

A Pilot Investigation into the Effect of Micronutrients on Anxiety and Stress
in Canterbury Children: A Multiple Baseline Design

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Abstract

Anxiety disorder can negatively affect many areas of a child's life, including social and academic development, and increase the risk of mental health problems in adolescence and adulthood. Although psychotherapy is an effective treatment for children with anxiety, it is not widely available, while psychiatric medications are recommended for use in only the most severe cases. For these reasons, investigation into other possible treatments for problems with anxiety is necessary. The present study examined the effect of a broad-based micronutrient formula called EMPowerplus (EMP+) on children suffering from elevated levels of anxiety, following a multiple baseline design. The final sample comprised 14 participants, aged between eight and 12 years, who were randomised into one of three baseline groups, ranging from one to three weeks in length. Following the baseline period, participants took part in an open-label trial of EMP+ for eight weeks, after which a three-month follow-up was conducted. Although there was a trend toward a decrease in symptom severity over the baseline period, there was a much greater decline in symptoms during the intervention phase. Modified Brinley plots revealed decreases in anxiety and improvements in overall functioning for 10 out of 11 participants who completed the intervention. A comparison of group means confirmed statistically significant change between baseline and end of trial, while gains were maintained over the follow-up period. Furthermore, those participants who were compliant with the intervention tended to improve more than participants who were not compliant and side effects were generally mild and transient. This study provides evidence for the potential of micronutrient interventions in effectively treating anxiety in children. It also opens the door for future research utilising placebo-controlled designs, as well as comparisons to other conventional treatments.

1. Introduction

1.1 Anxiety in Children

Anxiety itself is an adaptive response, the effect of stimulation of the sympathetic nervous system. It allows the body to prepare to respond to danger, meaning anxiety is often an appropriate reaction to a threatening or dangerous situation. Everybody will at some point feel anxious, although it might be described as something else, for instance feeling ‘stressed out’ or ‘uptight’(Bushnell et al., 1998). Stimulation of the sympathetic nervous system produces nervous and endocrine system changes resulting in a rapid and generalised response, the fight-or-flight response. The physiological changes which occur because of this response allow an individual to attack, run from or freeze in the face of a threat and can include tachycardia, increased perspiration, tremor, increased blood glucose concentrations, constriction of blood vessels, slowing of non-essential systems such as digestion and the immune system, pupil dilation, muscle tension and an increase in breathing rate (Fraser & Solovey, 2007). As part of this psychophysiological response, the hypothalamic-pituitary-adrenal (HPA) axis is activated to release norepinephrine and cortisol into the bloodstream (Tufnell & DeJong, 2009). The overall response allows the body to cope with the source of the stress and anxiety over a period of time, and then gradually return to normal functioning after a stressor is removed.

However, the response can also be triggered in situations where there is perceived threat rather than real threat, or when the threat has long passed. Indeed, in today’s society many threats cannot be resolved through fighting or fleeing. Instead these modern threats are often long-lasting or recurrent and allow the individual little control over removal of the threat, resulting in continuous or repeated activation of the body’s stress systems (Bushnell et al., 1998). This could be likened to continual activation of the freeze response, when an animal has no option but to endure the threat and hope for survival. In such situations as

these, anxiety can often become chronic, resulting in impairment in learning through deficiencies in memory and concentration, and difficulties at home and with peers due to behavioural repercussions, such as impaired affect modulation and impulse control. This chronic anxiety can have negative physical effects on the body such as causing persistent gastrointestinal issues or headaches, weakening of the immune system, generally higher disease burden and even impaired brain development (Gruner, 2006; Sparrow, 2007). In adults, high levels of anxiety or stress have been linked to increased risk of cardiovascular incidents and stroke (Gruner, 2006). Anxiety itself, as well as its secondary effects, can cause a great deal of distress for a child and can be amplified when the child expects further stressful stimuli. The child can end up in a vicious circle whereby distress continues to increase anxiety, impairing performance, having more negative effects on the child's life and thus, increasing distress (Sparrow, 2007). Alleviating anxiety disorder once it occurs will allow a child to grow and learn unhindered by chronic anxiety's negative effects and prevent anxiety affecting the child's life as they move into adolescence and adulthood.

Anxiety and stress in childhood is often a natural, common and short-lived experience with the presentation varying according to the individual's developmental stage (Barrett, 2000). A number of younger children experience separation anxiety, while a common source of anxiety for older children can be school and tests (Beidel & Alfano, 2011; Vallance & Garralda, 2008). Dealing with stress and anxiety successfully teaches children coping skills they can use and develop throughout life, yet much of the literature acknowledges our understanding of anxiety in children is limited (Albano, Chorpita, & Barlow, 2003).

In some cases the natural fears and anxieties of childhood can be the precursor for more serious and debilitating illness (Beidel & Alfano, 2011). Once anxiety rises to levels that interfere with social, emotional and/or academic development, is culturally or developmentally inappropriate, or causes a child or his/her family significant distress, then

anxiety is seen as a disorder (American Psychiatric Association, 2013), a problem for the child which is likely to lead to further issues. Anxiety disorders are some of the most common psychiatric illnesses affecting children (Albano, Chorpita, & Barlow, 2003). Chronically high levels of anxiety are associated with significant impairment and often result in avoidance of activities including socialising and educational and recreational opportunities (Albano et al., 2003), ultimately interfering with development.

Research suggests significant anxiety can develop at an early age. Spence, Rapee, McDonald and Ingram (2001) found anxiety symptoms consistent with DSM-IV diagnostic categories present in a sample of children aged 2.5 to 6.5 years. Furthermore, there is evidence that anxiety disorder in childhood is predictive of psychiatric symptomatology as children move into adolescence (Achenbach, Howell, McConaughy, & Stanger, 1995) and later into adulthood (Ferdinand & Verhulst, 1995), whether specific to continued anxiety symptoms or other classifications of psychopathology. For instance, high anxiety in childhood has been found to result in increased risk of further anxiety disorder or depressive disorders in later life (Rockhill et al., 2010). Other evidence suggests, if left untreated or for those who respond less favourably to treatment, childhood anxiety disorders can lead to adverse outcomes and further psychiatric illness in adolescence, such as substance abuse (Kendall, Safford, Flannery-Schroeder, & Webb, 2004).

Individuals with high anxiety or an anxiety disorder have specific reoccurring fears or worries in relation to certain situations, or have anxiety symptoms which may seem to appear unexpectedly, such as in panic disorder. Symptoms of anxiety disorder may present as behavioural and somatic symptomatology, including tantrums, being easily startled, ritualistic behaviour, avoidance (e.g. of situations or places), sleep disturbance, tearfulness, changes in eating patterns, school refusal, chest or abdominal pain, gastrointestinal symptoms, headaches, nausea, muscle tension, restlessness, body aches and sweating. Anxiety disorder

also presents in the form of emotional and cognitive symptoms such as worries, expecting the worst, difficulty concentrating, feeling helpless and distress (Bushnell et al., 1998; Kelly, 2005).

Community prevalence rates for all anxiety disorders range from 3.1% to 17.5% in children and adolescents (Rockhill et al., 2010). In New Zealand, approximately 7% of children will meet criteria for any anxiety disorder at age 11 years. By 18 years of age, this number will be just below 20%. Anxiety disorders tend to be equally prevalent in boys and girls during childhood, after which girls are more likely to be diagnosed (Cohen et al., 1993). In addition, at least one third of children with an anxiety disorder will meet criteria for another one or more anxiety disorders (Strauss & Last, 1993). Brady and Kendall (1992) found comorbidity rates of anxiety and depression for children and adolescents ranged from 16-62%, with anxiety tending to present earlier than depression.

International data from the WHO International Consortium in Psychiatric Epidemiology (ICPE) found the age of onset for anxiety disorders was remarkably similar across a range of countries and that more than 50% of cases had their onset before the age of 20 years (Lieb, 2005). Approximately 20% had their first onset before the age of 10 years (Lieb, 2005). Specific phobia and social phobia have been shown to have the earliest age of onset, usually in childhood or adolescence, while generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD) and panic disorder tend to first occur in late adolescence or early adulthood (Burke, Burke, Regie, & Rae, 1990; Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996; Wittchen, Lieb, Schuster, & Oldenhinkel, 1999a).

While an initial anxiety disorder may remit, there is also a risk that another anxiety disorder may develop in childhood (Last, Perrin, Hersen, & Kazdin, 1996) or in adolescence (Aschenbrand, Kendall, Webb, Safford, & Flannery-Schroeder, 2003). In addition, the more severe the disorder, the greater the level of impairment and the more likely it is that the

disorder will persist (Dadds et al., 1999; Manassis & Hood, 1998). Furthermore, children with anxiety disorders are at a greater risk of later being diagnosed with depression and substance abuse, not just other anxiety disorders (Connolly & Bernstein, 2007). These children are also at greater risk of experiencing educational underachievement, even after controlling for the confounding effects of socio-familial and individual factors (Woodward & Fergusson, 2001).

Anxiety disorders can have wide reaching effects on a child's development, including negative effects on social, family and academic functioning, as the symptoms of the disorders interfere with normal development in a number of areas (Connolly & Bernstein, 2007). This can have further effects on the child's self-image, including low self-esteem and a tendency to interpret situations negatively (Bögels & Zigterman, 2000). As discussed, there is also a chance that anxiety during childhood will persist into adolescence and adulthood, resulting in additional psychiatric problems and further negatively affect the individual's life.

