test of independence showed the two treatment condition groups varied on past treatment success *(X^2 (2,* n *= 88) = 8.42,* p *= .02).* Eleven percent of both the placebo and micronutrient condition groups reported past successful treatment of their anxiety and/or depression. Thirty-four percent of the placebo group reported past treatment was not successful and 54% reported partially successful past treatment, compared with 9% of the micronutrient group reporting unsuccessful past treatment, and 79% reporting partially successful past treatment.

Forty-one percent of the placebo group, and 45% of the micronutrient group reported ever having been prescribed psychiatric medications for their mental wellbeing. This included sleeping pills, anxiolytics and anti-depressants but not supplements or herbal treatments. Fifty percent of the placebo group reported having engaged in some kind of psychotherapy, compared with 37% of the micronutrient group. Chi-square tests of independence showed the groups did not differ significantly in either type of previous treatment experience. A Chi-square test of independence found the two treatment groups were similar in the types of trauma endorsed by participants (X^2 (8, n =72) = 10.0, p = .26). Twenty-five percent of the micronutrient group did not report the nature of their past traumatic event, compared with 16% of the placebo group. Of note is that 27% of the micronutrient group reported past childhood abuse compared to 16% of the placebo group, and 37% of the micronutrient group reported more than one traumatic event, compared with 26% of the placebo group. This difference was not statistically significant - X^2 (1, n =62) = .88, p = .35.

Table 4

Baseline Demographics and Clinical Characteristics of Both Treatment Groups

Characteristics	Placebo *n* = 32	Micronutrient *n* = 40	Total sample *n* = 72
Age, years : mean (SD)	39.16 (14.10)	39.13 (11.29)	39.0 (12.5)
Gender : *n* (%)			
Female	24 (75%)	30 (75%)	54 (75%)
Male	8 (25%)	10 (25%)	18 (25%)
Ethnicity : *n* (%)			
Pakeha/NZ European	23 (72%)	28 (70%)	51 (79%)
NZ Māori	4 (12%)	2 (5%)	6 (8%)
Other	4 (12%)	9 (22%)	14 (19%)
Unknown	1 (3%)	2 (5%)	1 (1%)
Household Income : *n* (%)	*n* = 29	*n* = 37	*n* = 66
less than $20,000	6 (21%)	5 (14%)	11 (17%)
From $20,000 to $40,000	4 (14%)	7 (19%)	11 (17%)
From $40,000 to $60,000	6 (21%)	3 (8%)	9 (14%)
From $60,000 to $80,000	5 (17%)	9 (24%)	14 (21%)
above $80,000	8 (28%)	13 (35%)	21 (32%)
NZSEI score*	*n* = 30	*n* = 38	*n* = 68
	56.4 (17.1)	56.7 (12.1)	56.6 (14.4)
	Range: 26-90	Range: 34-88	

Note. *New Zealand socio-economic index (NZSEI) (Fahy et al., 2017)

The two treatment condition groups did not differ in their expectations of the micronutrient intervention regarding their anxiety, depression or general wellbeing. The IES-R, DASS 42, GAD 7, PHQ 9 and QOLS scores did not differ significantly between the two groups at baseline

Primary Outcome Measure Analysis

Baseline to End of RCT phase

Within-subject Cohen's *d* ES for the IES-R for all participants reporting a baseline and end of RCT score were computed separately for the two treatment conditions. As shown in **Table 5**, there was a small ES (*d* = -0.38) for the micronutrient group compared to a medium ES (-0.62) for the placebo group, both in the direction of reduced IES-R scores from baseline to the end of RCT. The mean difference of the IES-R change scores between the two groups was 2.13[5], with the placebo group showing a larger mean change score; however, a Tukey post-hoc test revealed there was not a statistically significant difference between the two treatment groups IES-R change scores, (f(1)=0.172, p_{tukey} = .68). The between groups Cohen's *d* ES was 0.14 (95% CIs -0.53, 0.8).

Subscale analysis revealed there was a large ES in the placebo condition on reducing intrusions, and a medium ES reducing hypervigilance scores. The micronutrient group showed small effect size reductions in both these subscales. Both treatment conditions showed a trend towards a reduction in avoidance scores over time; however, this was not statistically significant.

The treatment conditions were further evaluated based on treatment response rates, computed as described previously. At the end of RCT, 45% of the placebo group who met criteria for probable PTSD were considered responders compared with 33% of the micronutrient group. A Chi-square test of independence showed there was not a significant relationship between treatment condition and responder status, $X^2(1, n = 24) = .548$, $p = .459$.

Treatment response determined by a 50% reduction in symptoms for those deemed of clinical concern showed a 29% response rate for the placebo group, and a 25% responder rate for the micronutrient group. When estimated IES-R scores for end of baseline (used when data were missing) were used, this increased the total number of participants included in the analysis to 24; however, the number of responders were equivalent in each group and there was no significant difference. Participants were also classified by their CGI-I score from baseline to end of RCT as responders and non-responders. Again, the two treatment conditions did not differ significantly by CGI-I responder status:

[5] Comparisons were based on estimated marginal means (Lenth, 2020)

53% of the placebo group and 42% of the micronutrient group were considered responders. X^2 (1, n = 72) = 0.86, p = .354. The CGI-I scores were compared for the two treatment conditions at the end of RCT and are displayed in **Figure *3***.

Open label phase

At the end of the OL phase, the micronutrient group had been exposed to the micronutrient treatment for 20 weeks (except for one participant completing only 15 weeks due to switching to OL early). In contrast, the placebo group had 10 weeks exposure to the micronutrient formula. Three participants had switched from the RCT placebo condition early to OL (at four, six and eight weeks of RCT). **Table *6*** shows the change in IES-R scores from baseline to the end of open label (OL) for participants who had both a baseline and end of OL IES-R score. The ES for total IES-R score shows that the placebo group had a similar small reduction in IES-R score to the micronutrient group at the end of RCT, and the medium ES demonstrated at the end of RCT for the placebo group had reduced in magnitude. While the micronutrient group ES remained small, it had increased and was similar to the placebo group response at the end of OL. Of note also is the IES-R total score at baseline for the data pairs included in the OL analysis. The micronutrient group had a mean baseline IES-R score of 30.4 (SD = 23.6) compared to a score of 19.3 (SD = 16.6) for the placebo group. An independent samples t-test was conducted and this difference was not statistically significant, $t(42) = -1.76$, p = .085. Subscale analysis shows both treatment conditions, although exposed to micronutrients for a different length of time, experienced similar but small reductions in each of the IES-R subscales during the OL phase.

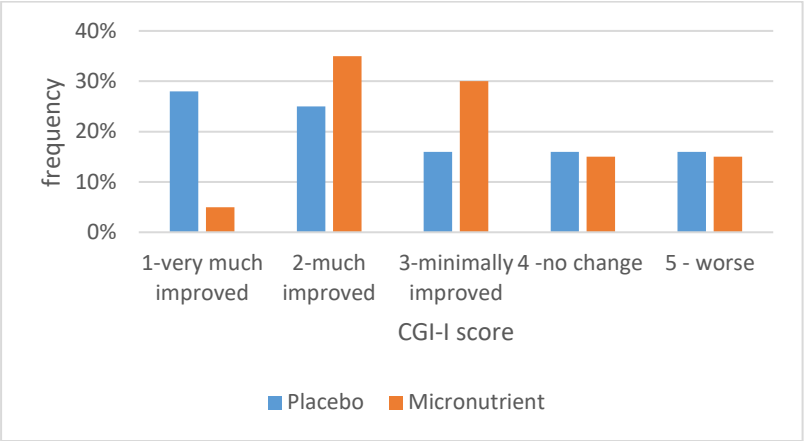
The mean difference of the IES-R change scores between the two groups was 3.41[6], with the micronutrient group showing a larger mean reduction in change score; however, a Tukey post-hoc test revealed there was not a statistically significant difference between the two treatment groups IES-R change scores, (f(1)=0.759, p_{tukey} = .389). The between groups Cohen's *d* ES was 0.27 (95% CIs -0.35, 0.88).

[6] Comparisons were based on estimated marginal means (Lenth, 2020)

Just one of the seven (14%) participants who met criteria for probable PTSD in the placebo group were considered responders at the end of OL compared with six of the 15 (40%) who met criteria for probable PTSD in the micronutrient group. A Chi-square test of independence showed there was not a significant relationship between treatment condition and responder status, $X^2(1, n = 19) = .83$, $p = .363$.

Figure 3

CGI-I Score Frequency by Treatment Group – Baseline to End of RCT



Thirty-one percent of the micronutrient group were deemed OL responders as determined by a 50% reduction in symptoms for those deemed of clinical concern, compared with 22% of the placebo group. A chi-square test of independence was performed and the relationship between treatment group and treatment response was not significant, X^2 (1, $n = 23$) = 0.17, $p = .679$. Again, when OL IES-R estimated scores were utilised to replace missing data, the Chi-square test was not significant, X^2 (1, $n = 23$) = 0.209, $p = .648$.

Participants were also classified by their CGI-I score from baseline to end of OL phase as responders and non-responders. Seventy percent of the placebo group were considered responders by the end of OL, while 53% of the micronutrient group were. A Chi-square test of independence found the groups did not differ significantly, X^2 (1, $n = 54$) = 1.22, $p = .269$. See **Figure *4*** .

Table 5

IES-R Baseline to End of RCT Means, Standard Deviations (SD) and Effect Sizes (ES) for Paired Data by Group

Variable	Intervention	Baseline	End of RCT	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
IES-R total	Placebo	25.1	14.7	-1.09	-0.14	**-0.62**	77%
	(*n*=15)	(18.0)	(15.5)				
	Micronutrient	30.8	22.4	-0.7	-0.55	**-0.38**	69%
	(*n*=24)	(22.9)	(21.2)				
Intrusions	Placebo	1.28	.61	-1.3	-.25	**-0.79**	81%
	(*n*=15)	(.93)	(.77)				
	Micronutrient	1.38	.94	-.75	-.90	**-.042**	71%
	(*n*=24)	(1.11)	(.94)				
Avoidance	Placebo	1.0	.74	-.7	.03	-.34	69%
	(*n*=15)	(.75)	(.79)				
	Micronutrient	1.4	1.1	-.63	.09	-.27	63%
	(*n*=24)	(.98)	(1.06)				
Hypervigilance	Placebo	1.13	.64	-1.02	-0.01	**-.52**	71%
	(*n*=15)	(1.02)	(.83)				
	Micronutrient	1.44	1.0	-.72	-.05	**-.39**	63%
	(*n*=24)	(1.8)	(1.02)				

Note. The IESR-R subscales are mean scores of items in each scale (Weiss, 2004).

PS or Common Language ES is the likelihood a randomly selected case will have an improved (reduced) score at end of the treatment phase compared to their baseline score (Lakens, 2013)

Table 6

IES-R Means, Standard Deviations (SD) and Effect Sizes (ES), Baseline to OL Paired Data by Group

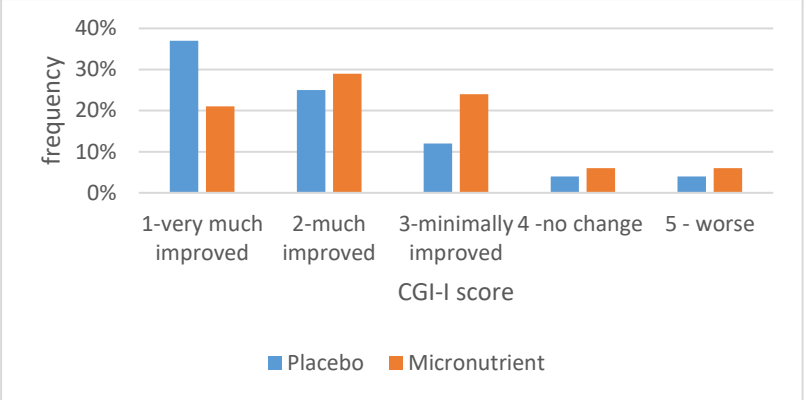
Variable	Intervention	Baseline	End of OL	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
IES-R total	Placebo	19.3	12.6	-0.7	-0.11	**-0.41**	53%
	(*n*=19)	(16.6)	(23.6)				
	Micronutrient	30.4	20.4	-0.75	-0.16	**-0.46**	75%
	(*n*=25)	(23.6)	(20.1)				
Intrusions	Placebo	1.03	0.55	-0.88	-0.19	**-0.54**	79%
	(*n*=19)	(0.93)	(0.86)				
	Micronutrient	1.34	0.91	-0.72	-0.1	**-0.41**	72%
	(*n*=25)	(1.09)	(0.98)				
Avoidance	Placebo	0.76	0.63	-0.61	0.23	-0.19	58%
	(*n*=19)	(0.65)	(0.69)				
	Micronutrient	1.4	1	-0.7	-0.08	**-0.4**	70%
	(*n*=25)	(1.08)	(0.93)				
Hypervigilance	Placebo	0.81	0.54	-0.56	-0.1	**-0.34**	77%
	(*n*=19)	0(.89)	(0.76)				
	Micronutrient	1.5	0.88	-0.89	-0.17	**-0.54**	76%
	(*n*=25)	(1.19)	(1.01)				

Note. The IESR-R subscales are mean scores of items in each scale (Weiss, 2004).

PS or Common Language ES is the likelihood a randomly selected case will have an improved (reduced) score at end of the treatment phase compared to their baseline score (Lakens, 2013)

Figure 4

CGI-I Score Frequency by Treatment Group – Baseline to End of OL

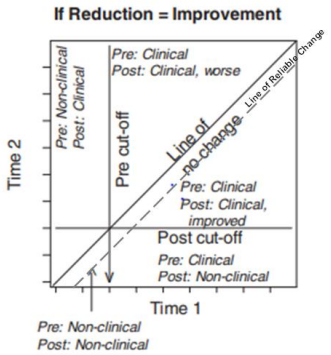


Modified Brinley Plot Analysis of IES-R Change

As discussed previously, mBPs (Blampied, 2017) were constructed to explore IES-R scores at an individual level across the phases of the trial. Interpretation of the plots is described in **Figure *5***.