1.2 Treatments for Childhood Anxiety

Pediatric anxiety disorders tend to be treatable conditions when prompt diagnosis is followed by prompt treatment, minimising the impact of anxiety on the individual and the family system (Kelly, 2005). Research suggests psychotherapy and pharmacotherapy are effective at reducing the symptoms of anxiety (Kelly, 2005). The intensity of treatment should be targeted to the severity of anxiety symptoms (Connolly & Bernstein, 2007). For instance, mild anxiety may be best treated with brief psychotherapy. However, more severe anxiety or moderate to severe anxiety which requires acute symptom reductions may require more intensive psychotherapy or a combination of psychotherapy and pharmacotherapy in order to reduce symptoms (Connolly & Bernstein, 2007; Kelly, 2005). It is not recommended that pharmacotherapy be the sole treatment for pediatric anxiety disorders unless there is no

or little response to psychotherapy (Connolly & Bernstein, 2007). Indeed, many traditional medications are not recommended for use with children, either through lack of effect, adverse side effects or poor research methods and designs which result in inadequate conclusions (Kelly, 2005). It has been recommended that treatment be delivered by a multidisciplinary team and take a multimodal approach for optimal gains and resolution of anxiety (Connolly & Bernstein, 2007). In addition, a combination of therapies tailored to the individual and the family is most likely to relieve symptoms and improve quality of life (Ali, 2007).

1.2.1 Psychotherapy. Psychological therapies used in the treatment of high anxiety and anxiety disorders often take the form of cognitive behavioural therapy (CBT; Ali, 2007). CBT is a highly adaptable therapy focusing primarily on the link between an individual's thoughts, feelings and behaviour, but in which a number of different techniques can be incorporated to best fit the individual client and his/her symptomatology. Namely CBT for children with anxiety includes at least some of the following components: psychoeducation for parents and child, training in somatic symptom management skills, cognitive restructuring, teaching problem-solving and coping strategies, exposure tasks and relapse prevention (Albano & Kendall, 2002; Bernstein & Victor, 2007; Mor & Meijers, 2009). For example, exposure-based techniques are efficacious in treating certain types of anxiety such as phobias and can be readily integrated into a CBT framework (Compton et al., 2004). Furthermore, an emphasis should be put on monitoring and reducing functional impairment, not solely anxiety symptoms, as functional impairment can lead to further anxiety symptoms and other co-morbid disorders (Connolly & Bernstein, 2007). There is support for both the short-term and long-term effectiveness of CBT for the treatment of anxiety in children (Barrett, Duffy, Dadds, & Rapee, 2001; Kendall et al., 2004; Saavedra, Silverman, Morgan-Lopez, & Kurtines, 2010); however, it is not universally effective, with 20-50% of children

who have undergone CBT treatment still meeting criteria for an anxiety disorder following treatment (Kendall, 1994; Kendall et al., 1997).

Another approach which is used in the treatment of childhood anxiety is psychodynamic psychotherapy. This approach lacks research on its efficacy or effectiveness; however, some studies have shown positive effects on anxiety symptomatology (Connolly & Bernstein, 2007). One disadvantage to psychodynamic psychotherapy is the length and intensity with which it is administered. Often clients will see a therapist two to three times a week for at least a few months, making this type of therapy less accessible and more costly than the more time-limited and weekly sessions traditionally seen within CBT. In addition, CBT can also be delivered in a group format, both to children and to parents, reducing costs and decreasing waitlists compared to individual treatment. Bernstein and Victor (2007) suggest including parents or caregivers in treatment to improve symptom reduction and provide support for the child outside of therapy in terms of learning and using the new skills being taught within therapy sessions. This is particularly useful for young children and for children with severe anxiety symptoms or comorbid diagnoses and also serves to address any maladaptive parenting styles or techniques which may be contributing to anxiety (Bernstein & Victor, 2007). Ultimately, psychotherapy can help children to learn how to manage and reduce anxiety to normal, adaptive levels.

1.2.2 Pharmacotherapy. Selective Serotonin Reuptake Inhibitors (SSRIs) are the most common medication prescribed for the treatment of childhood anxiety disorders other than post-traumatic stress disorder (Bloch & Mc Guire, 2011; Connolly & Bernstein, 2007). A number of studies have demonstrated a significant decrease in anxiety symptoms with the treatment of SSRIs compared to placebo (e.g. Beidel et al., 2007; Birmaher et al., 2003;

Rynn, Siqueland, & Rickels, 2001). As such, SSRIs are considered the first line pharmacotherapy treatment of choice for pediatric anxiety disorders (Watson, 2011).

Studies have also investigated the effect of benzodiazepines on anxiety disorders in children and adolescents. In a review, Riddle et al. (1999) found that although overall there was a trend for improvement within the anxiety treatment groups, the studies were generally of short duration and there were high response rates within placebo groups. Furthermore, the authors recommended only short-term prescriptions given the risk of dependence and warned of the risk for reoccurrence of anxiety after ceasing drug treatment. Benzodiazepines, along with noradrenergic antidepressants and buspirone, are considered second or third-line pharmacotherapy alternatives (Watson, 2011). There is very little research supporting the use of noradrenergic antidepressants and buspirone in the treatment of paediatric anxiety disorders.

National Institute of Health and Care Excellence (NICE) guidelines are internationally recognised and constitute a series of clinical guidelines to ensure consistent, high quality and evidence based care within the health sector. The NICE (2005) guidelines for treatment of depression in children and young people recommend that SSRI's be used in the treatment of childhood depression only when: the depression is moderate to severe; after at least four to six sessions of an at least three month programme of a recommended psychological therapy in which there is no response; after psychological therapy for co-morbid difficulties or risk factors, additional psychological therapy for the child and perhaps psychological therapy for the parents and other family members in which there is no decrease in depression symptoms. Even then, fluoxetine should be offered to young people (aged 12-18 years) following specific treatment guidelines, and offered cautiously to children (aged 5-11 years) following the same treatment guidelines. In essence, the NICE guidelines indicate that antidepressant treatment should be the last treatment option for children and young people, except in the

instance where there are moderate to severe depressive symptoms, significant risk issues and no response from four to six weeks of psychological therapy. SSRI's should not be given for mild depression in children.

Similar, if not more conservative recommendations, could be made for anxiety disorders in children, especially considering the lack of evidence for the use of SSRI's for the treatment of anxiety disorders in this age group. Guidelines published by The Werry Centre for Child and Adolescent Mental Health Workforce Development suggest SSRI's only feature in the "promising treatment" category for OCD in children, but no other anxiety disorder (Dunnachie, 2007). Indeed, Fisher, Tobkes, Kotcher, and Masia-Warner (2006) assert that the US Federal Drug Association has not approved SSRI's for the treatment of any child anxiety disorder, other than OCD.

There is a relative lack of research into the use of psychiatric medications for anxiety treatment in children compared to the adult research literature. As such, it may be that with further research there is more evidence for using medication to treat anxiety disorders in children; however, the research on the use of medications for childhood anxiety is plagued by a large amount of controversy involving issues about poor research designs and methods, such as small sample sizes and short trial durations, high placebo response rates and publication biases (Riddle et al., 1999). There is also little research comparing medication with conventional treatments for anxiety (e.g. psychotherapy). One study by Beidel and colleagues (2007) compared Social Effectiveness Therapy (SET-C) to fluoxetine in a sample of 122 children and adolescents diagnosed with social phobia. They found both were more efficacious than placebo at reducing social distress and behavioural avoidance, as well as at increasing general functioning. However, SET-C was better than fluoxetine in terms of improvement in social anxiety, reducing behavioural avoidance and absence of social anxiety

diagnosis at the end of the trial. In addition, the researchers found SET-C provided continued improvement over three months, whereas fluoxetine reached maximum effect by two months.

Other criticisms of antidepressant research include the cost and benefit analysis when considering improvement rates for individuals taking medication compared to those on placebo, the number of participants who remain symptomatic and the side effects. Birmaher et al. (2003), using an intent-to-treat analysis, found 61% of participants on fluoxetine (SSRI) improved between much to very much, compared to 35% taking placebo. However, a significant group of those taking fluoxetine remained symptomatic despite improvement, while fluoxetine was also linked to mild and transient headaches and gastrointestinal symptoms. In this study, there were also instances of excitement, giddiness or disinhibition in seven participants taking fluoxetine and four participants taking placebo, with five of the fluoxetine participants having to discontinue the treatment. Another study investigating the effect of sertraline (SSRI) for anxiety found participants taking sertraline reported a greater number of adverse events than participants taking placebo, including more experiences of dry mouth, drowsiness, leg spasms and restlessness (Rynn, Siqueland, & Rickels, 2001). Similarly, Walkup and colleagues (2001) reported abdominal discomfort and increased motor activity were significantly more common in the group of participants taking fluvoxamine (SSRI) than in the placebo group. Furthermore, no study has compared different types of SSRI's with one another to determine which individuals these drugs might be most efficacious for, given, results suggest that SSRI's may have different levels efficacy for different anxiety disorders (Fisher et al., 2006). For instance, Birmaher et al. (2003) found a greater treatment effect for children with social phobia compared to those with separation anxiety disorder when treating anxiety with fluoxetine.