Figure 5

Illustration of the Conventions for Interpreting mBPs When Clinical Improvement is Reduction in Score.

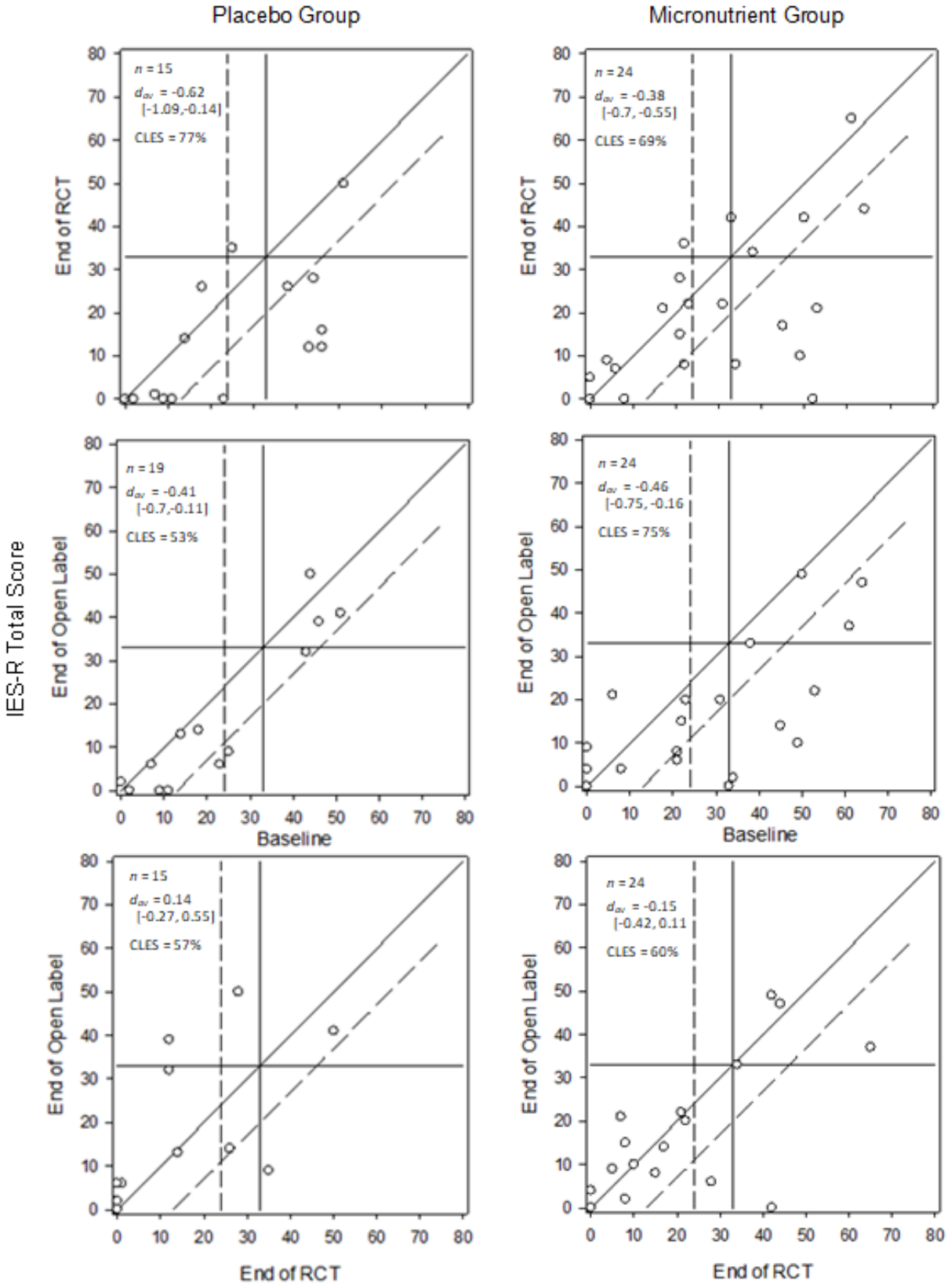


Note. The solid diagonal line represents the line of no change from time 1 to time 2; data points close to this line demonstrate little or no change. The dashed diagonal line, parallel to the line of no change, the line of reliable change denotes the lower bound of the RCI. Vertical and Horizontal lines denote clinical cut offs for the measure. The zones on the graph formed by the clinical cut off lines represent clinical status pre and post phase, as indicated on the figure (Blampied, 2017).

Plots are presented in **Figure *6***in three sets for each treatment condition comparing baseline scores to end of RCT and OL phases, and also comparing end of RCT to OL phase. Importantly, due to the inconsistent endorsement of trauma and lack of IES-R data at all time-points, individual cases plotted in each phase vary. Both treatment groups show movement of those with scores above the two

Figure 6

Modified Brinley Plots Showing IES-R total score comparisons by phase for both treatment groups.



clinical cut offs towards less clinically concerning IES-R scores, as demonstrated by individual data points that fall in the bottom right-hand corner of the plot. The end of OL compared to baseline plots show the placebo group is somewhat separated into a treatment non-response cluster, and a cluster of cases that had lower scores and remained low. The micronutrient group plots show at the end of OL some cases remained above the PTSD cut off, some demonstrated clinical improvement, and others started in the low range and remained there. The end of RCT to end of OL plots show a cluster of cases in the micronutrient group that started the phase with scores below cut offs, and remained there, four cases that had very little change during OL and one that demonstrated considerable clinical improvement. In comparison, the placebo group, who were first exposed to the micronutrient intervention during this phase, generally showed little change, some increase in symptoms and only one case demonstrated clinical improvement.

Secondary Outcome Measures Analysis

Baseline to End of RCT Phase

Cohen's *d* ES and PS ES were calculated for secondary outcome measures from baseline to end of RCT for cases with IES-R scores at both time-points and is shown in **Table 7**. Additional calculations are provided for the full sample in Appendix 6, **Table 9**.

Both treatment conditions demonstrated large effect sizes in reducing DASS, GAD-7 and PHQ-9 score. The micronutrient group showed a larger ES reduction in total DASS score; however, the placebo group had a larger percent likelihood of having a lower DASS scores at the end of RCT than at baseline. DASS subscale scores by group over the RCT and OL phases are presented as mBPS (***Figure 7***) and demonstrated the similarities between both treatment conditions in the RCT phase. The placebo group demonstrated greater reduction in the DASS depression subscale and a much larger ES for PHQ-9 reduction, and a 97% chance a participant scored lower at end of RCT compared with baseline. Both treatment groups had similar reductions in the DASS anxiety subscale and the GAD-7, and the micronutrient treatment group had a larger ES on reducing DASS stress subscale scores, although similar percent superiority to the placebo group. Both treatment conditions produced small non-significant ES improvements in QOLS scores.

Table 7

Baseline to End of RCT Phase Effect Sizes (ES) for Secondary Outcome Variables by Treatment Group for Cases with IES-R Scores

Variable	Intervention	Baseline	End of RCT	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
DASS-42	Placebo (*n*=15)	49.7 (27.03)	28.27 (26.32)	-1.27	-.28	**-0.78**	84%
	Micronutrient (*n*=24)	55.58 (21.31)	36 (24.48)	-1.33	-.36	**-0.85**	79%
Dep	Placebo (*n*=15)	19.87 (10.65)	11.87 (10.41)	-1.29	-.22	**-0.76**	80%
	Micronutrient (*n*=24)	21.17 (11.33)	14.17 (11.93)	-1.06	-.13	**-0.60**	72%
Anx	Placebo (*n*=15)	10.4 (9.51)	5.47 (8.09)	-1.0	-.1	**-0.56**	76%
	Micronutrient (*n*=24)	12.83 (8.66)	8.17 (7.53)	-1.04	-.1	**-0.58**	70%
Stress	Placebo (*n*=15)	18.8 (10.3)	10.93 (9.79)	-1.36	-.18	**-0.78**	78%
	Micronutrient (*n*=24)	21.58 (7.66)	13.67 (8.01)	-1.5	-.46	**-1.01**	81%
GAD 7	Placebo (*n*=15)	8.93 (5.64)	3.8 (4.84)	-1.58	-0.35	**-0.98**	84%
	Micronutrient (*n*=24)	11.75 (6.19)	6.46 (5.58)	-1.36	-0.42	**-0.9**	82%
PHQ 9	Placebo (*n*=15)	14.8 (5.66)	5.07 (4.43)	-2.77	-1.03	**-1.92**	97%
	Micronutrient (*n*=24)	14.29 (4.93)	8.42 (5.35)	-1.66	-0.62	**-1.14**	87%
QOLS	Placebo (*n*=15)	70.13 (15.37)	73.07 (13.63)	-0.15	0.55	0.2	62%
	Micronutrient (*n*=23)	68.91 (14.41)	72.48 (16.27)	-0.13	0.59	0.23	60%

Note. PS or Common Language ES is the likelihood a randomly selected case will have an improved (reduced) score at end of the treatment phase compared to their baseline score (Lakens, 2013).
DASS 21 scores converted to DASS 42 equivalent scores.
Dep – DASS 21 depression subscale, Anx – DASS 21 anxiety subscale, Stress – DASS 21 stress subscale

Baseline to End of Open Label Phase

Cohen's *d* ES and PS ES were calculated to compare treatment conditions from baseline to the end of OL and are shown in Table 8. As discussed above, at the end of OL, the placebo group had been receiving micronutrients for 10 weeks, and the micronutrient group had been receiving micronutrients for 20 weeks. The micronutrient group demonstrated a larger ES for the total DASS, but lower PS at the end of OL, which was the same pattern as at the end of RCT. MBPs including both the RCT and OL phases DASS subscale scores visually demonstrate the similar patterns in treatment response for the two treatment conditions over time, see **Figure 7**. Again, the placebo group had a larger effect size reduction on the depression subscale and both groups demonstrated a large ES for reductions on the PHQ-9. The placebo group had a smaller ES reduction in PHQ-9 at the end of OL than at the end of RCT. The groups were again similar on changes in the DASS anxiety scores and the GAD-7.

The micronutrient group showed a large effect size in reduction of stress on the DASS, compared with a medium effect size for reduction in stress for the placebo group, which was a similar pattern at the end of RCT. Both groups showed a small effect size in QOLS score improvement; however, only the micronutrient group ES had a CI that did not include zero change and thus significantly different from zero.

Pearson correlation results showed baseline to end of RCT IES-R change scores were positively correlated with DASS change scores ($r(45) = .526$, $p < .001$). The correlation was larger ($r(19) = .684$, $p = .001$) for the placebo group, and was not significant for the micronutrient group ($r(26) = .37$, $p = .063$). At the end of the OL phase the IES-R change score had a medium positive correlation with the DASS change score ($r(44) = .301$, $p = .047$), and no significant correlation for the placebo condition ($r(19) = .205$, $p = .401$) or the micronutrient condition ($r(25) = .322$, $p = .117$).

Table 8

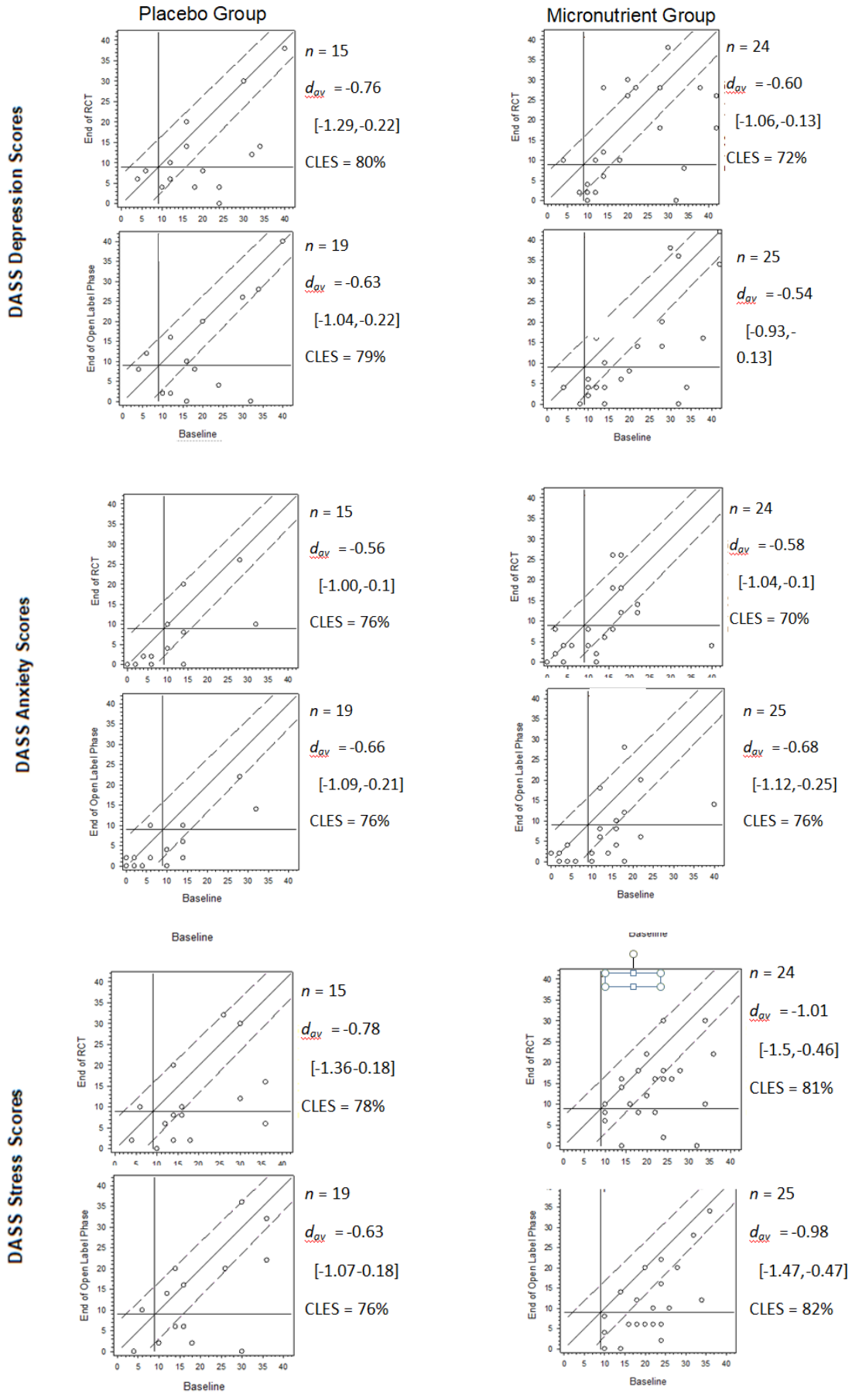
Baseline to End of OL Phase Effect Sizes Secondary Outcome Variables by Treatment Group

Variable	Intervention	Baseline	End of OL	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
DASS-42	Placebo (n=19)	45.16 (24.21)	28.32 (22.45)	-1.12	-.31	**-0.72**	84%
	Micronutrient (n=25)	55.36 (23.87)	34.56 (25.18)	-1.31	-.38	**-0.85**	80%
Dep	Placebo (n=19)	18.11 (19.83)	11.68 (10.61)	-1.04	-0.22	**-0.63**	79%
	Micronutrient (n=25)	20.72 (11.7)	14.32 (12.13)	-0.93	-0.13	**-0.54**	71%
Anx	Placebo (n=19)	9.37 (9.09)	4.32 (5.97)	-1.09	-.21	**-0.66**	78%
	Micronutrient (n=25)	12.4 (8.94)	6.8 (7.26)	-1.12	-.25	**-0.68**	76%
Stress	Placebo (n=19)	17.68 (8.41)	12.32 (8.62)	-1.07	-.18	**-0.63**	76%
	Micronutrient (n=25)	22.24 (7.94)	13.44 (9.93)	-1.47	-.47	**-0.98**	82%
GAD 7	Placebo (n=19)	9.63 (6.3)	4.32 (4.22)	-1.64	-0.33	**-0.99**	78%
	Micronutrient (n=25)	11.96 (6.46)	6 (5.84)	-1.46	-0.46	**-0.97**	82%
PHQ 9	Placebo (n=19)	13.11 (5.18)	6.42 (5.85)	-1.71	-0.69	**-1.20**	95%
	Micronutrient (n=25)	14.76 (5.1)	8.16 (6.07)	-1.7	-0.64	**-1.18**	87%
QOLS	Placebo (n=18)	72.06 (14.56)	75.78 (16.5)	-0.02	0.5	0.24	67%
	Micronutrient (n=25)	67.88 (14.3)	73.12 (15.51)	0.06	0.64	**0.35**	69%

Note. PS or Common Language ES is the likelihood a randomly selected case will have an improved (reduced) score at end of the treatment phase compared to their baseline score (Lakens, 2013).
DASS 21 scores converted to DASS 42 equivalent scores.
Dep – DASS 21 depression subscale, Anx – DASS 21 anxiety subscale, Stress – DASS 21 stress subscale

Figure 7

Modified Brinley Plots Displaying DASS Subscale Scores by Treatment Group Across Treatment Phases



Predictors of Treatment Response

As response to treatment during the RCT phase did not consistently differ on average between conditions, univariate analyses of change scores on the IES-R (for those above the clinical concern cut off for the IES-R at baseline) and CGI-I from baseline to end of RCT were undertaken, using appropriate *t*-tests, Chi-square and correlation coefficients. The predictors considered were: gender, ethnicity, age, NZSEI score, IES-R baseline score, history of psychotropic medication use, history of psychotherapy, symptom duration, trauma type (as defined in **Table *2***), reporting of more than one traumatic event, and the broader trauma grouping of single of recurring types of trauma previously discussed. Additionally, potential predictors that related to the participants' participation in the trial were also analysed, including their expectations about nutrients effectiveness for anxiety, mood and wellbeing, which condition they believed they were randomised to when asked at the end of RCT and the level of PI contact (as rated by the PI) throughout the RCT phase. Detailed results are shown in **Table 11**, in Appendix 6.

A reported history of previous psychotropic medications was found to be a significant predictor of treatment response for those who were regarded as of clinical concern based on their IES-R baseline scores, with those who did not report previous medication use having a mean change score of 28.1 (SD =12.7) compared with a mean change score of 3.25 (SD = 13.9) for those who reported past medication use, t(15) = 3.85, p = .002; and the ES (Cohen's d) was 1.87 (95% CI .531,3.15) and d = 1,87 (95%CI .531, 3.15) for those for reporting no prior psychotropic medication as a treatment response predictor regardless of experimental group assignment.

The univariate analysis also identified that participants guessing they were taking the active intervention (the micronutrient), was associated with IES-R change scores for those considered to be of clinical concern. People who guessed they were in the micronutrient condition had a mean change score of 25.5 (SD = 16.8) and those guessing they were in the placebo condition had a mean change score of 8.13 (SD = 13.8). Treatment condition guess success rate was evaluated in a chi-square test of independence and guesses by participants were not accurate, X^2 (1, n = 62) = 0.17, p = .68.

The level of PI contact throughout the RCT phase was identified as being associated with CGI-I response status. Level of contact during the RCT was rated by the PI from 1 being minimal to 7 being

maximum. For the 18 participants who had baseline IES-R scores above 24, the mean level of contact scores for responders was 1.63 (SD = 1.06), compared with 2.91 (SD=1.38) for non-responders, showing non-responders had more contact with the PI. This was a significant difference t(17) = 2.20, p = .042.

Exploratory Analysis of Previous Medication as a Predictor of Treatment Response

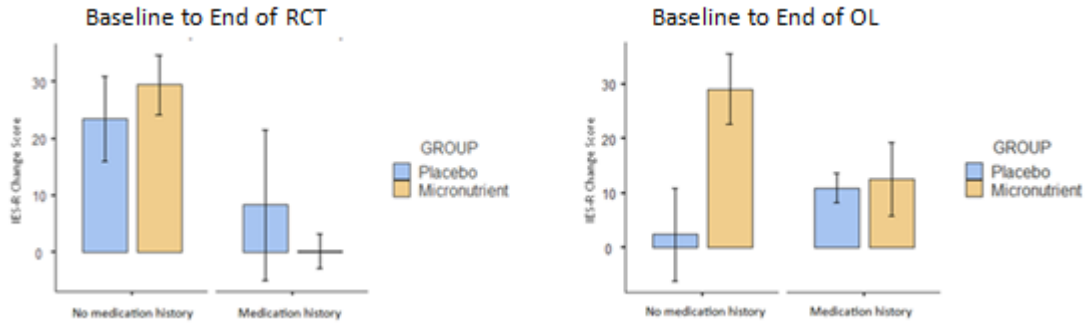
Exploratory analysis of the interaction of previous medication history and treatment condition was conducted using ANCOVA. This analysis included a small sample of participants, 12 in the micronutrient condition and five in the placebo condition who were above the clinical concern cut off at baseline and had been asked about their previous medication history, and therefore does not include those under the IES-R clinical concern score (24) cut off, and who did not provide detail about their past medication use. The ANCOVA revealed non-significant results, likely due to the very small sample size, however this does suggest some interaction between past medications and micronutrient intervention. This is graphed in ***Figure* 8** and demonstrates the differences between the two treatment conditions based on the participants previous medication use. The ES of past medication on the micronutrient group change in IES-R score was *d* = 2.12 (0.57, 3.67), less change; and for the placebo group, the ES of past medication was *d* = 1.1 (-0.93, 3.13), again less change. An ANCOVA was conducted to analyse the interaction between past medication use and treatment group based on the end of OL IES-R change score on the IES-R at the end of OL phase relative to baseline, for participants regarded as being of clinical concern at baseline. The micronutrient group (as noted previously, had 20 weeks exposure at the end of OL) showed larger change scores than the placebo group (who had had 10 weeks exposure to micronutrients by end of OL) when neither sets of participants had been medicated. The micronutrient group had smaller change scores if they had a reported history of psychotropic medication use; however, their improvement was larger than at the end of RCT, and comparable to the placebo group at the end of RCT.

The pattern of reduced treatment response for trauma symptoms is further demonstrated in **Figure 9**. Here the mBPs previously reported have been coded to highlight those cases which had reported past psychotropic medication use, those who reported no use and those who did not report either (not coded). These mBPs illustrate that cases who reported past use of psychotropic medications tended to sit above the line denoting the RCI, whereas those reporting no prior use, are moving toward symptom

reduction at the end of OL. Case B is labelled in the mBPs to demonstrate this trend. Case D from the placebo condition showed worsening of symptoms over RCT, and a lowering during OL.

Figure 8

IES-R Baseline to End of RCT and End of OL Change Scores for Participants of Clinical Concern Comparing Past Psychotropic Medication History Status by Treatment Group.

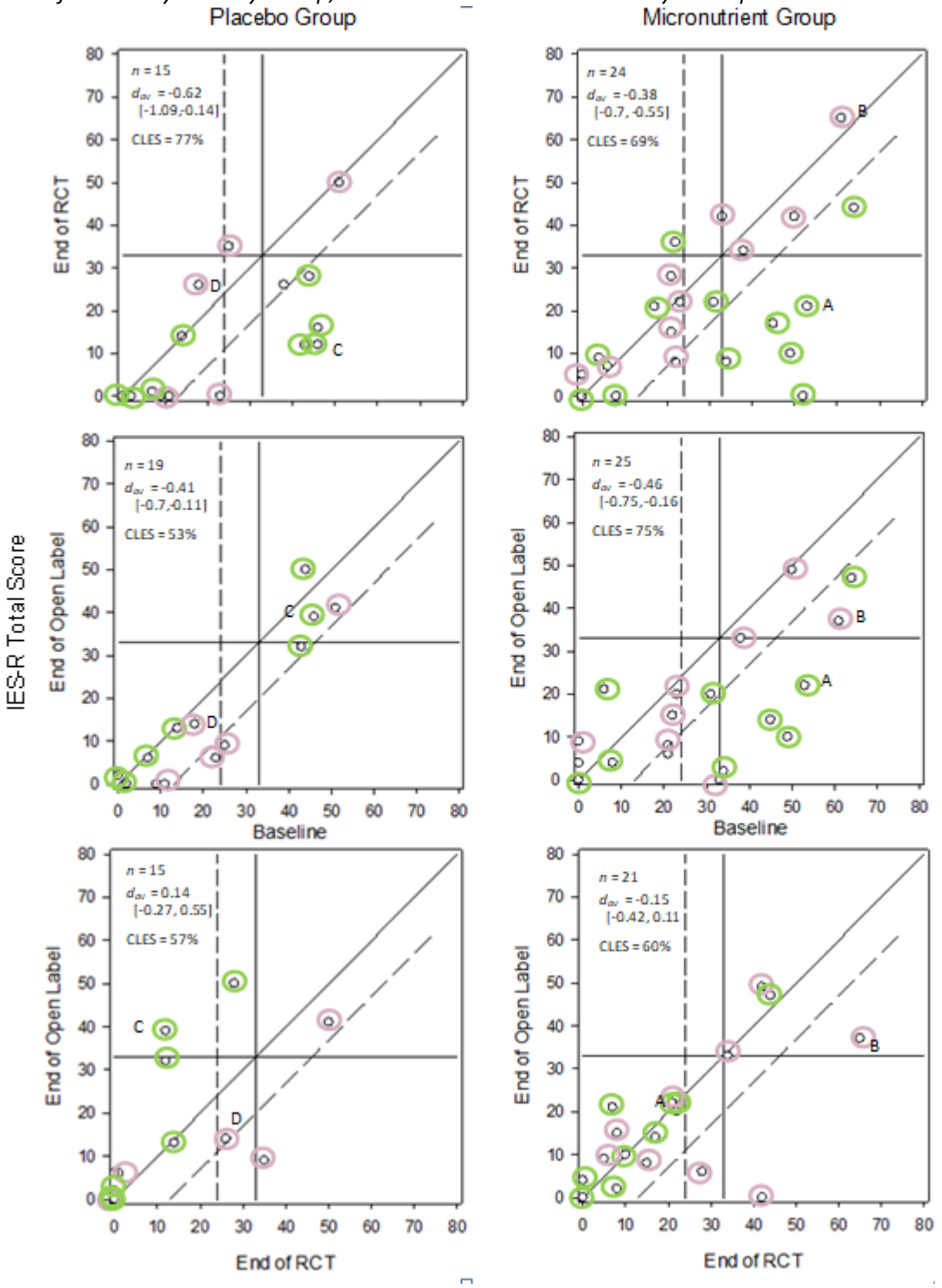


Note. Estimated marginal means and 95% CI bars are plotted by group and status. Individual observed scores are plotted.