Some researchers and clinicians have argued there is an advantage for medication, in that it has a quicker therapeutic action than psychotherapies. However, although both Rynn et

al. (2001) and Walkup et al. (2001) reported finding a trend towards improvement by week four of their trials, it took nine weeks on fluoxetine before this treatment became significantly better than placebo. This suggests that the usually recommended eight to 12 sessions of psychological therapy for these disorders, occurring weekly, will see an improvement in anxiety symptoms at an equal, if not quicker rate than medication, without the need for continued medication use and without side effects. In addition, psychological therapy teaches children ways to manage their anxiety, which given the association between childhood anxiety and later psychopathology, could possibly also reduce the seriousness of, or prevent, later mental health issues.

Overall, SSRI's are recommended for treatment of anxiety in the short-term, for those with whom psychotherapy has had little or no effect and for those who cannot access psychotherapy (Dunnachie, 2007; Fisher et al., 2006; Watson, 2011). Psychotherapy, particularly CBT, should be the first line treatment for children with anxiety disorders, although more research is necessary into both psychotherapy and medication treatments, in order to have a clearer picture of which treatments might be most appropriate and efficacious for certain individuals and the way in which these should be delivered. It is also important to note that some individuals prefer not to take medication to help control their mental illness, either because of the side effects or because they do not want to use drugs as matter of personal preference. Yet, psychotherapy may not be available to these individuals, as it is not usually publically funded for those with illness that is mild to moderate in severity, resulting in the exclusion of a significant number of people who suffer from anxiety. Furthermore, attending psychotherapy sessions privately can be costly, meaning this maybe not be an option for some individuals either. Thus, other treatments need to be explored to increase treatment accessibility and widen the range of choice for children and families suffering from

anxiety disorders. Micronutrients may be another such treatment option. This will be explored in the following sections.

1.3 Why Micronutrients Should Be Considered

Micronutrients are the vitamins and minerals which allow the brain and body to function, making them necessary for physical and mental health. Micronutrients are essential for many aspects of brain functioning, including energy metabolism, synthesis of neurotransmitters and maintaining blood supply to brain tissue (Haller, 2005). In fact, blood supply to the brain has been found to be effected by long-term vitamin deficiency, which can lead to tissue death and other pathological processes affecting mental and physical health (Haller, 2005). The B vitamins are particularly important in this respect, with depletion associated with such syndromes as Wernicke's and Korsakoff's syndromes and neuropsychiatric symptoms, such as low mood and irritability (Haller, 2005). Zinc and iron deficiencies have been implicated in some neurological degenerative disorders, such as Alzheimer's disease (Bray & Levy, 2005; Pinero & Connor, 2005). Other micronutrients are important for brain development, including zinc for its role in cognitive development (Haller, 2005) and iodine for its role in thyroid development (Lazarus, 2005). Deficiency of iodine prenatally can lead to increased stillbirths, infant mortality and congenital abnormalities, while deficiency of iodine in children and adults can lead to hypothyroidism and impaired mental functioning (Lazarus, 2005). Micronutrients serve as essential cofactors for neurotransmitter synthesis, with more than one third of enzymes needing a vitamin or mineral cofactor (Haller, 2005). Simply, without micronutrients survival would be impossible, let alone good health.

The increase in mental health disorders which has been observed over the last few decades has been linked to the deterioration of the Western diet, which is characterised by

high amounts of processed foods and a lack of fruits and vegetables, ultimately leading to micronutrient deficiencies (Lakhan & Vieira 2008; Jacka et al., 2010). This could be further compounded by the depletion in mineral content of soils due to agricultural practices (Mayer, 1997), and thus of foods such as fruits and vegetables (Thomson & Robinson, 1980; Ekholm et al., 2007). As micronutrients have such a wide ranging and important role in normal brain functioning and have been implicated in a number of syndromes and disorders with psychiatric and behavioural effects, they are worthy of consideration within the field of mental health research. This would be even without knowledge of the link between an increase in mental health disorders and the Western diet deterioration. In addition, given anxiety disorders are such a debilitating illness, affecting such a number of individuals, any contribution to its treatment is worth pursuing. As Lakhan and Vieira (2010) acknowledge, the universality of nutritional and herbal remedies in many cultures over thousands of years makes this avenue an appropriate one to take. Furthermore, the side effects of some anti-anxiety medications, the questionable effectiveness and efficacy of those medications, the lack of availability of psychotherapy and personal preference, all point towards exploring different types of treatment for anxiety. The research demonstrating the efficacy of micronutrients for treatment of some mental health disorders is growing, as is the research demonstrating the safety of micronutrient interventions and mild side effect profile.

1.4 Theories about Micronutrient Deficiencies and Mental Health Symptoms

There have been a number of theories proposed about the role of micronutrient deficiencies in mental health and the expression of psychiatric symptoms. Evidence suggests that the B-vitamins may be particularly important in terms of ameliorating symptoms of stress and anxiety (Camfield et al., 2013). Folate, B6 and B12, as well as some other B-vitamins, are involved in a process whereby homocysteine is cleared from the body, through

converting homocysteine back to methionine (Camfield et al., 2013). Homocysteine is produced during metabolism of methionine and methionine metabolism is important for the methylation of a number of substances, including DNA (Camfield et al., 2013). If homocysteine is not converted back to methionine, then some methylation processes cannot occur, despite methylation being a very important process within the brain. The large amounts of homocysteine that build up when it is not converted back to methionine have been found to cause oxidative stress and damage to DNA and mitochondrial membranes (Camfield et al., 2013). The link between increased homocysteine and stress has been demonstrated by Kang et al. (2005) and Stoney (1999).

An effect on mood has also been implicated in this process. This is because methionine is required for the synthesis of S-adenosyl-methionine (SAME; Bottiglieri, 1996). SAME is required for a number of different reactions including the synthesis of neurotransmitters such as serotonin (Papakostas, Alpert and Fava, 2003). Many studies have linked folate and B12 deficiencies to mood via elevated plasma homocysteine and low SAME levels, while treatment of depression with SAME has had positive effects in open and randomised, controlled trials (Papakostas et al., 2003).

It is well known that stress results in many physiological changes throughout the brain and body, including altering the gut's ability to absorb nutrients (Kaplan et al., 2007). Thus, it is also important to note that stress and anxiety may impair the above methylation reactions via affecting nutrient absorption by the gut. Furthermore, inadequate absorption could have a negative flow-on effect to the nutrients required for neurotransmitter synthesis and therefore any processes or functions these neurotransmitters may be utilised in (Kaplan et al., 2007).

Another proposed link between micronutrient deficiencies and the symptoms of mental illness is via inborn errors in metabolism. Ames (2004) demonstrated that at least one third of genetic mutations reduced the binding affinity of coenzymes. Suboptimal levels of

coenzymes, of which include a number of micronutrients, would reduce rates of metabolic activity because of decreased binding rates (Kaplan & Leung, 2011). It may be that for some mental health disorders where there is significant heritability, the cause of the symptoms is due to inborn errors of metabolism which slow metabolic activity, such that micronutrient treatment might increase that activity (Kaplan and Leung, 2011).

Mitochondrial dysfunction has also been implicated in the underlying pathophysiology of some disorders (Rucklidge & Kaplan, 2013). Mitochondrial dysfunction could negatively affect the energy metabolism of neurons and glial cells, thus affecting their ability to functioning optimally. This would compromise neurotransmitter synthesis and synaptic communication for instance (Rucklidge & Kaplan, 2013). Relatively new research suggests that ATP (the source of cellular energy created by mitochondria) manufacturing is reduced in bipolar disorder, attention-deficit hyperactivity disorder (ADHD) and other mental health disorders (Russell et al., 2006; Young 2007), with Gardner and Boles (2005) proposing a model which includes reduction in mitochondrial energy metabolism as one of the predisposing factors in certain chronic mental health problems. Young (2007), in an editorial in the *Journal of Psychiatry and Neuroscience*, discussed the potential role of impaired mitochondria in contributing to bipolar disorder. He argued that if energy metabolism is reduced, this may lead to subtle neural damage, which may be more evident in those who suffer from bipolar disorder and result in lasting cognitive impairment. A number of micronutrients are involved in the processes which create ATP, while traditional mitochondrial diseases are commonly treated with nutrients, rather than drugs (Rucklidge & Kaplan, 2013).

Ames's (2010) triage hypothesis proposes that our body naturally rebalances our metabolism when the availability of micronutrients is not at optimal levels, such that available micronutrients are directed towards those processes necessary for survival. This

occurs at the expense of long-term health in some cases, eventually leading to degenerative disorders through the cumulative effects of nutrient deficiencies. This may be particularly relevant to those individuals who experience mental illness later in life (Kaplan et al., 2007).

Another theory is that some mental illness may be caused by alterations in gene expression due to nutrient deficiency. It is well-established within the fields of nutrigenomics and epigenetics that nutrient status can alter genetic expression (Kaplan and Leung, 2011). Kaplan et al. (2007) acknowledge that, like all of these theories, this one overlaps with other theories but that different theories can be compatible. Nutrient deficiencies which alter gene expression could affect methylation processes for instance.

While there are theories and evidence to suggest some possible routes for the effect that micronutrients may have on the brain and body, the biological evidence is still in its infancy. However, the biological explanations for some anxiety disorders themselves are also incomplete (Lakhan & Vieira, 2010).

1.5 Research Specific to Anxiety and Stress: The Effect of Single Ingredient Interventions on Anxiety and Stress Symptoms

Research has found evidence that single micronutrients can relieve symptoms of anxiety and stress in adults. A study by De Souza, Walker, Robinson & Bollard (2000) found a small effect of daily dietary supplementation with 200mg/day magnesium and 50mg/day vitamin B₆ on decreasing premenstrual anxiety. A significant effect was not found when the participants consumed magnesium or vitamin B₆ alone or when taking placebo, although these interventions did lead to a decrease in anxiety compared to baseline (De Souza et al., 2000).