Cases with no reported history of psychotropic medication use tended to fall into the clinical improvement quadrant (lower right-hand side) and in the micronutrient condition, to remain stable, for example Case A on the plots. While cases reporting no past medication use showed a treatment response to the placebo intervention, such as case C, this was not maintained during the OL phase, this case in fact showing an increase in symptoms. Case D is marked to demonstrate a case with past medication history improving minimally during the OL phase. A linear regression analysis was conducted using previous medication history, pill guess and expectations about the effect of micronutrients on anxiety as predictor variables, as identified as being significant in predicting percentage change in IES-R score for participants who had a baseline IES-R over

Figure 9

Modified Brinley Plots by Group, Over Treatment Phases with Psychotropic Medication History



Note. Green circles highlight no-reported psychotropic medication history, pink circles highlight reported past mediation history and letters A, B, C and D denote individual cases of interest.

24. A model including all there potential predictors accounted for 72% of the variance, and was a significant predictor of treatment response, $F(3,16) = 13.87$, $p < .001$. Previous medication history contributed significantly to the model (B = .69, $p < .001$), as did expectation of the effect of

micronutrients on anxiety (B = .5, *p* = .002); however, pill guess was not a significant contributor to the model (B = .13, *p* =.349).

Discussion

Summary of findings

The present study investigated the efficacy of a broad-spectrum micronutrient formula for participants in the NoMAD trial who endorsed having experienced a past traumatic event. Participants were recruited to the RCT trial for functionally impairing anxiety and/or depression and of the 117 participants recruited to the NoMAD trial prior to 1 December 2020, 72 (62%) endorsed having experienced a traumatic event in the past. There were no differences in treatment effect on traumatic stress symptoms between treatment conditions groups during the RCT phase and some evidence of the micronutrient condition more consistently reducing trauma symptoms after 20 weeks exposure to the intervention.

Characteristics of People Presenting with Depression and Anxiety Who Endorsed Experiencing a Traumatic Event

Of those recruited to the NoMAD study and included in the present study, 62% reported having experienced a past traumatic event. It was hypothesised that participants in the NoMAD trial who had clinically concerning levels of PTSD symptoms, would have more severe anxiety and/depression, and a lower quality of life than those who did not have clinically concerning levels of PTSD symptoms. The only measure from this study that was statistically significantly different between those endorsing a past trauma and those who did not endorse a trauma was the DASS anxiety subscale, which was higher for those with a past trauma; and placed them in the extremely severe range for anxiety, compared to the severe range for those without a trauma history. The IES-R was moderately correlated with the DASS anxiety and stress scales and only weakly correlated with the depression measures (DASS depression and the PHQ-9) and the GAD-7 anxiety measure.

The higher anxiety scores for participants with past trauma, and the moderate correlation between anxiety and stress, and trauma symptoms is unsurprising given the close relationship between traumatic stress disorders and anxiety disorders; however, is not consistent with the literature reviewed suggesting that people who have trauma histories will have higher levels of both anxiety and depression than those without trauma histories (Barbano et al., 2019). However, as this sample was

recruited for functionally impairing anxiety and depression, regardless of trauma history, this was a sample of people with high levels of both anxiety and depression.

Baseline group means showed participants were experiencing clinically significant depression and anxiety, placing them in the 'extremely severe' range for all DASS subscales, and above the clinical cut offs for an anxiety disorder (GAD-7) and depression (PHQ-9). The QOLS scores for this sample (around 70) placed them well below the healthy adult average of 90 out of 112, but above an average of 61 reported in a study Israeli patients with PTSD (Burckhardt & Anderson, 2003). Quality of life was higher for those who were identified with lower DASS depression, DASS stress and PHQ-9 scores.

Posttraumatic stress response symptoms

The mean IES-R score for participants in both treatment groups fell above the clinical concern cut off of 24, and below the probable PTSD cut off of 33. This is perhaps reflective of the historical nature of the trauma many participants endorsed, and scores above 33 would be considered unusual (Weiss, 2004).

Participants who indicated they had experienced trauma of an ongoing nature, similar to the Complex PTSD criteria mentioned previously (World Health Organization, 2018), were found to have higher posttraumatic stress scores on the IES-R than participants endorsing a single event trauma. For the present study, reported past traumatic events such as childhood abuse and intimate partner abuse were considered ongoing or recurrent whereas traumatic events such as a disaster or accidents were considered a single event trauma. Interestingly, the mean IES-R scores for the people reporting potentially recurring trauma fell above the probable PTSD cut off, whereas the mean score for people reporting a single trauma was below the clinical concern cut off. While this finding should be interpreted with caution as the reporting of traumatic events was optional, and these self-report data were collected qualitatively; it tends to support the notion that people experiencing ongoing trauma present differently to those experiencing a single event trauma (Brewin et al., 2017; Horowitz, 2011; Weiss, 2004).

Micronutrient Treatment Response

Overall, no between treatment group differences were found during the RCT and OL phases of the trial. The hypothesis that people with more severe PTSD will respond more slowly was partially

supported. Both treatment conditions showed improvements in trauma symptoms during the RCT phase, with the placebo condition showing a moderate ES for reductions in IES-R scores, and the micronutrient condition demonstrating a small ES. The two conditions' ES were more similar at the end of the OL phase and modified Brinley plot (mBP) analysis suggests that the micronutrient group continued to improve or stabilised during the OL phase, whereas the placebo group regressed or maintained high levels of PTSD symptoms. The mBPs for the IES-R show a number of cases with high IES-R scores at baseline who remained above clinical cut offs at end of RCT and OL, with only slight improvement, for both treatment conditions.

The two treatment conditions had similar ESs on depression, anxiety and quality of life measures during the RCT phase. Based on effect sizes, the placebo group showed larger improvements in depression scores compared to the micronutrient group, and the micronutrient intervention appeared to be better at reducing stress. There was no statistically significant difference in the global improvements rated by the PI for each group. By the end of the OL phase, the placebo and micronutrient groups remained similar for most measures; however, the micronutrient group had larger improvements on stress and quality of life. Of note is that the ES for QOLS score improvement would be considered small by usual conventions (Lakens, 2013); however, the micronutrient group ES of d =0.35 is above the average QOLS ES change reported by Burckhardt and Anderson (2003), suggesting that on a measure that is not overly sensitive to change, the micronutrient intervention provided significant and personally relevant improvement. The hypothesis that depression, anxiety and stress scores would reduce as trauma symptoms reduced during the trial was supported regardless of the treatment condition over both the RCT and OL phases. The reduction in IES-R scores was not as large as the ES reductions seen in previous micronutrients for PTSD studies (Rucklidge et al., in press).

The hypothesis that participants receiving micronutrient treatment for 20 weeks would have fewer symptoms than those receiving only 10 weeks of treatment was supported by the Common Language / PS ES analysis. At the end of OL, for the micronutrient group there was 75% chance that a randomly selected case would have a lower IES-R score, and therefore fewer traumatic stress related symptoms at the end of the OL phase than at baseline, compared to a 53% chance of this for a case

from the placebo group. The two conditions had similar PS ESs on measures of depression, anxiety and stress.

Treatment Response Predictors

Given that previous research (Blampied et al., 2020) has found micronutrients are more effective than placebo in reducing psychological symptoms it was surprising to find no group differences in treatment response in the present study. Predictors of treatment response were explored in order to determine if individual factors might explain these findings. Univariate and mBP analysis revealed a pattern of treatment response that appeared to be influenced by previous psychoactive medication use. The data were looked at considering the participant's reported past history of psychotropic medication use. Participants who reported any history at all of psychoactive medication use for their mental health difficulties were less likely to be identified as a treatment responder. This effect was larger during micronutrient treatment phases. That is, past psychotropic medication use was more likely to result in smaller improvements of trauma symptoms when participants were taking the micronutrient intervention than when taking the placebo. This pattern of response may be partially explained by known interactions between micronutrients and psychoactive medications (Mehl-Madrona & Mainguy, 2017; Popper, 2014). While participants were required to have discontinued psychoactive medications at least four weeks prior to the trial start, it is unclear how long they had been medication-free and how long they had been using prescribed medications.

In light of the literature on withdrawal syndromes, especially persistent withdrawal syndromes where medication side effects and withdrawal symptoms may be experienced for many months or years (Cosci & Chouinard, 2020), it is possible that previous medication use continues to impact neurotransmitter or other physical functioning. While the mechanisms of action require further exploration, the last effects of a psychoactive medication may occur as a result of the half-life of the medication leaving the drug in the system, or as a result of the medications altering neurobiological processes; the extent of which is determined by individual genetics (Fava et al., 2015). The potential ongoing impacts of the medications on neurobiological processes could then interact with the micronutrient intervention causing psychiatric symptom rebound effects or side effects. SSRI anti-

depressants were by far the most reported previously used psychoactive medication in the sample of participants who had experienced trauma.

Cosci and Chouinard (2020) report the most common withdrawal symptoms are the listed side effects of the medications used. Commonly reported SSRI side effects include, among other symptoms, symptoms common in anxiety and stress disorders such as: insomnia, agitation, anxiety, restlessness and worsening depression and/or suicidality (Health Navigator New Zealand, 2021). Should these withdrawal symptoms be triggered by the post drug-micronutrient interactions, this may lead to increased reporting of these symptoms during the trial, and could present as worsening or failure to improve and may explain some cases of worsening symptoms for some people in the present study.

Data collection in the present study on previous medication use was limited, and the univariate analysis was exploratory in nature due to the small number of participants who completed the measures at all time-points, who provided detail around previous medication use and who had clinical concerning levels of trauma related stress symptoms. This finding of a potential effect of previous drug treatments influencing response to micronutrients, at least in the short-term, is best considered as the detection of a phenomenon that requires further investigation. Future studies investigating the treatment response to micronutrient interventions should consider the potential influence of participant's past medication use.

The impact of past medication use can also be considered more broadly with respect to the participants' previous exposure to treatment of any kind. Ninety-three percent of the participants in the present study had engaged in some kind of treatment in the past and for whatever reason (although a likely reason could be that 89% of those same participants reported not achieving full remission of depression and anxiety symptoms in past treatment) participants were dissatisfied with previous treatment and elected to try a nutritional intervention. There is insufficient information about previous treatment efficacy or the duration of treatment; however, many participants in the present study would likely be considered to be treatment resistant. As discussed in the introduction, TRPTSD (Starke & Stein, 2017) is defined as being when people do not respond to recommended first line treatments. The management of TRPTSD involves monitoring patients while trying adjunctive and/or

alternative therapies to achieve remission and targeting core symptoms. This can take months or years (Starke & Stein, 2017).

Starke and Stein (2017) outlined clinical characteristics that are associated with increased treatment resistance for people with PTSD. Risk factors include: longer duration of time since trauma exposure; higher PTSD severity; chronic symptoms; and comorbid depression. In contrast, Ehlers and colleagues (2005) found these same characteristics did not affect treatment response in their CT trial. Gathering more information about the clinical characteristics of the participants may provide a clearer understanding of treatment response to micronutrients and treatment more broadly. It is likely that even without medication-micronutrient interactions, past experience of ineffective therapy for chronic mental health difficulties contributes to the length of time needed to respond to treatment, including novel treatments such as micronutrients.

The present study demonstrated a moderate placebo response rate, ranging from 25 to 53% depending on the treatment response criteria utilised. Antidepressant trials typically report placebo response rates of between 35 and 40% (Furukawa et al., 2016), which is similar to that observed in the present study. From their systematic review of the placebo response in antidepressant trials, Furukawa and colleagues (2016) report that a supportive therapeutic healthcare environment where there is the expectation of improvement is likely to increase placebo response in patients with major depression. The present study likely created similar conditions, and could be regarded an active treatment in its own right. Participants were referred by a GP who we can assume had positive expectations about the micronutrient intervention. Contributing to the positive expectations is that micronutrient research has been conducted in the Waitaha Canterbury rohe for over ten years, with media coverage making the research well known to many interested in alternative treatment for mental health. Expectation ratings from participants showed they held moderate expectations that micronutrients would help them.

Interestingly, participants guessing they were taking the micronutrient pill during the RCT phase was also a predictor of treatment response. Because only one pill guess was made, at the end of RCT, and guesses were not particularly accurate, it is unclear if the micronutrient guess was made because they had improved and this improvement was attributed to micronutrients due to their expectations, or if their guess was static throughout the RCT phase and led to a treatment response

based on their pill guess. Future studies could ask for a treatment condition guess at different time-points of the RCT phase to see how this might change over time, and how it predicts treatment or placebo response.

In addition to the treatment expectations, involvement in the trial included weekly phone, text and/or email contact with the PI, who was a supportive, registered clinical psychologist, who we can also assume built therapeutic rapport with participants. While the online study design was initially considered a way to reduce the effects of therapeutic alliance on treatment response, this may not be the case as people have become more accustomed to social and professional relationships being established through technology, and the flexibility of an online intervention is often considered highly supportive (Lopez et al., 2019). Feedback gathered indicated *all* participants in the present study felt heard, understood and respected by the PI. In many ways, this was an active placebo condition. Somewhat contrary to this, the univariate analysis revealed that fewer PI contacts predicted treatment response. In the present study, this association might be explained by increased PI contact being a response to worsening wellbeing, or non-adherence to data collection requests; and contact was likely initiated by either the PI or participant because of the deterioration.

Based on Furukawa and colleagues' (2016) review comments, it is likely that all participants experienced some placebo effect to some degree in the present study. Participants were recruited for difficulties with depression, and baseline measures showed the sample was experiencing clinically significant rates of depression. Over the initial 10-week RCT phase, the placebo condition showed greater reductions in depression scores than the micronutrient condition. In consideration of Furukawa and colleagues' comments that a therapeutic environment coupled with expectations of intervention success increased the placebo response for patients with major depression, it is conceivable that the high rate of depression reported in the present study increased the likelihood of a placebo response. The placebo condition also had a larger effect on depression symptoms than the micronutrient condition, suggesting the therapeutic environment of the RCT acted as an active treatment condition.

The initial treatment response for both placebo and micronutrient groups may also be attributed to regression to the mean. Regression to the mean is the tendency for participants selected to join a trial or treatment programme to show change in the direction of the population mean. The

more extreme their score is, the more room there is to move toward the population mean. Therefore, what may appear to be placebo or treatment effect, can be accounted for by the tendency to regress to the mean (Morton & Torgerson, 2003). The present trial recruited people with higher than average levels of depression and anxiety, and people tend to join trials and treatment programmes when they are at their worst, thus creating more opportunity to improve. The present study did not include multiple baseline measurements of the trauma symptoms which would enable 'best practice' averaging of scores across the baseline phase (Morton & Torgerson, 2003).

The present study sought to build on previous findings that micronutrient interventions reduced traumatic stress symptoms and improved mental wellbeing in the weeks and months following a traumatic event. The improvements in both groups in the present study over the 10-week RCT and 10-week OL phases were smaller than previous research looking at the effectiveness of micronutrients on acute PTSD symptoms in the weeks following a disaster. All three disaster-related studies showed a pattern of large reductions in the IES-R and DASS scores (Kaplan et al., 2015; Rucklidge et al., in press; Rucklidge et al., 2012) following micronutrient treatment. This may be explained by the expectation that PTSD symptoms will naturally reduce over time, and that in the initial time period after a traumatic event there will be a rapid decline in symptoms (Weiss, 2004) which contributed to the large ESs observed. Of note is that the present study participants had a lower IES-R score at baseline that in the three disaster studies. Given that these studies occurred post-disaster and employed translational science approaches, a placebo controlled study was unethical and not employed; however, the use of active-controls and treatment-as-usual comparators demonstrated the treatment effects could not be accounted for by regression to the mean or natural remission after acute trauma alone (Kaplan et al., 2015; Rucklidge et al., in press; Rucklidge et al., 2012).

The three previous studies using micronutrients for posttraumatic stress differed in trauma type. The ongoing nature of the earthquake aftershock sequence and stress relating to insurance and government decision that formed the basis of the Rucklidge and colleagues (2012) micronutrient for posttraumatic stress study can be considered a recurring trauma, similar to the differentiation used in the present study. The flood event trauma (Kaplan et al., 2015) occurred over several days and the mosque massacre was an extremely intense but short traumatic event (Rucklidge et al., in press). The

three studies differ from the present study in that treatment was administered in the weeks following the trauma. Given that trauma type and time-lapsed since the trauma exposed has previously been suggested as a predictor of treatment success, this may account for the large difference in treatment response rate between the previous studies and the present study. Micronutrient supplementation as a preventative intervention after an acute traumatic event remains a useful intervention. This may be of particular interest to clinicians and emergency responders as a post trauma exposure response because both psychotherapy and pharmacological interventions are not recommended for as an immediate treatment for trauma exposure (National Institute for Health and Care Excellence, 2018).

The present study also sought to increase the recruitment of and participation by Māori in the NoMAD trial. Increased efforts in 2019 and 2020 to raise awareness of the trial in the community and to build relationships with kaupapa Māori service providers did not result in an increase in the rate. Efforts were hindered by the 2020 COVID19 lockdown, and the subsequent pause in recruitment and may have reduced the effectiveness of kanohi ki kanohi introductions prior to lockdown. Larger increases in Māori participation will likely require ongoing reciprocal relationship building in conjunction with the department and the university more broadly, including the inclusion of kaupapa Māori research methods teaching, kaupapa Māori research staff at the university and utilisation of the relationship with local iwi research groups.

Limitations

The present study utilised the gold standard RCT study design, which was further enhanced by the use of a well-designed placebo pill. This included successful masking thorough the use of riboflavin to induce urine colour change, and the management of the DEN odour which could have led to detection. The study had a high retention and compliance rate, and no serious side effects were reported. The use of online and phone contact methods may have contributed to the acceptability of the trial for participants across the rohe. Interestingly, moderate effect sizes were found despite minimal intervention from the study co-ordinators.

A major limitation of this study was the missing IES-R data at the end of RCT and the end of OL due to the online administration of the IES-R being based on the endorsement of stem questions at each time-point. This created two different samples at the end of RCT and end of OL as some

participants endorsed one but not the other. The missing data resulted in many cases being unable to be tracked through the study phases, and a smaller sample size in the analyses over all. While estimations were able to be used to some extent, future studies using a measure of traumatic stress should ensure online questionnaires include the IES-R at all time-points for participants endorsing a traumatic event at baseline by way of a forced-response option on the online questionnaire, or as a part of the regular trial contact and psychometric administration process.

The use of the IES-R in this study allowed for comparisons with previous micronutrient studies as an intervention for chronic stress. Previous research on nutritional supplementation and trauma that formed the basis of this study included participants recruited in the weeks and months immediately following a traumatic event (Kaplan et al., 2015; Rucklidge et al., in press; Rucklidge et al., 2012). The present study included participants reporting historical and sometimes recurring or repeated trauma. The IES-R was designed to assess the impact of a single traumatic event. This presents two issues. Firstly, Weiss (2004) describes ongoing trauma as 'trickier' and likely to present with heterogeneous symptom clusters; and we know people who experience ongoing trauma, such is the case with childhood or intimate partner abuse, tend to experience symptoms of PTSD along with more entrenched difficulties in self-organisation, self-identity and/or personality, or Complex PTSD (Brewin et al., 2017; Horowitz, 2011; World Health Organization, 2018). Weiss further highlights that research to date demonstrates that different classes of traumatic event tend to have differing symptom presentations, particularly the more severe the trauma, and the higher the level of exposure, the worse the symptoms. The different symptom presentation of different types of trauma exposure may have reduced the comparability of the IES-R across studies in this case.

The second issue concerning the use of the IES-R in this study is the sequalae of traumatic stress over time. Weiss (2004) clarifies there are no cut-off scores for the IES-R, one reason being that it is often entirely normal to experience high levels of PTSD symptoms in the immediate aftermath of a traumatic event, and that the levels for clinical concern will change over time. For the present study we were not privy to exact detail of when each participant's traumatic event occurred; nor is it clear what symptom presentation we would consider 'normal' at any time point after the trauma. Previous micronutrient intervention studies for trauma were conducted in the immediate aftermath of the

traumatic events, and the IES-R may not sufficiently capture the symptoms and difficulties associated with more chronic trauma symptoms. As discussed previously, obtaining detail about the nature and time since the traumatic event may increase our understanding of trauma treatment efficacy over time, and a measure such as the Traumatic Exposure Severity Scale (Elal & Slade, 2005), for example may enhance future analyses.

It is important to note participants were not recruited to the trial based on their difficulties with posttraumatic stress, and the choice of the measures in the NoMAD were focused on measuring changes in depression and anxiety, using online data collection. Future research on treatment effectiveness for improving posttraumatic stress symptoms should employ traumatic stress measures designed for use with recurring, multiple and historical traumas. Alternative measures could include both a self-rated (for example, the Post-traumatic Diagnostic Scale, or the Self-Rated Davidson Trauma Scale) and clinician administered scales (for example the Clinician Administered PTSD Scale) (Hoskins et al., 2015).

The length of the present trial, while consistent with the length of typical antidepressant medication and psychotherapy trials (6-12 weeks) may not have been sufficiently long enough to demonstrate a consistent treatment ES for the chronic and severe symptoms experienced by the participants in the present study. Blampied and colleagues (2020) report the length of nutritional trials vary and make it difficult to ascertain the length of time to needed to respond to interventions. Research specific to broad-spectrum micronutrient trials suggests the benefits for mental health increase over time (Rucklidge, Frampton, et al., 2014; Rucklidge et al., 2011). Full reporting on the NoMAD trial will include 12-month follow up data; however, future micronutrient trials involving participants with chronic, potentially treatment resistant posttraumatic stress disorders may need to have longer treatment phases to detect change. In addition to this, the use of a single baseline measure for the IES-R and corresponding secondary outcome measures did not allow for any monitoring of the baseline score for potential regression to the mean or improvement over time making it more difficult to detect treatment effects, and future research design should ensure multiple baseline measurement (Hawkins et al., 2007).

The lack of clinical information about participants available in the present study restricted further analysis of treatment predictors, and future analyses would benefit from data gathered from structured interviews detailing previous treatment history, and potentially obtaining medical records to gather prescription histories, and further detail around current psychotherapy or other mental health practices used by the participant during the trial.

Future Directions

Psychotherapy and pharmacological interventions are effective treatments for PTSD, depression and anxiety for some, but a large proportion of participants in this study did not report these interventions sufficient in relieving their difficulties in the past. Trauma-focused CT, CBT and EDMR demonstrate efficacy, provide long term benefit and due to medication side effects, are perhaps more tolerable than pharmaceutical interventions. Future research could explore the benefit of using micronutrients as an adjunctive treatment to evidence-based psychotherapy such at CBT, CT and EDMR. A key aspect of trauma-focused psychotherapy is exposure-based treatment, where the flight or fight response is likely activated in order to increase tolerance of the fear response and extinguish it. Given this process involves an acute stress response in order to improve a chronic stress disorder; the use of a micronutrient supplement during the course of an evidence-based psychotherapy treatment may support our brains and bodies to adapt and improve resilience to stress.

Previous psychoactive medication history was identified as a factor that reduced treatment response. Further research into the impacts of psychoactive medications on neurotransmission, hormones and other neural processes is necessary as is the data raise the possibility of a concerning interaction for people both starting and ceasing psychoactive medications that may have far reaching effects. Research to extend the knowledge base in this area could include replication of the Mehl-Madrona and Mainguy (2017) trial of a micronutrient supplement as an adjunctive treatment to pharmacological interventions for PTSD, anxiety and depression, in addition to further research exploring the longer term effects of psychoactive medications for anxiety and depression. More generally, research looking at the effects of unsuccessful treatment on future treatment response would be a valuable contribution to the literature guiding the treatment of mental health.

Conclusion

The present study contributes to the expanding body of research identifying efficacious treatment options for PTSD. The use of micronutrient treatments has well-established efficacy for reducing posttraumatic stress symptoms, improving mental wellbeing and reducing the risk of developing PTSD for people dealing with acute stress. The present study found micronutrients was not found to better than placebo for people experiencing chronic posttraumatic stress responses with co-occurring anxiety and/or depression. There are a number of reasons why group differences were not observed: including the short duration of the trial; the therapeutic effects of being in the RCT; the influence of past psychotropic medication; the suitability of the measures used to measure chronic symptoms; and the impact of treatment expectations. PTSD treatment decision making must be guided by evidence, and further research is required to establish the clinical characteristics of micronutrient treatment responders.

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Appendix

Appendix 1 Pill Ingredients

Active Intervention: Daily Essential Nutrients (DEN)

Ingredients:	**1 capsule**	**12 capsules**
Vitamin A (as retinyl palmitate)	480 IU	5,760 IU
Vitamin C (as ascorbic acid)	50 mg	600 mg
Vitamin D (as cholecalciferol)	250 IU	3,000 IU
Vitamin E (as d-alpha tocopheryl succinate)	30 IU	360 IU
Vitamin K (75% as phylloquinone; 25% as menaquinone-7)	10 mcg	120 mcg
Thiamin (as thiamin mononitrate)	4 mg	60 mg
Riboflavin	1.5 mg	18 mg
Niacin (as niacinamide)	7.5 mg	90 mg
Vitamin B6 (as pyridoxine hydrochloride)	5.8 mg	69.9 mg
Folate (as L-methylfolate calcium)	66.8 mcg	801 mcg
Vitamin B12 (as methylcobalamin)	75 mcg	900 mcg
Biotin	90 mcg	1080 mcg
Pantothenic acid (as d-calcium pantothenate)	2.5 mg	30 mg
Calcium (as chelate)	110 mg	1,320 mg
Iron (as chelate)	1.15 mg	13.8 mg
Phosphorus (as chelate)	70 mg	840 mg
Iodine (as chelate)	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: Choline bitartrate		
Alpha-lipoic acid		
Shilajit		
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)
Germanium sesquioxide (as chelate)
Boron (as chelate)
Vanadium (as chelate)
Lithium orotate (as chelate)
Nickel (as chelate)
Other ingredients:
Cellulose
Glycine
Citric acid
Magnesium stearate
Silicon dioxide

Placebo Intervention

Ingredients:	**1 capsule**	**12 capsules**
Fiber Acacia Gum	300 mg	3,600 mg
Maltodextrin	395.90 mg	4,750.8 mg
Cocoa Powder	4 mg	48 mg
Riboflavin Powder	0.10 mg	1.2mg

Appendix 2

Information contained on the study website https://mmp.net.nz

Main page:

This will have general information about the study, as is contained in the information pamphlets available for GPs and potential participants.

It will contain a brief explanation of micronutrient intervention, links to relevant research and briefly outline the study.

It will also have the contact details for the principal investigator but will direct potential participants back to their GP to discuss any concerns they have about their mental health and any potential participation in the study.

The main page will also have information about the prevalence of anxiety and depression in New Zealand and will contain links to other information sites including:
http://www.health.govt.nz/your-health/conditions-and-treatments/mental-health
https://www.mentalhealth.org.nz/

https://depression.org.nz/

http://www.healthinfo.org.nz/

It will also explain what to do if people are worried about themselves or someone that they love and provide the following information for support and crisis services:

Lifeline (Available 24/7) 0800 543 354

Depression Helpline (Available 24/7) 0800 111 757

Healthline (Available 24/7) 0800 611 116

Samaritins (Available 24/7) 0800 726 666

Suicide Crisis Helpline (Available 24/7) 0508 828 865 (0805 TAUTOKO) Crisis Resolution Services (Available 24/7), Canterbury 0800 920 092

This crisis support information will also appear if participants endorse increased risk while completing their psychometrics

General Practitioner Page:

This page will also contain contact details for the principal investigator and a copy of the information in the GP information pamphlet. This will contain the electronic referral portal for GPs to make referrals to the trial. The electronic referral form will ask for contact details for the potential participant. It will ask the GP to confirm that the potential participant is not taking anti-depressant medication. It will require the GP to confirm they have reviewed the exclusion and inclusion criteria with the potential participant and that the potential participant meets these criteria. A copy of the inclusion and exclusion criteria will be available. It will ask the GP to nominate a preferred communication method for information to be sent from the trial to the GP. It will require their prescriber number in order to complete and submit the referral form.