Research has also examined the effects of selenium and thiamine (vitamin B₁) on stress and anxiety. A randomised, double-blind, placebo-controlled study of 63 participants

taking 200mg/day selenium over 12 months found those participants taking selenium experienced significantly less anxiety compared to the placebo-treated participants (Shor-Posner, et al., 2003). In a small study investigating the impact of daily 100mg thiamine on nine participants with GAD and low blood thiamine levels at baseline, the researchers found thiamine supplementation significantly improved scores on the Hamilton Anxiety Rating Scale, indicating this also decreased anxiety (Luong & Nguyen, 2011). Furthermore, the authors reported an increase in appetite and well-being, as well as a decrease in fatigue in those participants taking thiamine (Luong & Nguyen, 2011).

Other studies have investigated the effect of compounds which are not vitamins or minerals on stress and anxiety. For instance, some research has investigated the effect of inositol. Inositol is a part of the intracellular phosphatidyl inositol second messenger system and a naturally occurring vitamin-like chemical found in a plants and animal tissue (Kofman, Einat, Cohen, Tenne & Shoshana, 2000). It has been linked to a number of neurotransmitter receptors, thus, the levels of this compound in the brain have the potential to alter neurotransmitter levels and synaptic communication (Mukai, Kishi, Matsuda & Iwata, 2014). Inositol supplementation is utilised in medicine for a range of reasons, such as treating respiratory distress syndrome in premature infants (Kofman, et al., 2000). Inositol has been shown to benefit patients with panic disorder and OCD. In a double-blind, placebo-controlled crossover study by Fux, Levine, Aviv and Belmaker (1996) 13 patients with OCD had significantly lower scores on the Yale-Brown Obsessive Compulsive Scale after taking 18g/day of inositol for one month when compared to placebo. Another double-blind, placebo-controlled, crossover design study investigated the impact of 12mg/day inositol on 21 participants with Panic Disorder (with and without agoraphobia; Benjamin et al., 1995). This study found that both the frequency and severity of panic attacks decreased more with inositol administration than with placebo. There was also a significant decrease in the

severity of agoraphobia following inositol administration compared to placebo (Benjamin et al., 1995). Furthermore, a double-blind, crossover study compared Hamilton Rating Scale for Anxiety scores for 20 participants with Panic Disorder who took inositol for one month versus those same participants after taking fluvoxamine for one month. No significant differences were found, although nausea and tiredness were more common with fluvoxamine, thus the authors concluded inositol may provide an attractive treatment for those cannot take or who prefer not to take psychiatric medication (Palatnik, Frolov, Fux, & Benjamin, 2001).

Kava-kava, a preparation made from the plant *Piper methysticum*, has been utilised as a treatment for anxiety in a number of studies. The first randomised, placebo-controlled, double-blind study of kava-kava in relation to its anxiolytic effects was conducted with 101 participants who had been diagnosed with an anxiety disorder. The researchers found participants who had been taking kava-kava over the 25 week trial period had an improvement in anxiety symptomatology above that of those taking placebo (Volz & Kieser, 1997). These results have been replicated in a further five RCT's, although another four RCT's have found no such result (see Lakhan & Vieira, 2010). This suggests some potential efficacy of kava-kava but that more research into why there is inconsistency across studies should be conducted. There has been some concern over the safety of kava-kava supplements, as it was linked to the potential for severe liver damage. However, reviews investigating safety have found serious side effects may have occurred due to poor quality, overdose, prolonged use and use with other medications (Lakhan & Vieira, 2010).

St John's Wort has been investigated for its anxiolytic effects. Some research suggests that St John's Wort may reduce anxiety in participants diagnosed with OCD, while other studies have found no such link. For instance, one open label study by Taylor and Kobak (2000) with 13 participants diagnosed with OCD found significant improvements in anxiety symptoms, comparable to those improvements seen with SSRI treatment. A randomised

controlled trial of 60 participants diagnosed with OCD found no significant difference between the treatment group and placebo group after 12 weeks (Kobak et al., 2005).

The effect of passionflower on anxiety has been investigated in a small number of studies, with evidence of an anxiolytic effect (Lakhan & Vieira, 2010). A double-blind, placebo-controlled study compared oxazepam and passionflower in a sample of 36 participants diagnosed with GAD. The researchers found no significant difference between the two treatments, leading them to conclude that passionflower may be as effective as a traditional benzodiazepine in reducing anxiety symptomology (Akhondzadeh et al., 2001).

A number of researchers have noted the contribution of individual vitamins, minerals or other compounds in the treatment of psychiatric symptoms (eg: Kaplan et al., 2007; Lakhan & Vieira, 2010). While there is evidence that at least some of these compounds have an anxiolytic effect, the effect is usually modest and inconsistent between studies (Rucklidge & Kaplan, 2013). As mentioned above, the body and brain require a number of different micronutrients to function optimally, thus multi-nutrient compounds are also worthy of investigation, as the combined effect of multiple nutrients may be more powerful than the effect of single nutrients.

1.6 The Effect of Multi-Ingredient Interventions on Anxiety and Stress Symptoms

Since the year 2000, the number of studies investigating the effect of nutrient interventions containing multiple ingredients has increased substantially (Kaplan & Leung, 2011). This seems in direct contrast to the scientific method which guides quality modern research today. The scientific method holds that one single independent variable should be changed in an experiment so as to determine cause and effect, thus micronutrient formulas, with multiple different ingredients, have received criticism in the research literature for containing so many “independent variables” (Rucklidge and Kaplan, 2013). As Burford-

Mason (2009) reported, this concept as applied to nutrition, is problematic given the complexity of the human system and the way its physiology functions, while two decades ago Mertz (1994) acknowledged that the idea of “one-disease–one-nutrient” was outdated. Given humans require so many different nutrients and that the imbalance of nutrients can have a flow on effect to other nutrients, single-nutrient interventions might actually create deficiencies by disturbing homeostasis (Mertz, 1994). Pauling (1995) added to this position by stating that “biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimum concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients.” Multi-ingredient formulas allow for the molecular environment of the brain to be optimised when the amounts of nutrients needed for this to occur are above those provided by an individual’s diet or biological make-up (Pauling, 1995). Research using multi-ingredient micronutrient compounds in the treatment of stress and anxiety will now be reviewed.

A number of studies have investigated the impact of high dose B vitamin formulas on stress and anxiety, including five randomised controlled trials. The B vitamin formulas also commonly contain other vitamins and minerals, but the main ingredients are B vitamins. One study investigated the effect of three months administration of ‘Blackmores Executive B Stress Formula’ in a typical form and in a sustained release form, compared to placebo in 80 participants (Stough et al., 2011; 19 ingredients). After controlling for the effects of personality and individual work demands, the researchers found those participants in the treatment groups experienced significantly lower personal strain following the three month intervention than the placebo group, as well as a reduction in the tension-anxiety subscale of the Profile of Mood Scale (Stough et al., 2011). However, there was no treatment effect for anxiety as measured by the State-Trait Anxiety Inventory and no significant difference in

treatment effect when comparing the typical and sustained release forms of the intervention (Stough et al., 2011).

Four studies have investigated the effect of the same formula, Berocca™ (Bayer [Leverkusen, Germany]; 12 ingredients), on stress or anxiety, with positive results. Carroll, Ring, Suter and Willemsen (2000) investigated the effect of Berocca™ on the psychological well-being of 80 healthy, young males over 28 days in a double-blind, placebo-controlled trial. The researchers found that compared with placebo, those taking Berocca™ experienced significant reductions in anxiety and perceived stress, as well as improvements in tiredness and concentration. Another study also investigated the effect of Berocca™ on healthy males. Kennedy et al. (2010), in a double-blind, placebo-controlled trial of 215 males, reported that those taking Berocca™ experienced less perceived stress than those taking placebo after the 33 day intervention.

Another double-blind, placebo controlled study examining the impact of Berocca™ reported a significant difference in stress-related symptoms in those participants taking Berocca™ for one month, compared to those in the placebo group (Schlebusch et al., 2000). This study included a large sample of 300 participants, from two different centres.

The final study investigating the effect of Berocca™ also investigated the effect of a micronutrient formula called CNE™, containing 36 ingredients, with vitamins, minerals, amino acids and antioxidants (Rucklidge et al., 2012). This was an unblinded study with 116 participants and compared Berocca™ to two different doses of CNE and a non-randomised control group over four weeks following a large earthquake. All treatment groups experienced a significant reduction in anxiety, stress and earthquake-related distress when compared to the control group, while those taking the higher dose of the broader range formula experienced a greater benefit overall than those taking Berocca™ (Rucklidge et al., 2012).

Another study by Rucklidge and colleagues (2011) examined the impact of a micronutrient formula called EMPowerplus (EMP+), with the same ingredients as CNE, on stress and anxiety in 36 adults with ADHD. Two weeks following a 7.1 earthquake in Christchurch, NZ, those participants taking EMP+ reported significantly less anxiety and stress symptoms than those participants not taking EMP+. These differences could not be explained by other variables, including age, gender, ethnicity, SES, IQ, baseline measures of emotions, or personal loss and damage following the earthquake (Rucklidge et al., 2011).