The GP page will also provide links to various organisations that might assist GPs in the future, including Work and Income New Zealand and the Ministry of Health.

Participant Page:

This page will require participants to create a unique log-in after completing screening with the principal investigator. It will contain all information about the trial, risks associated with participation and who to contact during the trial (see Participant Information Sheet- Consent Form). It will collect all written consent from the participant. This portal will also include access (once consent has been given) to the demographic questions and study questionnaires. Participants will also access their weekly questionnaires through this participant portal and can sign up for weekly email reminders to complete their questionnaires. Once participants have reached the end of the RCT phase, they will be directed to complete another consent form for the open label phase if they wish to participate in this phase of the study.

Appendix 3 Bicultural /Te Reo Māori Resources

ELIGIBILITY CRITERIA

INCLUSION:
1) between 18 and 65 years, 2) regular access to the internet, 3) considered reliable and compliant with the protocol (including the ingestion of as many as 12 capsules/day with food), and 4) and be presenting to their GP with functionally impairing anxiety or depressive symptoms which cannot be better accounted for by a medical condition. 5) Living in Canterbury.

EXCLUSION:
1) Neurological disorders involving brain or other central function (e.g., 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), 2) Any serious medical condition, 3) Any patient known to be allergic to the ingredients of the intervention, 4) Any other medication with primarily central nervous system activity, including psychotropic medication (e.g. SSRIs, tricyclics, benzodiazepines). Participants must have been off of these medications for a minimum of four weeks prior to the trial. Participants are not encouraged to come off of a medication in order to participate in the trial. All exclusions will be reviewed by study physician.

Check out the study website
www.mmp.net.nz
For more on Te Puna Toiora, check out:

www.bit.ly/UCnutrition
www.facebook.com/

mentalhealthandnutrition
www.instagram.com/
ucmentalhealthandnutrition

WHAKAPĀ MAI

CONTACT US

To refer patients to the trial, please visit www.mmp.net.nz and complete the referral form under Information For General Practitioners.

You can also contact Meredith Blampied (Principal Investigator) on:
Phone:
022 153 3702

Email:
mindmappsychology@gmail.com

This study has received ethical approval by the New Zealand Human and Disabilities Ethics Committee (UTN: U111111994026).

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

NoMAD trial: Nutrients for Mental Health, Anxiety and Depression

Taiora me te hauora hinengaro (mate pāpōuri, me te āwangawanga hoki)

Are micronutrients (taiora) effective in treating symptoms of anxiety and depression?

Mental Health and Nutrition Research Group

Te Puna Toiora

NoMAD:Trial Information

What are micronutrients?

Micronutrients include the following:

- Vitamins A, B6, B12, C, D, E, K
- Thiamin, Riboflavin, Niacin
- Folate, biotin, Pantothenic acid
- Calcium, Iron, Phosphorous
- Iodine, Magnesium, Zinc
- Selenium, Copper, Manganese
- Chromium, Molybdenum, Potassium

Taiora (micronutrients) are essential in the development of amino acids and also in the production of neurotransmitters.

Evidence suggests that vitamin and mineral play an important role in hauora hinengaro (mental health) difficulties and that providing micronutrient supplementation can reduce symptom severity (Kaplan et al 2007)

What is the evidence?

Recent research has investigated the role of digestion and the gut on the development of mental health issues (Schlebusch et al, 2000; Davidson & Kaplan, 2012; O'Kennedy, 2016).

Individuals with poor hauora hinengaro (mental health) continue to report nutrient-poor diets when compared to healthy controls (Kaplan et al, 2015; Davidson & Kaplan, 2012).

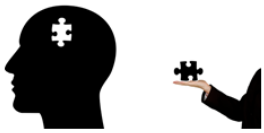
Initial case studies using micronutrients to treat a range of disorders were promising (Kaplan et al, 2002; Popper, 2002; Rucklidge, 2009; Rodway et al, 2012)

More recent trials have demonstrated efficacy of micronutrients in improving emotion regulation, reduce stress and improving attention, concentration and hyperactivity symptoms and improving insomnia with limited side effects (Gariballa & Forster, 2007; Rucklidge et al, 2011; Rucklidge et al, 2014; Popper, 2014; Lothian et al, 2016).

Further research is needed to explore the potential of micronutrients as a treatment specifically for symptoms of anxiety and depression.

What is the trial?

200 people will be randomised to a placebo or treatment condition. The treatment condition will involve taking 12 micronutrient tablets per day (4 pills, 3 times a day) for 10 weeks.



The trial will also include a 2 week initial baseline phase, where no treatment or placebo will be offered. Participants will complete initial questionnaires and weekly monitoring of their symptoms.

Participation in the trial is all conducted over the internet. Clinical oversight is provided throughout the trial.

After the trial, all participants will be offered micronutrients for a further 10 weeks in an open label phase. There is no cost to participating. All product will be provided free of charge during the trial and open label.

Appendix 4

Participant Information Sheet and Consent Form - RCT

Mental Health & Nutrition Research Group

Department of Psychology

University of Canterbury

Private Bag 4800

Christchurch

New Zealand

PARTICIPANT INFORMATION SHEET

Study title: The effectiveness of micronutrients as a treatment for anxiety and depression: A community trial.

Principal investigator: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

Research co-ordinator & PhD student: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

Locality: University of Canterbury, Christchurch, New Zealand

Ethics ref: 17/STH/131

Other investigators: Professor Julia Rucklidge, Dr Caroline Bell, Claire Gilbert.

You are invited to take part in a study investigating the impact of a micronutrient (vitamin and mineral) formula for adults experiencing symptoms of depression and anxiety. Diagnosis of clinical depression or anxiety is not required for entry into this study although this will be measured as part of the study. **The product we use is not the recommended intervention for clinical depression or anxiety**. The recommended intervention for anxiety and depressive symptoms is psychotherapy and antidepressant medication. Should you wish to find out more about the recommended interventions, please discuss these options with your GP.

Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This participant information sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to provide written consent by signing at the bottom of this page. Please make sure you have read and understood all the information on this form, including the consent form and list of ingredients of the products we use.

What is the purpose of the study?

Following the randomised controlled trial phase of the study where you took either the micronutrient product or placebo for 10 weeks, this part of the study ensures all participants will take the micronutrient formula we are testing. This phase of the study is called an open label phase since both you and the researchers know that you are taking the product. The product we are studying has been researched previously and has shown to have beneficial effects on depression, anxiety and stress. The researchers would therefore like to give all participants the opportunity to try the product.

What will be studied?

The formula we are studying is called *Daily Essential Nutrients*, a revised formula of the product we've tested in previous research. This product contains a blend of vitamins, minerals, amino acids and antioxidants and is consumed in capsule form. A list of the ingredients for the product are provided at the bottom of this webpage.

What will my participation involve?

Participants who have taken part in the randomised controlled phase who are not currently taking psychiatric medication are eligible. If you are taking any psychiatric medication, please let us know. We do not want you to stop taking medication in order to be in this trial. Please discuss any decision to stop taking medication with your GP.

If you decide to participate in this phase of the study, the principal investigator from the University of Canterbury will ring you for approximately 30 minutes to review information about this phase of the study, ask any questions you may have and will then arrange to have you give written consent to participate in the study. During this time, you will be asked to complete questionnaires that you have taken previously. You may also be asked to attend a face-to-face appointment at the university if the principal investigator thinks this is necessary.

You will also be given 2 weeks supply of the micronutrient product to begin taking the following day. The day after you collect the capsules, you will begin taking one capsule, three times per day and increase the dose by three capsules every second day until a maximum dose of four capsules taken three times per day is achieved. This means that a total of twelve capsules will be taken per day. You will be asked to continue taking the maximum dose of 12 capsules per day for 10 weeks. During the open label phase, you will be monitored every fortnight via online questionnaires, taking no more than 10 minutes to complete. You will be required to submit photos of unused pills as you have done previously. After 2 weeks, you will receive a 4 week supply of micronutrient product and a following 4 week supply the month after that. If you are unable to complete any of the questionnaires or take/send the photos, please let the principal investigator know via email or phone call and we will discuss other options with you.

What are the possible benefits of this study?

There may or may not be any benefit to you as a result of taking part in this study. Previous research has shown beneficial effects of micronutrient formulas on mood and anxiety in children as well as adults. The research suggests that your symptoms of depression and anxiety may improve as a result of taking the product; however, there is no guarantee that your symptoms will improve and you may experience an increase in your symptoms.

What are the possible risks of this study?

There are risks when taking an experimental treatment. Side effects reported by people taking the micronutrients include headaches, stomach aches and nausea. These side effects are typically mild and transitory and can be avoided by taking capsules **on a full stomach**. We therefore suggest that you *always take your capsules with food and plenty of water*. Another way to prevent these side effects is to increase the dose more slowly. Please don't hesitate to contact us at any stage to discuss side effects or dosing of the nutrients. Information on how to contact the principal investigator is on the website and will be on your pill bottle. We will review side effects with you every week and make a referral to a medical practitioner if necessary.

Can I take other medications?

The product you will be taking has the potential to interact with other medication or drugs so if possible you should avoid taking other medicines or supplements for the duration of the study. For this reason, we are only including individuals in the study who *are not being concurrently treated for their illness using prescribed medications.* With respect to other medications, such as over the counter medications to treat colds, flu, stomach upset, sleep problems, you should first discuss with a pharmacist before use as such medications may interact with the product. Pain relief medication such as aspirin, paracetamol, ibruprofen, Neurofen and Panadol have not shown to interact with the product and would be safe to take alongside the capsules.

If you need to take an antibiotic or antifungal agent orally at any time during the trial, please let us know. We ask this because antibiotics and antifungal drugs may interfere with the absorption of the micronutrients. Additionally, you will be asked to avoid trying any alternative medicines, supplements or other forms of therapy until after completion of this study.

What if my symptoms increase or I have a reaction to the product?

Your safety is of the utmost importance. If you experience an increase in symptoms, please let us know as soon as possible. If we feel your symptoms have increased to a clinically significant degree or that the product is causing any harm, we may discuss with you the possibility of withdrawing you from the trial. If at any time you do discontinue the trial, we will follow up with you. In the event of a psychiatric emergency or if you feel at risk to harming yourself or others, you must contact the Crisis Resolution Team on 0800 920 092 or visit the emergency department immediately. Information about what to do if you need emergency mental health support is on the website.

Should you experience any serious physical symptoms after taking the capsules, you should go immediately to the emergency department. All bottles of pills have a contact number which you should provide to the physician so that they can call to obtain information about the study and the ingredients of the capsules you are taking.

Who pays for the study?

Participation in this study will not incur any costs to you. The product we are testing is provided free of charge by the manufacturers. The manufacturer (Hardy Nutritionals) do not provide any financial support and are not involved in the study in any other way. There are no restrictions on any publications from this research. The costs of this study are being funded by the University of Canterbury and the University of Canterbury Foundation. This funding will cover the costs of a $10 petrol voucher you will receive if you need to visit the university in order to reimburse you with transportation costs. You will also have access to a free car park at the university when you attend appointments for this study.

What if something goes wrong?

In the unlikely event of a physical injury as a result of your participation in this study, you must first present to the emergency department. You may be eligible for compensation from ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic, and your case will need to be assessed by

ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still may not receive any compensation – as compensation depends on a number of factors. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, please contact your nearest ACC office, or one of the investigators. If you have private health insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What are my rights?

Participation in this part of the study is entirely voluntary (your choice). You are free to decline to participate or withdraw from the research at any time without experiencing disadvantage in any way. Declining or withdrawing participation from the study will in no way affect your continuing health care. However, if you do decide to withdraw from the study at any time, we will contact your GP to inform them. The researchers may also contact you at a later stage to ensure your wellbeing. You have the right to access any information collected about you as part of the study and will be told of any new information about any adverse or beneficial effects related to the study that becomes available and may have an impact on your health.

All information collected in this study will remain strictly confidential. The only people who will have access to the information are the study investigators and designated staff. We are very careful in dealing with confidential information. Any information you disclose will be kept in a confidential file, which will be stored in a locked filing cabinet at all times.

Members of all cultures will be encouraged to participate in the study. Respect for Māori customs and traditions are of the highest priority and, if necessary, any appointments at the university can include a cultural advisor. The researchers are available to discuss the research with the whanau to assist in developing their understanding of the clinical disorders and how the disorders can impact the te taha hinengaro (mental wellbeing), whanaungatanga (family relationships), taha wairua (spiritual wellbeing) and taha tinana (physical wellbeing).

What happens after the study or if I change my mind?

At one year following your baseline assessment, you will be invited to complete some online assessments about yourself and your physical and mental health via the same website you have been using in the study. If you are unable to complete these assessments for any reason, please let the researcher know and we will ring you to discuss alternatives. However, should you decide to withdraw from the open-label trial, we would still like to follow up with you at the time you withdraw and again a year after your baseline assessment, to ensure your wellbeing and give you the opportunity to complete assessments should you wish.

After you have completed the study, you will not receive any further funded micronutrients. If you wish to purchase the micronutrients, we will assist you to do so at your own cost.

All data that you provide will be stored at the University of Canterbury for 10 years after collection, in accordance with university and health regulations and will be destroyed securely in accordance with the university guidelines. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Health and Disability Ethics Committee.