Two case studies have been reported in the literature using micronutrients to treat anxiety. Both of these case studies investigated the impact of EMP+ on OCD symptoms in on-off designs. Rucklidge (2009) demonstrated control over anxiety and obsessions in an ABAB designed case study of an 18-year old male with OCD, who had previously undergone CBT for one year with a partial response, followed by a return to the severe anxiety range and development of major depression within another year. A case study by Kaplan, Crawford, Gardner and Farrelly (2002) on an eight year boy with atypical OCD (obsessions without discernible compulsions), ADHD, mood liability and explosive rage revealed significant reductions in obsessional thoughts, along with significant improvements in mood liability and an overall calmer demeanour and more well controlled temper.

Haskell and colleagues (2010) examined the effect of a micronutrient formula on cognitive function and fatigue, as well as anxiety, in a sample of 216 healthy female participants following a placebo-controlled, double-blind, randomised study design. However, this study found no significant treatment effects in terms of anxiety when comparing the micronutrient and placebo treatment groups. It is important to note that many studies use healthy participants, thus authors are limited in their ability deduce much about the effect of micronutrients on anxiety symptoms which could be considered disorder.

Long and Benton (2013) also investigated the impact of micronutrient supplementation in a large sample. These researchers utilised Centrum™ Advanced 50+ (25 ingredients) and examined stress in a sample of 202 young adult men. They compared Centrum™ Advanced 50+ supplementation alone to supplementation with DHA fatty acids, supplementation with both Centrum™ Advanced 50+ and DHA fatty acids and placebo in a 12 week double-blind, randomised trial. The researchers found a significant decrease in perceived stress in the micronutrient group when compared to placebo, but not in the DHA fatty acid only or combined group when compared to placebo (Long & Benton, 2013).

An interesting study by Gruenwald, Graubaum and Harde (2002) studied the effect of a micronutrient formula which also contained probiotics over 6 months. This study found a significant reduction in stress and anxiety in 42 adults suffering from stress or exhaustion. Stress and anxiety are known to affect the health of the gastrointestinal system through affecting the absorption of nutrients and thus may lead to deficiencies. Also, chronic stress and anxiety can compromise intestinal flora, such that the intestines and colon can become damaged (Gruenwald et al., 2002). This is because of the constant arousal which occurs due to anxiety, leading to the release of adrenaline and other sympathetic nervous system functions including the diversion of blood from the intestines to the muscles. Depending on the type of bacteria present in the intestines and the dietary substances being ingested, toxic compounds can amass then exit the intestines through the damage in the intestinal lining, entering the bloodstream (Gruenwald et al., 2002). Rucklidge and Kaplan (2013), in a recent expert review of broad-spectrum micronutrient formulas in the treatment of psychiatric symptoms, highlight the importance of the role that bacteria play in relation to the gut-brain connection. These authors suggest combining micronutrients with probiotics will be important in future research so as to optimise nutrient absorption and gut health, thus maximising treatment response.

One study investigating the impact of micronutrients on anxiety in children, other than the above case studies, was found during the literature search. This study by Zhang et al. (2012) examined the impact of micronutrient supplementation (21 ingredients; formula name not specified by the authors) on anxiety in elementary school children living in rural China. Randomly selected schools were placed in either a control or treatment condition, with 2730 students participating in total, taking the intervention for 36 weeks. The researchers found a significant reduction in anxiety in the treatment condition compared to the placebo condition.

The above studies demonstrate the potential efficacy of micronutrients in the treatment of stress and anxiety, with one study and two case studies showing the effectiveness of micronutrient formulas at reducing anxiety in children (Kaplan et al., 2002; Rucklidge, 2009; Zhang et al., 2012). Two trials (Rucklidge et al., 2011; Rucklidge et al., 2012) and two case studies (Kaplan et al., 2002; Rucklidge et al., 2009) utilised EMP+ or an equivalent formula in their research. This broad-spectrum formula has been widely used in research for a number of different psychiatric conditions and is the most researched of the above reviewed formulas. The research on EMP+ will be briefly reviewed in the following section.

1.7 Literature on EMP+

EMP+ is a broad-spectrum micronutrient formula which contains 16 trace minerals, 14 vitamins, three amino acids and three antioxidants. An ingredient list of EMP+ is included in Appendix A. David Hardy and Anthony Stephan created EMP+ based on Stephan's agricultural knowledge about the treatment of aggression in livestock, initially for the treatment of bipolar disorder. Twenty-one articles have been published on the use of EMP+ for the treatment of psychiatric symptoms, including one systematic review of the safety and tolerability of the formula, randomised controlled trials and case studies.

The formula itself has gone through three revisions. The first reduced the number of capsules needing to be taken to achieve the recommended dose from 32 to 15 capsules per day and occurred in November 2002, meaning research since this time has used the newer but equivalent formula. CNE is another formula equivalent to EMP+ which is marketed for the general population. The most recent revision created two further formulas which provide similar amounts of the same nutrients as EMP+, but are proposed to be easier on the gut for those who had gastrointestinal side effects with EMP+. These are Daily Essential Nutrients, which is marketed at individuals with mental or physical health difficulties, and Daily Self Defense™, which is marketed at the general population. EMP+ remains available at the time of writing and is also available in a powder form which can be mixed into liquid.

Simpson and colleagues (2011) systematically reviewed the safety and tolerability of EMP+ for use within mental health given the formula is so widely used and the recommended dosage provides some ingredients at levels higher than recommended daily allowance. The researchers utilised data from both published and unpublished studies and found no abnormal blood tests or clinically meaningful negative outcomes due to toxicity. They found only minor and brief reports of headaches and nausea associated with the currently available version of EMP+ and concluded that these results were reassuring in terms of safety and tolerability.

1.7.1 EMP+ and mood. Seven published studies have investigated the impact of EMP+ on bipolar disorder. Kaplan and colleagues (2001) utilised an open label design to examine the effect of EMP+ on the symptoms of bipolar disorder in 11 adults over six months. The researchers found the number of psychotropic medications the participants were on decreased with the intervention, while they also found a significant decrease in scores on measures assessing depression, mania and general psychiatric status, with large effect sizes

for these primary measures. Eighty-six percent of participants were deemed responders, with at least a 20% reduction of symptoms on all three primary measures. In the same year, Popper (2001) trialled EMP+ with 22 children and adults who also had bipolar disorder. He found 19 of those patients had a positive response, including 10 with marked improvement, while 11 out of the 15 participants who had been on psychiatric medication when they began the trial, had been stable for six to nine months without medication.

Simmons (2003) also investigated the effect of EMP+ on bipolar disorder using an open label design. He found clinical improvement in 16 participants out of a sample of 19 adults with bipolar disorder taking EMP+ for between five and 21 months. Furthermore, 13 participants who were on medication remained stable when the sole intervention was EMP+. Frazier, Fristad and Arnold (2012) examined the effect of EMP+ on bipolar spectrum disorders in 10 children over six and a half months. Seven children completed the study, with all completers experiencing a decrease in depression and mania, while there remained a significant decrease in mania when using an intent-to-treat analysis.

Case studies have also been completed investigating the effect of EMP+ on bipolar disorder. Frazier and colleagues (2009) reported an outcome which was superior to conventional treatment after a 14 month intervention with EMP+ for a 12-year-old boy with early-onset bipolar I disorder mixed with psychotic features, GAD and OCD. Previous conventional treatments had resulted in intolerable side effects or inadequate treatment response. However, the participant was able to remain stable throughout a nine month follow-up period on EMP+. Rucklidge and Harrison (2010) utilised an ABAB design with a one year follow-up in investigating the impact of EMP+ on the psychiatric symptoms of a 21-year-old female diagnosed with bipolar II disorder, ADHD, social anxiety and panic disorder. This participant demonstrated improvement while on EMP+, but remitted to baseline in terms of

depression scores with a worsening in ADHD and anxiety symptoms when off EMP+. At one year follow-up the participant was in remission from all psychiatric disorders.

Two case studies by Kaplan et al. (2002) have demonstrated the effect of EMP+ on mood, temper and explosive rage in two boys aged eight and 12 years. In both cases there was a significant effect on mood lability and temper control with a clear pattern of improvement while on the intervention and regression when the formula was withdrawn.

Gately and Kaplan (2009) completed a database analysis of the effect of EMP+ on adults diagnosed with bipolar disorder, while Rucklidge, Gately and Kaplan (2010) completed a database analysis of the effect of EMP+ on children and adolescents diagnosed with bipolar disorder. Gately and Kaplan's (2009) analysis found an overall 45% decrease in bipolar symptomology after 6 months on EMP+ in a total sample of 358 adults with bipolar disorder, while linear regression analysis over the first 6 months showed a decrease in medication. This medication reduction was also associated with an increase in the dosage of EMP+. Rucklidge et al. (2010) found a 46% drop in symptomology compared to baseline in their sample of 120 children and adolescents with bipolar disorder. This analysis also revealed that 46% of the sample had experienced an improvement which was greater than 50% symptom reduction after 6 months on EMP+. The researchers also found no significant differences in results when comparing those children or adolescents diagnosed with bipolar disorder to those who also meet criteria for ADHD.

An open-label case series of 11 children aged eight to 15 years completed by Kaplan, Fisher, Crawford, Field and Kolb (2004) investigated the effect of EMP+ on mood and behavioural problems. The children in the study had a range of disorders including bipolar, ADHD, ODD, Asperger's, depression, anxiety, rage and Prader-Willi syndrome. Nine children completed the trial, with an average trial duration of 13.6 weeks. The researchers

reported significant improvements in mood and anxiety for all who completed the trial, with effect sizes in the large range.

The above studies support the use of EMP+ in the treatment of mood disorders in both children and adults. However, RCT studies are necessary to strengthen these claims and rule out placebo effects.

1.7.2 EMP+ and Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder and other applications. A study by Rucklidge, Taylor and Whitehead (2011) investigated the effect of EMP+ in a group of 14 adults with ADHD and severe mood dysregulation over an eight week open label trial with follow-up. The researchers found significant improvements on a number of measures, with moderate to large effect sizes. Of particular note was that mood and hyperactivity normalised. The above study by Kaplan and colleagues (2004) found a significant reduction in attention problems after intervention with EMP+ in their sample of 11 children which included five with a diagnosis of ADHD as well as mood problems. Similarly, the above mentioned case study by Rucklidge and Harrison (2010) found a significant improvement in ADHD symptomatology after intervention with EMP+. A recent double-blind, randomised, placebo-controlled trial by Rucklidge, Frampton, Gorman and Boggis (2014) found significant differences in self- and observer-rated measures of ADHD, favouring the micronutrient treatment group. Furthermore, the clinicians rated those in the micronutrient group as more improved than those in the placebo group in terms ADHD symptoms and global functioning. There was also a larger improvement in mood for those who were moderately to severely depressed at baseline for the treatment group compared to placebo. This study, in light of the other studies completed, provides strong evidence for the potential of micronutrients in the treatment of ADHD, however further

replication is necessary before micronutrients can be recommended to patients as another empirically supported treatment for their symptoms.

Mehl-Madrona, Leung, Kennedy, Paul and Kaplan (2010) compared micronutrients to standard medication in the management of autism using a naturalistic case-controlled design. The researchers reported that both treatment groups saw significant improvement on the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale. However, the micronutrient group experienced greater improvement than the medication group on the total Aberrant Behaviour Checklist scores. The micronutrient group had lower self-injurious behaviour intensity scores and greater improvement on the Clinical Global Impressions scale. While there were improvements in both groups, there were more advantages for the micronutrient treatment group than the medication treatment group. This suggests some potential of EMP+ in the management of behaviours associated with autism, although more research is necessary before EMP+ could become a recommended treatment.

Other applications of EMP+ have also been investigated. For instance Harrison, Rucklidge and Blampied (2013) have proposed that EMP+ and micronutrient formulas like it may be useful in substance abuse following a case study by these researchers. The researchers found on-off control of psychiatric symptoms, as well as on-off use of cannabis and cigarettes during treatment with micronutrients for ADHD.

Rodway, Vance, Watters, Lee, Bos and Kaplan (2012) investigated the efficacy of EMP+ in relation to childhood psychosis. They reported on a case study of an 11 year-old boy with a three year history of mental illness. After intervention with EMP+ the participant experienced complete remission of psychosis and a significant reduction in anxiety and obsessions. These gains remained present at a four-year follow-up. The authors concluded there is potential in the treatment of childhood psychosis with micronutrient formulas,

especially in light of the fact that treatment with EMP+ cost only 1% of the participant's inpatient mental healthcare (Rodway et al., 2012).

As demonstrated, EMP+ has been widely researched for a number of different applications within the mental health field and shows potential for the treatment of a number of different disorders.

1.8 Aims and Hypotheses

The aim of the following study is to examine the effect of a broad-based micronutrient formula, EMP+, on anxiety in children. This research is completed as a pilot study to determine if the positive treatment effects of micronutrients on stress and anxiety in adults are also seen in a sample of children with elevated anxiety. The previous research on the effect of EMP+ on anxiety in children has been limited to case studies, often with participants whose other comorbid mental health disorders are the presenting problem. This research focuses on a group of children with significant anxiety as their primary difficulty and is the first study of EMP+ with such a focus to the best of the author's knowledge.

It is hypothesised that this study will find the following:

1. The micronutrient formula will be associated with improvements in anxiety
2. The micronutrient formula will be associated with improvements in overall functioning and in mood where mood is also elevated
3. The micronutrient formula will not be associated with significant side-effects and that if present, side-effects will be minor and transitory
4. Participants will be able to swallow eight pills per day and be compliant at doing so
5. Improvements will be maintained over the follow-up period if the participants remain on EMP+

2. Method

2.1 Participants

Participants were recruited in Canterbury, New Zealand, between August 2012 and September 2013 via referrals from general practitioners, clinical psychologists and online and paper advertising. From 36 referrals, 14 children aged between 8 and 11 years old, with significant difficulties with anxiety, participated in this study. Out of the 36 caregivers who completed the online screening questionnaire, 30 of their children met the required cut-off in terms of their child's level of anxiety to allow them to participate (see inclusion criteria). Every person who reached the screening cut-off and all other eligibility criteria was contacted via email and offered an appointment to talk about potential participation.

One child was excluded because they were taking medication for anxiety and two more children were excluded because they lived outside of Canterbury. Two families who completed online screening and attended the initial baseline appointment chose not to consent to the study; one withdrew due to family stress and the another due to the amount to travelling which would be involved given they lived rurally. All caregivers who chose not to participate were provided with a list of services and agencies that might be able to assist their child if they wished to seek treatment. One other family who meet online screening criteria was better suited for another study being completed within the research group.

All study procedures were approved by both the Human Ethics Committee at the University of Canterbury and the Upper South A Regional Health and Disability Ethics Committee. The trial was registered prospectively with the Australian New Zealand Clinical Trials Registry (ACTRN12612000671864).

2.1.1 Inclusion and exclusion criteria. In order to be considered for entry into the study, participants had to meet the clinical cut-off of 25 points on the Screen for Child

Anxiety Related Disorders (Parent Version; SCARED). This score may indicate the presence of an anxiety disorder (Birmaher et al., 1999). Participants did not have to meet full criteria for an anxiety disorder, as identified in the DSM-IV. Also, participants were not excluded if they had a comorbid diagnosis, as non-exclusion would provide a more representative sample in terms of clients being treated in the community. Individuals were only considered if they were not taking psychiatric medications (or had been medication free for at least 4 weeks)

Other inclusion criteria included:

- 1) Participants had to be between 8-11 years of age.
- 2) Each participant had to have a level of understanding sufficient to complete the questionnaires and examinations required by the protocol and be considered reliable and compliant with the protocol (including the ingestion of 8 capsules/day).
- 3) Participants had to be able to eat at least a snack two times per day, so that the capsules would not be ingested on an empty stomach.
- 4) Participants had to have a score of at least 50 (within the 41-50 point range, indicating a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area) on the Children's Global Assessment Scale.

Other exclusion criteria included:

- 1) Any individual living outside of the Canterbury region.
- 2) Any participant with a neurological disorder involving brain or other central function (e.g., epilepsy, MS, narcolepsy). Purely peripheral neurological problems were not excluded (e.g., Raynaud's, peripheral diabetic neuropathy).
- 3) Any participant with a serious medical condition for which major medical interventions were anticipated during the duration of the trial.

- 4) Any participants known to be allergic to the ingredients of the intervention (including ginkgo biloba, germanium sesquioxide, or grape seed).
- 5) Any participant with a known abnormality of mineral metabolism (e.g., Wilson's disease, haemochromatosis).
- 6) Participants were excluded temporarily if they have taken an oral antibiotic in the previous 6 weeks.
- 7) Consumption of any type of nutritional or herbal supplement, known to have a centrally-acting effect, would result in a participant's exclusion. However, participants who had been taking supplements such as omega 3s or melatonin were permitted to enter the study if a) they had been taking these agents for at least one month prior to the study, and b) they continued on these agents throughout the study.
- 8) Any participant judged clinically to be at serious risk for suicide or violence in the opinion of the researchers.

These criteria resulted in three participants being excluded as noted above. Another participant was temporarily excluded after beginning a course of oral antibiotics.

2.1.2 Final Sample. Eleven participants completed the entire trial. Current and past anxiety disorder diagnoses, as well as current supplement intake for each participant, are presented in Table 1. Ten out of 14 (71%) participants met a DSM-IV anxiety disorder diagnosis at the time of entry into the study based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (Present and Lifetime version). As shown in Table 1, six participants (43%) had Separation Anxiety Disorder, four participants (29%) had Specific Phobia, six participants (43%) had Generalised Anxiety Disorder and one participant (7%) had Post-traumatic Stress Disorder. One participant also had a diagnosis of Attention Deficit Hyperactivity Disorder and another had a Specific Learning Disorder. Two

participants had difficulties with sleep and had been taking melatonin prior to participation. All diagnoses were discussed with a senior clinical psychologist before being confirmed.

One participant completed the baseline phase but chose to withdraw from the study prior to commencing the treatment phase due to illness in the family. Another participant failed to attend any appointments after week two of the intervention phase. Another participant withdrew after week six of the intervention phase due to parental separation. In addition, this participant had not taken the micronutrient since week four of the study, although they had not attended an appointment since week two of the intervention. Eleven out of fourteen of the final sample had sought some type of treatment prior to participating in the study, including herbal remedies and attending sessions with a mental health professional.