The study findings will be published in a peer reviewed scientific journal and disseminated at conference presentations. We can send you a summary of the results should you wish. However, please be aware that a significant delay may occur between data collection and publication of the results.

Who do I contact for more information or if I have any concerns?

If you have and questions, concerns or complaints about the study at any stage, you can contact the principal investigator:

Principal investigator: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

If you want to talk to someone who isn't involved in the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the Health and Disability Ethics Committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

This study has been reviewed and given ethical approval by the Human and Disabilities Ethics Committee and the Human Ethics Committee at the University of Canterbury. This means that the committee may check at any time that the study is adhering to ethical procedures. We have also consulted with Te Komiti Whakarite and the Māori Research Advisory Group at the University of Canterbury. Part of this research study will contribute towards a PhD qualification undertaken by Meredith Blampied.

Thank you for taking the time to read this information sheet.
Should you decide to participate in this research, you will be asked to read the consent form below and indicate your consent.

Mental Health & Nutrition Research Group

Department of Psychology

University of Canterbury

Private Bag 4800

Christchurch

New Zealand

CONSENT FORM

If you need an interpreter, please let us know

Please read and sign if you consent to the following:

I have read and I understand the Participant Information Sheet.
I have been given sufficient time to consider whether or not to participate in this study.
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without any disadvantage.		
I consent to the research staff collecting and processing my information.		
I consent to my GP being informed about my participation in the study and of any significant outcomes that may arise. Please provide contact details at the end of this form.		
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I know who to contact if I have any questions about the study, if I experience any side effects related to the study intervention, if I have any upcoming medical procedures or have been prescribed new medication, if anything occurs which I think would be a reason to withdraw from the study or if I experience an increase in symptoms.		
I understand my responsibilities as a study participant, the provisions which will be made for the reimbursement of expenses involved in this study and the compensation provisions in case of injury during the study.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree to being contacted one year after I started the study to collect follow up information.	Yes ☐	No ☐
I consent to the use of my data for future related studies, which have been given ethical approval from the Health and Disability Ethics Committee.	Yes ☐	No ☐
I consent to my name being placed in a separate database so that I can be contacted in the future should there be other studies which I might like to participate in, with the understanding that I can choose whether to participate in such studies or not.	Yes ☐	No ☐

GP contact details:

Name:
Phone:

Surgery address:

Declaration by participant:

I hereby consent to take part in this study.

Yes ☐ No ☐

Participant's name:

Participant's signature:

Date:

Email address for results:

This will be completed by the principal investigator after completion of your phone screening interview.

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

Yes ☐ No ☐

I believe that the participant understands the study and has given informed consent to participate.

Yes ☐ No ☐

Researcher's name:

Date:

Ingredients: Daily Essential Nutrients

Ingredients:	**1 capsule**	**12 capsules**
Vitamin A (as retinyl palmitate)	480 IU	5,760 IU
Vitamin C (as ascorbic acid)	50 mg	600 mg
Vitamin D (as cholecalciferol)	250 IU	3,000 IU
Vitamin E (as d-alpha tocopheryl succinate)	30 IU	360 IU
Vitamin K (75% as phylloquinone; 25% as menaquinone-7)	10 mcg	120 mcg
Thiamin (as thiamin mononitrate)	4 mg	60 mg
Riboflavin	1.5 mg	18 mg
Niacin (as niacinamide)	7.5 mg	90 mg
Vitamin B6 (as pyridoxine hydrochloride)	5.8 mg	69.9 mg
Folate (as L-methylfolate calcium)	66.8 mcg	801 mcg
Vitamin B12 (as methylcobalamin)	75 mcg	900 mcg
Biotin	90 mcg	1080 mcg
Pantothenic acid (as d-calcium pantothenate)	2.5 mg	30 mg
Calcium (as chelate)	110 mg	1,320 mg
Iron (as chelate)	1.15 mg	13.8 mg
Phosphorus (as chelate)	70 mg	840 mg
Iodine (as chelate)	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:		
Choline bitartrate		

Alpha-lipoic acid
Shilajit
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)
Germanium sesquioxide (as chelate)
Boron (as chelate)
Vanadium (as chelate)
Lithium orotate (as chelate)
Nickel (as chelate)
Other ingredients:
Cellulose
Glycine
Citric acid
Magnesium stearate
Silicon dioxide

Appendix 5

Participant information sheet and consent form: Open label

Mental Health & Nutrition Research Group

Department of Psychology

University of Canterbury

Private Bag 4800

Christchurch

New Zealand

PARTICIPANT INFORMATION SHEET

Study title: The effectiveness of micronutrients as a treatment for anxiety and depression: A community trial.

Principal investigator: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

Research co-ordinator & PhD student: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

Locality: University of Canterbury, Christchurch, New Zealand

Ethics ref: 17/STH/131

Other investigators: Professor Julia Rucklidge, Dr Caroline Bell, Claire Gilbert.

You are invited to take part in a study investigating the impact of a micronutrient (vitamin and mineral) formula for adults experiencing symptoms of depression and anxiety. Diagnosis of clinical depression or anxiety is not required for entry into this study although this will be measured as part of the study. **The product we use is not the recommended intervention for clinical depression or anxiety**. The recommended intervention for anxiety and depressive symptoms is psychotherapy and antidepressant medication. Should you wish to find out more about the recommended interventions, please discuss these options with your GP.

Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This participant information sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to provide written consent by signing at the bottom of this page. Please make sure you have read and understood all the information on this form, including the consent form and list of ingredients of the products we use.

What is the purpose of the study?

Following the randomised controlled trial phase of the study where you took either the micronutrient product or placebo for 10 weeks, this part of the study ensures all participants will take the micronutrient formula we are testing. This phase of the study is called an open label phase since both you and the researchers know that you are taking the product. The product we are studying has been researched previously and has shown to have beneficial effects on depression, anxiety and stress. The researchers would therefore like to give all participants the opportunity to try the product.

What will be studied?

The formula we are studying is called *Daily Essential Nutrients*, a revised formula of the product we've tested in previous research. This product contains a blend of vitamins, minerals, amino acids and antioxidants and is consumed in capsule form. A list of the ingredients for the product are provided at the bottom of this webpage.

What will my participation involve?

Participants who have taken part in the randomised controlled phase who are not currently taking psychiatric medication are eligible. If you are taking any psychiatric medication, please let us know. We do not want you to stop taking medication in order to be in this trial. Please discuss any decision to stop taking medication with your GP.

If you decide to participate in this phase of the study, the principal investigator from the University of Canterbury will ring you for approximately 30 minutes to review information about this phase of the study, ask any questions you may have and will then arrange to have you give written consent to participate in the study. During this time, you will be asked to complete questionnaires that you have taken previously. You may also be asked to attend a face-to-face appointment at the university if the principal investigator thinks this is necessary.

You will also be given 2 weeks supply of the micronutrient product to begin taking the following day. The day after you collect the capsules, you will begin taking one capsule, three times per day and increase the dose by three capsules every second day until a maximum dose of four capsules taken three times per day is achieved. This means that a total of twelve capsules will be taken per day. You will be asked to continue taking the maximum dose of 12 capsules per day for 10 weeks. During the open label phase, you will be monitored every fortnight via online questionnaires, taking no more than 10 minutes to complete. You will be required to submit photos of unused pills as you have done previously. After 2 weeks, you will receive a 4 week supply of micronutrient product and a following 4 week supply the month after that. If you are unable to complete any of the questionnaires or take/send the photos, please let the principal investigator know via email or phone call and we will discuss other options with you.

What are the possible benefits of this study?

There may or may not be any benefit to you as a result of taking part in this study. Previous research has shown beneficial effects of micronutrient formulas on mood and anxiety in children as well as adults. The research suggests that your symptoms of depression and anxiety may improve as a result of taking the product; however, there is no guarantee that your symptoms will improve and you may experience an increase in your symptoms.

What are the possible risks of this study?

There are risks when taking an experimental treatment. Side effects reported by people taking the micronutrients include headaches, stomach aches and nausea. These side effects are typically mild and transitory and can be avoided by taking capsules **on a full stomach**. We therefore suggest that you *always take your capsules with food and plenty of water*. Another way to prevent these side effects is to increase the dose more slowly. Please don't hesitate to contact us at any stage to discuss side effects or dosing of the nutrients. Information on how to contact the principal investigator is on the website and will be on your pill bottle. We will review side effects with you every week and make a referral to a medical practitioner if necessary.

Can I take other medications?

The product you will be taking has the potential to interact with other medication or drugs so if possible you should avoid taking other medicines or supplements for the duration of the study. For this reason, we are only including individuals in the study who *are not being concurrently treated for their illness using prescribed medications.* With respect to other medications, such as over the counter medications to treat colds, flu, stomach upset, sleep problems, you should first discuss with a pharmacist before use as such medications may interact with the product. Pain relief medication such as aspirin, paracetamol, ibruprofen, Neurofen and Panadol have not shown to interact with the product and would be safe to take alongside the capsules.

If you need to take an antibiotic or antifungal agent orally at any time during the trial, please let us know. We ask this because antibiotics and antifungal drugs may interfere with the absorption of the micronutrients. Additionally, you will be asked to avoid trying any alternative medicines, supplements or other forms of therapy until after completion of this study.

What if my symptoms increase or I have a reaction to the product?

Your safety is of the utmost importance. If you experience an increase in symptoms, please let us know as soon as possible. If we feel your symptoms have increased to a clinically significant degree or that the product is causing any harm, we may discuss with you the possibility of withdrawing you from the trial. If at any time you do discontinue the trial, we will follow up with you. In the event of a psychiatric emergency or if you feel at risk to harming yourself or others, you must contact the Crisis Resolution Team on 0800 920 092 or visit the emergency department immediately. Information about what to do if you need emergency mental health support is on the website.

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Who pays for the study?

Participation in this study will not incur any costs to you. The product we are testing is provided free of charge by the manufacturers. The manufacturer (Hardy Nutritionals) do not provide any financial support and are not involved in the study in any other way. There are no restrictions on any publications from this research. The costs of this study are being funded by the University of Canterbury and the University of Canterbury Foundation. This funding will cover the costs of a $10 petrol voucher you will receive if you need to visit the university in order to reimburse you with transportation costs. You will also have access to a free car park at the university when you attend appointments for this study.

What if something goes wrong?

In the unlikely event of a physical injury as a result of your participation in this study, you must first present to the emergency department. You may be eligible for compensation from ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic, and your case will need to be assessed by

ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still may not receive any compensation – as compensation depends on a number of factors. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, please contact your nearest ACC office, or one of the investigators. If you have private health insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What are my rights?

Participation in this part of the study is entirely voluntary (your choice). You are free to decline to participate or withdraw from the research at any time without experiencing disadvantage in any way. Declining or withdrawing participation from the study will in no way affect your continuing health care. However, if you do decide to withdraw from the study at any time, we will contact your GP to inform them. The researchers may also contact you at a later stage to ensure your wellbeing. You have the right to access any information collected about you as part of the study and will be told of any new information about any adverse or beneficial effects related to the study that becomes available and may have an impact on your health.

All information collected in this study will remain strictly confidential. The only people who will have access to the information are the study investigators and designated staff. We are very careful in dealing with confidential information. Any information you disclose will be kept in a confidential file, which will be stored in a locked filing cabinet at all times.

Members of all cultures will be encouraged to participate in the study. Respect for Māori customs and traditions are of the highest priority and, if necessary, any appointments at the university can include a cultural advisor. The researchers are available to discuss the research with the whanau to assist in developing their understanding of the clinical disorders and how the disorders can impact the te taha hinengaro (mental wellbeing), whanaungatanga (family relationships), taha wairua (spiritual wellbeing) and taha tinana (physical wellbeing).

What happens after the study or if I change my mind?

At one year following your baseline assessment, you will be invited to complete some online assessments about yourself and your physical and mental health via the same website you have been using in the study. If you are unable to complete these assessments for any reason, please let the researcher know and we will ring you to discuss alternatives. However, should you decide to withdraw from the open-label trial, we would still like to follow up with you at the time you withdraw and again a year after your baseline assessment, to ensure your wellbeing and give you the opportunity to complete assessments should you wish.

After you have completed the study, you will not receive any further funded micronutrients. If you wish to purchase the micronutrients, we will assist you to do so at your own cost.

All data that you provide will be stored at the University of Canterbury for 10 years after collection, in accordance with university and health regulations and will be destroyed securely in accordance with the university guidelines. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Health and Disability Ethics Committee.

The study findings will be published in a peer reviewed scientific journal and disseminated at conference presentations. We can send you a summary of the results should you wish. However, please be aware that a significant delay may occur between data collection and publication of the results.

Who do I contact for more information or if I have any concerns?

If you have and questions, concerns or complaints about the study at any stage, you can contact the principal investigator:

Principal investigator: Meredith Blampied

Phone: 022 153 3702

Email: mindmappsychology@gmail.com

If you want to talk to someone who isn't involved in the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the Health and Disability Ethics Committee (HDEC) that approved this study on:

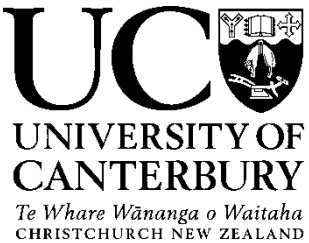
Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

This study has been reviewed and given ethical approval by the Human and Disabilities Ethics Committee and the Human Ethics Committee at the University of Canterbury. This means that the committee may check at any time that the study is adhering to ethical procedures. We have also consulted with Te Komiti Whakarite and the Māori Research Advisory Group at the University of Canterbury. Part of this research study will contribute towards a PhD qualification undertaken by Meredith Blampied.

Thank you for taking the time to read this information sheet.

Should you decide to participate in this research, you will be asked to read the consent form below and indicate your consent.



Mental Health & Nutrition Research Group

Department of Psychology

University of Canterbury

Private Bag 4800

Christchurch

New Zealand

CONSENT FORM

If you need an <u>interpreter</u>, please let us know

Please read and sign if you consent to the following:

I have read and I understand the Participant Information Sheet.		
I have been given sufficient time to consider whether or not to participate in this study.		
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without any disadvantage.		
I consent to the research staff collecting and processing my information.		
I consent to my GP being informed about my participation in the study and of any significant outcomes that may arise. Please provide contact details at the end of this form.		
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I know who to contact if I have any questions about the study, if I experience any side effects related to the study intervention, if I have any upcoming medical procedures or have been prescribed new medication, if anything occurs which I think would be a reason to withdraw from the study or if I experience an increase in symptoms.		
I understand my responsibilities as a study participant, the provisions which will be made for the reimbursement of expenses involved in this study and the compensation provisions in case of injury during the study.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree to being contacted one year after I started the study to collect follow up information.	Yes ☐	No ☐
I consent to the use of my data for future related studies, which have been given ethical approval from the Health and Disability Ethics Committee.	Yes ☐	No ☐

I consent to my name being placed in a separate database so that I can be contacted in the future should there be other studies which I might like to participate in, with the understanding that I can choose whether to participate in such studies or not.	Yes ☐	No ☐

GP contact details:

Name:
Phone:
Surgery address:

Declaration by participant:

I hereby consent to take part in this study.

Yes ☐ No ☐

Participant's name:

Participant's signature:

Date:

Email address for results:

This will be completed by the principal investigator after completion of your phone screening interview.

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

Yes ☐ No ☐

I believe that the participant understands the study and has given informed consent to participate.

Yes ☐ No ☐

Researcher's name:

Date:

Ingredients: Daily Essential Nutrients

Ingredients:	**1 capsule**	**12 capsules**
Vitamin A (as retinyl palmitate)	480 IU	5,760 IU
Vitamin C (as ascorbic acid)	50 mg	600 mg
Vitamin D (as cholecalciferol)	250 IU	3,000 IU
Vitamin E (as d-alpha tocopheryl succinate)	30 IU	360 IU
Vitamin K (75% as phylloquinone; 25% as menaquinone-7)	10 mcg	120 mcg
Thiamin (as thiamin mononitrate)	4 mg	60 mg
Riboflavin	1.5 mg	18 mg
Niacin (as niacinamide)	7.5 mg	90 mg
Vitamin B6 (as pyridoxine hydrochloride)	5.8 mg	69.9 mg
Folate (as L-methylfolate calcium)	66.8 mcg	801 mcg
Vitamin B12 (as methylcobalamin)	75 mcg	900 mcg
Biotin	90 mcg	1080 mcg
Pantothenic acid (as d-calcium pantothenate)	2.5 mg	30 mg
Calcium (as chelate)	110 mg	1,320 mg
Iron (as chelate)	1.15 mg	13.8 mg
Phosphorus (as chelate)	70 mg	840 mg
Iodine (as chelate)	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:		
Choline bitartrate		
Alpha-lipoic acid		
Shilajit		
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)		
Germanium sesquioxide (as chelate)		
Boron (as chelate)		
Vanadium (as chelate)		
Lithium orotate (as chelate)		
Nickel (as chelate)		
Other ingredients:		
Cellulose		
Glycine		
Citric acid		
Magnesium stearate		
Silicon dioxide		

Appendix 6 Questionnaires

Baseline Questions

Demographic questions:

Age (in years)

Sex:

Female, Male, Other (text box)

Please indicate which of the following ethnic groups you below to (you may select more than one)

- NZ Maori
- Pakeha/NZE
- Samoan
- Tongan
- Niuean
- Chinese
- Indian
- Other (text box)

Please indicate your highest educational qualification

- No school certificate/No NCEA
- School certificate in one or more subject
- NCEA Level 1
- Sixth form certificate or university entrance in more than one subject
- NCEA Level 2
- University Bursary or Scholarship
- NCEA Level 3
- Overseas qualification (Text box)
- Post-secondary (e.g diploma, trade certificate)
- Bachelor degree
- Post-graduate university degree
- Other qualification (text box)

What is your occupation (text box)

Please indicate which of the following best describes your total household income before tax (include income from all sources):

Less than $20,000

From $20,000 to $40,000

From $40,000 to $60,000

From $60,000 to $80,000

More than $80,000

How many people live in your household?

1 to 8 or more

Do you have any children?

y/n

How many children do you have and what are their ages? (text box)

What is your marital status?

Single

Not married but living with a partner

Married and living together

Divorced

Separated

Widowed

Other (text box)

Baseline questions:

1. How long have you been experiencing symptoms of anxiety and/or depression?
   Less than 12 months
   12 months- 2 years
   2-5 years
   5+ years
2. Have you had previous treatment for anxiety and or depressive symptoms? (treatment includes things like self-help, counselling, cognitive behaviour therapy, psychotherapy, medication, complementary/alternative medicine).
   y/n
   If y- What?
   If y, has this treatment been successful?
   Y, N, partially successful

3. Thinking about the phone conversation with Meredith Blampied, please rate this conversation by placing a mark on the line nearest the description that best fits your experience:

4. Could you please tell me, do you think that this nutrient supplement will help:

	Anxiety	Mood	General wellbeing
Not at all			
Just a little			
Somewhat			
Very much			

5. Please estimate out of 100% (where 100% is all of the time) how much time over the past 24 hours you've spent thinking about in the:

Past:

Present:

Future:

%'s do not need to add to 100%.

6. Have you accessed any other treatments for mental health issues over the past week?

If so, what?

7. How many days have you taken off work/study the past month for health reasons
8. How many visits to your GP have you made in the past month?

9. How much medical intervention have you had over the last 3 months (estimate)?

Not at all
Just a little
Somewhat
Very much

10. Have you been diagnosed with any new medical problems over the PAST MONTH:

y/n check box

Please detail what medical problems you have experienced:

11. Have you been prescribed any new medication over the PAST MONTH:
    y/n check box
    Please name the new medication you have been prescribed and for what condition it has been prescribed for:

12. Have you been hospitalised over the PAST MONTH:
    y/n check box
    For what condition were you hospitalised and for how long:
13. Over the past month, have you smoked a cigarette?
    y/n
14. How soon after waking did you smoke your first cigarette?
    a. Within 5 mins
    b. 5-30 mins
    c. 31-60 mins
    d. 60+ mins
15. How many cigarettes a day did you smoke?
    a. 10 or fewer
    b. 11-20
    c. 21-30
    d. 31 or more

Weekly Questions

1. Have you accessed any other treatments for mental health issues over the past week?

If so, what?

2. How many days have you taken off work/study this week for health reasons?
3. Have you been diagnosed with any new medical problems over the PAST WEEK:

   y/n check box

   Please detail what medical problems you have experienced:

4. Have you been prescribed any new medication over the PAST WEEK:
   y/n check box
   Please name the new medication you have been prescribed and for what condition it has been prescribed for:

5. Have you visited your GP over the past week?
   y/n check box

6. Have you been hospitalised over the PAST WEEK:
   y/n check box
   For what condition were you hospitalised and for how long:

   Text boxes:
   Is there anything else you would like to tell us? If yes, please detail in box below.
   Do you have any questions? If yes, please detail in box below.

End of RCT and End of OL Questions

Weekly questions:

16. Could you please tell me, did you think that this nutrient supplement helped:

	Anxiety	Mood	General wellbeing
Not at all			
Just a little			
Somewhat			
Very much			

17. Please estimate out of 100% (where 100% is all of the time) how much time over the past 24 hours you've spent thinking about in the:

Past:

Present:

Future:

%'s do not need to add to 100%.

18. Have you accessed any other treatments for mental health issues over the past week?

If so, what?

19. How many days have you taken off work/study this week for health reasons?
20. Have you visited your GP over the past week?
    y/n check box

21. Have you been diagnosed with any new medical problems over the PAST WEEK:

    y/n check box

    Please detail what medical problems you have experienced:

22. Have you been prescribed any new medication over the PAST WEEK:
    y/n check box
    Please name the new medication you have been prescribed and for what condition it has been prescribed for:

23. Have you been hospitalised over the PAST WEEK:
    y/n check box
    For what condition were you hospitalised and for how long:

    Text boxes:
    Is there anything else you would like to tell us? If yes, please detail in box below.
    Do you have any questions? If yes, please detail in box below.

END OF RCT ONLY:

Do you think you were taking the micronutrient product or placebo?

Micro (tick box)

Why do you think this? (Text box)

Placebo (tick box)

Why do you think this? (Text box)

Not sure (tick box)

Why do you think this? (Text box)

(PI to also answer the same question for each participant)

Appendix 7 Additional Tables

Table 9

Baseline to End of RCT Phase Effect Sizes Secondary Outcome Variables by Treatment Group for Full Trauma Sample

Variable	Intervention	Baseline	End of RCT	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
DASS-42	Placebo (*n*=26)	48.08 (25.91)	25.23 (26.36)	-1.27	-0.47	**-0.87**	86%
	Micronutrient (*n*=35)	51.6 (24.09)	32.11 (26.23)	-1.06	-0.38	**-0.77**	77%
Dep	Placebo (*n*=26)	18.77 (10.75)	10.15 (10.35)	-1.19	-.43	**-0.82**	85%
	Micronutrient (*n*=24)	19.66 (11.85)	13.03 (11.94)	-0.94	-.16	**-0.56**	69%
Anx	Placebo (*n*=26)	10.38 (8.39)	4.69 (7.86)	-1.08	-.31	**-0.7**	79%
	Micronutrient (*n*=35)	11.71 (8.32)	6.91 (8.19)	-0.95	-.21	**-0.58**	71%
Stress	Placebo (*n*=26)	18.92 (10.06)	10.38 (9.7)	-1.32	-.39	**-0.86**	80%
	Micronutrient (*n*=35)	20.23 (8.52)	12.17 (8.6)	-1.36	-.51	**-0.94**	81%
GAD 7	Placebo (*n*=24)	9.79 (5.66)	4.96 (5.61)	-1.34	-0.37	**-0.86**	79%
	Micronutrient (*n*=33)	10.79 (6.17)	6.24 (5.6)	-1.13	-0.4	**-0.77**	80%
PHQ 9	Placebo (*n*=24)	14 (5.28)	6.04 (6.25)	-1.93	-.8	**-1.38**	91%
	Micronutrient (*n*=33)	14.06 (5.07)	7.6 (5.97)	-1.6	-0.72	**-1.17**	88%
QOLS	Placebo (*n*=23)	73.13 (14.94)	76.78 (14.93)	-0.02	0.5	0.24	65%

Table 10

Baseline to End of OL Phase Effect Sizes Secondary Outcome Variables by Treatment Group for Full Trauma Sample

Variable	Intervention	Baseline	End of OL	95% Confidence Interval on *d*		ES *d*	PS
		mean (SD)		Lower bound	Upper bound		
DASS-42	Placebo (n=22)	47.64 (25.72)	28 (21.95)	-1.3	-0.33	**-0.82**	80%
	Micronutrient (n=30)	52 (24.38)	33.73 (23.16)	-1.2	-0.33	**-0.77**	76%
Dep	Placebo (n=22)	18.73 (10.79)	10.82 (10.12)	-1.25	-.25	**-0.76**	76%
	Micronutrient (n=30)	19.47 (11.84)	13.73 (11.28)	-0.88	-.11	**-0.5**	69%
Anx	Placebo (n=22)	10.18 (8.77)	4.54 (5.86)	-1.2	-.3	**-0.76**	79%
	Micronutrient (n=30)	11.53 (8.54)	6.13 (6.87)	-1.08	-.3	**-0.7**	76%
Stress	Placebo (n=22)	18.73 (9.47)	12.64 (9.45)	-1.09	-.18	**-0.64**	74%
	Micronutrient (n=30)	21 (8.46)	13.87 (9.22)	-1.27	-.33	**-0.81**	75%
GAD 7	Placebo (n=22)	10 (6.15)	4.77 (4.33)	-1.57	-0.38	**-0.98**	79%
	Micronutrient (n=30)	11.27 (6.27)	5.8 (5.37)	-1.38	-0.48	**-0.94**	81%
PHQ 9	Placebo (n=22)	13.5 (5.14)	6.77 (6.23)	-1.64	-.71	**-1.18**	95%
	Micronutrient (n=30)	14.6 (5.07)	7.5 (5.78)	-1.8	-0.79	**-1.3**	89%
QOLS	Placebo (n=20)	74.25 (15.34)	77.85 (16.86)	-0.01	0.45	0.22	67%
	Micronutrient (n=30)	68.37 (13.35)	74 (14.61)	0.13	0.67	**0.4**	72%

Table 11

Associations Between Outcome Measures and Putative Predictor Variables as p-values

	IES-R change score (Baseline IES-R > 24) *n* = 19	CGI-I responder (All trauma participants) *n* = 72
Demographic variables		
Gender	.403	.365
Ethnicity	.766	.458
Age	.103	.219
NZSEI	.189	.098
Clinical characteristics		
IES-R baseline score	.746	.129
History of psychotropic medication (yes/no)	**.002**	.796
History of psychotherapy (yes/no)	.071	.57
Symptom duration	.332	.257
Trauma type	.39	
More than one traumatic event reported	.371	.59
Broad trauma type (single or recurring)	.222	.213
RCT characteristics		
Nutrient expectation		
Anxiety	.165	.348
Mood	.150	.644
Wellbeing	.662	.640
Guessed Micronutrient condition	**.031**	.01
PI contact level	.079	**.042**