Table 1: *Current Anxiety Diagnoses, Past Anxiety Diagnoses and Current Supplement Intake of the Final Sample of Participants*

Participant (age)	Current Anxiety Diagnoses	Past Anxiety Diagnoses	Current supplements
Participant 1 (11)	Separation Anxiety Disorder Specific Phobia Generalised Anxiety Disorder Post-traumatic Stress Disorder		
Participant 2 (8)	Generalised Anxiety Disorder		
Participant 3 (9)	Generalised Anxiety Disorder	Generalised Anxiety Disorder	Fish oil, 300mg
Participant 4 (8)			
Participant 5 (8)	Generalised Anxiety Disorder		
Participant 6 (10)	Generalised Anxiety Disorder		
Participant 7 (9)	Separation Anxiety Disorder Specific Phobia	Specific Phobia Post-traumatic Stress Disorder	Melatonin, 3mg
Participant 8 (8)	Separation Anxiety Disorder Specific Phobia Generalised Anxiety Disorder	Separation Anxiety Disorder	Fluoride, 0.5mg
Participant 9 (8)	Separation Anxiety Disorder		

Participant 10 (8)

Participant 11 (10) Separation Anxiety Disorder
Specific Phobia

Fish oil, 5ml
Melatonin, 3mg

Participant 12 (10)

Participant 13 (8)

Participant 14 (9) Separation Anxiety Disorder

2.2 Measures

2.2.1 Measurement of demographic variables.

History Questionnaire. This questionnaire was used to assess demographic variables including the child's ethnicity, parental marital status, parent occupation, household income, information about any previous or current contact with mental health professionals, any previous or current medication, family history of mental health disorders, antibiotic use history, allergies and other important relevant medical information.

New Zealand Socioeconomic Index of Occupational Status. (NZSEI; Davis, McLeod, Ransom, and Ongley, 1997). The NZSEI is based on 1991 New Zealand Census data and provides an estimate of socioeconomic status (SES) based on an individual's occupation. Scores range from 10 to 90 and higher scores indicate higher SES.

2.2.2 Parent-rated dependent measures.

Screen for Child Anxiety Related Disorders – parent version (SCARED). The SCARED (Birmaher et al., 1999) is a 41 item parent-rated measure of a broad range of anxiety symptoms in children. The SCARED assesses five factors of anxiety, namely panic disorder or significant somatic symptoms (e.g. “when my child feels frightened, it is hard for him/her to breathe”), generalised anxiety disorder (e.g. “My child worries about what is going

to happen in the future”), separation anxiety (e.g. “My child doesn’t like to be away from his/her family”), social anxiety disorder (e.g. “It is hard for my child to talk with people he/she doesn’t know well”) and significant school avoidance (e.g. “My child is scared to go to school”). Answers are indicated on a 3-point Likert scale (“not true or hardly ever true” [0], “somewhat true or sometimes true” [1] and “very true or often true” [2]) and a score greater than 25 may indicate the presence of an anxiety disorder. Scores can range from 0 to 81 points. The scale has an α -coefficient of 0.9 with a test-retest reliability of 0.86 and has been widely used in the community and in research. Furthermore, the total score is able to discriminate between children with anxiety disorders and those with non-anxiety disorders (Birmaher et al., 1999).

Pediatric Emotional Distress Scale (PEDS). The PEDS (Saylor, Swenson, Reynolds, & Taylor, 1999) is a brief measure designed to detect elevated anxiety symptoms or behaviour in children following a traumatic event. The PEDS has three individual factors. These are acting out (e.g. “Wants things right away”), fearful (e.g. “Has trouble going to bed/falling asleep”) and anxious/withdrawn (e.g. “Seems sad and withdrawn”). Answers are given on a 4-point Likert scale (“almost never” [1], “sometimes” [2], “often” [3] or “very often” [4]), with a score of 28 or greater indicating clinically significant anxiety. Scores can range from 21 to 84 points. The scale has an alpha coefficient of 0.85 with moderate test-retest reliability and inter-rater reliability, as well as evidence of convergent and discriminant validity (Saylor et al., 1999).

Mood and Feelings Questionnaire – parent version (MFQ). The MFQ (Costello & Angold, 1988) is a parent rated measure of symptoms of depression in children. This questionnaire asks the parent how his/her child has been feeling and acting over the previous two weeks. The MFQ is rated on a 3-point Likert scale (“not true” [0], “sometimes” [1] and “true” [2]) and contains questions such as “s/he at more than usual” and “s/he cried a lot”.

Scores can range from 0 to 68. The MFQ has been shown to reliably differentiate between depressed and non-depressed youth when using a clinically significant cut-off score of 27 and shows moderate to high criterion validity in both clinic and non-clinic settings (Kent, Vostanis, & Feehan, 1997; Daviss et al., 2006). The MFQ has high internal consistency with an α -coefficient of 0.96 and compares favourably with other measures of depression in children (Daviss et al., 2006).

Strengths and Difficulties Questionnaire – parent version (SDQ). The SDQ (Goodman, 1997) is a brief measure of prosocial behaviour and psychopathology for 3-16 year olds. It asks about a range of positive and negative attributes, rated on a 3-point Likert scale (“not true” [0], “somewhat true” [1] and “certainly true” [2]) to produce scores on 5 scales; emotional symptoms (e.g. “many worries, often seems worried”), conduct problems (e.g. “often lies or cheats”), hyperactivity/inattention (e.g. “constantly fidgeting or squirming”), peer relationship problems (e.g. “rather solitary, tends to play alone”) and prosocial behaviour (e.g. “helpful if someone is hurt, upset or feeling ill”). A clinically significant cut-off of 17 is used to indicate abnormally elevated scores for total difficulties, with a range from 0 to 40. The SDQ compares well to other valid and reliable behavioural screening questionnaires (Goodman, 1997). The parent version of the SDQ demonstrates reasonable correlations with the child-rated version and has a Cronbach’s α of 0.82 and a test-retest reliability over four to six months for the total scale of 0.72 (Goodman, 2001). Furthermore, scores above the 90th percentile predict a significantly increased probability of having a psychiatric disorder (Goodman, 2001).

2.2.3 Child-rated dependent measures.

Revised Children’s Manifest Anxiety Scale (RCMAS). The RCMAS, also titled “*What I Think and Feel*” (Reynolds & Richmond, 1978) is a self-report measure assessing anxiety

in children. Each item is rated as “Yes” (1 point) or “No” (0 points) depending on whether the child thinks that item is true about them. The RCMAS produces three scales; physiological anxiety (e.g. “It is hard for me to get to sleep at night”), worry/oversensitivity (e.g. “I worry about what is going to happen”) and social concerns/concentration (e.g. “Others seem to do things easier than I can”), as well as a social desirability scale. A clinically significant cut-off of 19 out of 28 is recommended (Stallard, Velleman, Langsford & Baldwin, 2001). The reliability coefficient for the RCMAS scale is 0.83 and the measure demonstrates good construct and convergent validity (Reynolds, 1982; Reynolds & Richmond, 1979).

Measure Yourself Medical Outcome Profile (MYMOP). The MYMOP (Paterson, 1996) is a self-report outcome questionnaire asking about the symptoms and side-effects which the patient considers the most important, allowing for measurement of change. While some symptoms were assigned to all participants in this study, the scale allows for participants to choose some of the symptoms they would like to measure based on their own view of the symptoms importance and impact on themselves. The item is rated on a 5-point Likert scale from “major problem this week” (4 points) to “excellent – zero problems” (0 points). This questionnaire shows construct and criterion validity as well as sensitivity to change when compared to another medical outcome measure.

2.2.4 Clinician-rated dependent measures.

Clinical Global Impressions Scale (CGI). The CGI (Guy, 1976; Spearing, Post, Leverich, Brandt & Nolen, 1997) is a three-item rating of the clinician’s assessment of symptoms in relation to the clinician’s total experience with a patient. Its goal is to allow the clinician to rate the effectiveness of treatment, change over time and the severity of illness. Scales range from “normal, not ill” (1 point) to “very severely ill” (7 points) or from “very

much improved/markedly improved” (1 point) to “very much worse/markedly worse” (7 points) over a 7-point scale. Up to three different dimensions can be rated, such as anxiety or depression (Spearing et al., 1997). The CGI is one of the most widely used outcome measures for psychological research and has high interrater reliability (Spearing et al., 1997).

Children’s Global Assessment Scale (CGAS). The CGAS (Shaffer et al., 1983) is a global measure of social and psychiatric functioning in children. The CGAS is a single numerical scale from 1 (lowest functioning) through 100 (high functioning) that is separated into 10-point anchors with descriptors of functioning and psychopathology to guide scoring. The CGAS is based on the Global Assessment of Functioning measure for adults and can be used to track change over time. High reliability is usually found in clinical research (Storch, 2005) and test-retest reliability has been found to be around 0.85 (Rush, First & Blacker, 2008).

Child Depression Rating Scale (CDRS). The CDRS (Poznanski, Cook & Carroll, 1979) is a 16-item measure, used for children aged 6-12 years old, to assess the severity of depression. Assessment information is based on interviews with the child and parent and the scale was designed to be used in the same way as the Hamilton Depression Rating Scale. Items provide descriptive information for every point given on each individual item. Items are scored from 0 to 2, 3, 4 or 5 points depending on the item. Scores range from 16 to 63, with those above 30 indicating clinically significant elevation in symptoms (Shanahan, Zolkowski-Wynne, Coury, Collins & O’Shea, 1987). The CDRS offers an effective way to monitor treatment response and appears to be a valid measure of depression in children (Shanahan et al., 1987).

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime version (K-SADS-PL). The K-SADS-PL (Kaufman et al., 1997) is a semi-structured diagnostic interview that assesses current and lifetime history of psychiatric

disorders in children and adolescents in alignment with DSM-III-R and DSM-IV criteria. The interview is administered by a trained clinician. For this study, only the anxiety disorders sections (Screen Interview questions and Anxiety Disorder Supplement if necessary) were administered. Diagnoses are made through synthesising of parent and child responses. The K-SADS-PL has been widely used in research and has high interrater reliability (98%) and good test-retest reliability for any anxiety disorder ($\kappa=.80$ for 1-5 weeks; Kaufman et al., 1997).

2.3 Design and Procedures

Participants first completed the screening process then eligible participants were invited to participate in the study. Next participants completed a baseline period. The study followed a multiple baseline/multiple probe design (Cooper, Heron, & Heward, 2007), where participants were randomly assigned to a baseline period of one, two or three weeks in length and thereafter entered a treatment phase. The baseline and intervention phases had the character of a multiple probe design (Cooper, et al., 2007, pp 209-211), with probes in which dependent variables were gathered only at the beginning and the end of the assigned baseline period, such that all participants had two probes in baseline and four in the treatment phase. Probes, rather than daily or weekly measures, were used in this way to reduce the already large assessment burden on the child and her/his family. Subsequent to the baseline phase, participants completed an eight week intervention phase where they took micronutrients and visited the University of Canterbury for monitoring every two weeks. The final phase of the study was a follow-up appointment three months after the participant finished the intervention phase. All participants were monitored by a clinical psychology graduate student under a clinical psychologist's supervision.

2.3.1 Screening phase. Caregivers who were interested in the study completed the online screening questionnaire, which could be accessed via the Mental Health and Nutrition Research Group's website, www.mentalhealthandnutrition.co.nz. The screening questionnaire is displayed in Appendix B. It required contact information and answers to eligibility criteria, followed by completion of the SCARED. Applicants who met exclusion criteria were provided with a statement explaining why they were ineligible for the study, providing the researcher's contact details and thanked for their time. At the end of the questionnaire, the caregiver was given an opportunity to make any comments, after which they were thanked for completing the questionnaire, informed that the researcher would contact them about their child's eligibility to participate as soon as possible and provided with the researcher's contact details.

Applicants who met the study criteria were emailed and asked if they and their child would like to make an appointment to meet with the researcher at the University of Canterbury to discuss the study and participation.

During this initial appointment the participant was provided with an age appropriate information sheet and the caregiver was given a more detailed information sheet. See Appendix C for the information sheets, consent and assent forms. The study was explained to the participant and his/her caregiver, including the aims and purpose of the study, what would be required of the participant and his/her caregiver and the risks. Each family was given a chance to ask questions of the researcher about the study. Families were informed of other treatments available in the community and participants were not encouraged to come off conventional treatment which was working in order to participate in this trial. In addition, the researcher enquired about the nature of the child's difficulties in more detail than garnered through the screening questionnaire. Each family was provided with multiple opportunities to ask questions and participants were informed that they could withdraw from the study at any

time. Families were given time to talk without the researcher present and provided with the option to take time to consider participation and to contact the researcher at a later date prior to consenting. Informed consent was obtained from the caregiver and assent from the child.

2.3.2 Baseline phase. After a participant consented, he/she was assigned a participant identification number. Numbers were given in consecutive order, from one to 14. The participant was also informed of his/her baseline length. Baseline lengths were randomly assigned to identification numbers and the researcher was blinded to these. The caregiver completed the following questionnaires: SCARED, PEDS, MFQ, and History Questionnaire. The participant was assisted to complete the RCMAS and MYMOP. Once the caregiver and participant had completed all measures the researcher completed the CGI, CGAS and CDRS with the family. The participant was then provided with information on pill swallowing in the form of a video, a small box of candy to practice swallowing with and a pill-swallowing diary to complete over the baseline period. At each visit the caregiver was given a \$10 petrol voucher as compensation for travelling to attend the appointment.

One, two or three weeks following the initial baseline appointment, as determined by the random assignment to baseline length, the participant and caregiver returned for the final baseline appointment. At this appointment the caregiver completed the SCARED, PEDS, MFQ and SDQ, the participant completed the RCMAS and MYMOP and the clinician completed the CGI, CGAS and CDRS, as well as the Anxiety Disorder section of the K-SADS-PL. Then participants were given one bottle of EMP+, enough for four weeks, with instructions on how to take the micronutrient and titrating the dosage over the next four days. The caregiver was instructed to contact the researcher if the child experienced any adverse effects from the micronutrient.

Intervention, titration and dosage. EMPowerplus (EMP+) is a broad-spectrum micronutrient formula which contains 16 trace minerals, 14 vitamins, 3 amino acids and 3 antioxidants. An ingredient list of EMP+ is included in Appendix A. The development and history of EMP+ was discussed in the Introduction above. Participants titrated up their dose over four days to eight capsules per day, in two doses of four capsules, taken with food and water. Participants were provided with EMP+ at no cost for the duration of the study and provided with another bottle if they decided to continue with the intervention during the follow-up period. Some participants struggled to swallow the recommended quantity of capsules so took the equivalent dosage in powder form. For some participants the recommended daily dose caused side effects, thus the dose was divided into three doses or the dosage decreased then increased slowly over the following two weeks, if the participant remained side effect free. Emphasis was placed on the importance of taking EMP+ with plenty of food and water. Instructions for taking EMP+ are given in Appendix D.

2.3.3 Intervention phase. Participants and families were seen at two weeks, four weeks and six weeks post final baseline. At these appointments the participants' physical and mental health was reviewed and the following measures were completed: SCARED, PEDS, MFQ, RCMAS, MYMOP, CDRS, CGI and CGAS. A side effect questionnaire was completed at every appointment (see Appendix E). This questionnaire covered typical side effects of medications, such as dry mouth, headaches and nausea. A protocol for serious adverse events had been established, including stopping rules and discontinuation criteria, although this protocol was not utilised at any time throughout the study. Any issues with taking EMP+ were addressed and side effects monitored and remedied as necessary by reducing the dosage and adjusting diet.

At eight weeks post final baseline participants finished the trial. At this appointment, the participants' physical and mental health was reviewed and the following measures were completed: SCARED, PEDS, MFQ, SDQ, RCMAS, MYMOP, CDRS, CGI and CGAS. The participant and caregiver were asked how they felt the study had gone, if there were any changes they had noticed, any feedback for the researcher and whether they planned to continue taking EMP+. If the participant intended to remain on the micronutrient they were given another bottle of EMP+ or a similar micronutrient (a newer version of EMP+ with similar ingredients). They were also provided with contact details for the supplier of EMP+ if they wished to purchase it in the future. The participant and caregiver were thanked for participating in the study, and informed that the researcher would be in contact in approximately three months' time to follow-up on the participant's mental health and functioning.

2.3.4 Follow-up phase. Approximately three months after the end of the intervention phase families were contacted to attend a follow-up appointment. At this appointment the participants' physical and mental health was reviewed and the following measures were completed: SCARED, PEDS, MFQ, SDQ, RCMAS, MYMOP, CDRS, CGI and CGAS. The participant and caregiver were asked about the child's current experiences with anxiety, whether they continued to take the micronutrient and why they did or did not continue.

2.4 Statistical Analyses

The primary outcome measures were the SCARED, PEDS and CGAS. The SCARED reflects a broad spectrum of anxiety symptoms, while the PEDS assesses primarily anxiety symptoms associated with experiencing trauma given this study was conducted in a region recently affected by large earthquakes. The CGAS provided a measure of overall functioning.

Individual changes over experimental phases are analysed using modified Brinley plots (Blampied, 2007, 2014; Jacobson, Follette, & Revenstorf, 1984; Sobell, Sobell, & Gavin, 1995), shown for the primary outcome measures (SCARED, PEDS and CGAS) and then for the secondary outcome measures (RCMAS, MYMOP, MFQ, CDRS and SDQ). Group mean comparisons were made between baseline phases, between baseline and treatment phases, and between end of trial and three-month follow-up for the same set of variables. Group mean comparisons were conducted using paired sample *t*-tests, with *p*-values given for *t*-tests, as well as Cohen's *d* effect sizes. Changes between time points are illustrated by mean differences and 95% confidence intervals.

3. Results

The results of the intervention as assessed by the primary and secondary outcome measures are presented in the following sections. Individual changes over experimental phases analysed using modified Brinley plots (Blampied, 2007, 2014; Jacobson et al., 1984; Sobell et al., 1995) are shown first. Tables showing group mean comparisons between baseline phases (Table 4), then between baseline and treatment phases (Table 5), and lastly between end of trial and three-month follow-up (Table 6) are then displayed. Demographic characteristics of the final sample are presented in Table 2 below.

Table 2: *Demographic Characteristics of Final Sample*

Characteristic	Number	Mean	Standard deviation	Percentage
Sex				
Male	7			50
Female	7			50
Age in years (mean)		9.4	1.1	
Estimated household SES		94.7	42.1	
Ethnic group				
NZ European/Pakeha	11			79
Maori	2			14
Other	1			7

Note. Estimated household SES was calculated as the mean household score on the New Zealand Socioeconomic Index of Occupational Status where scores range from 10 to 90 whereby higher scores indicate higher SES (see method for more information).

3.1 Safety and Adherence

Adverse effects experienced by participants in the study were mild to moderate intensity (one participant experienced moderate level side effects) and able to be remedied by reducing dosage or with diet modification (e.g. taking the micronutrient with more food and water). This was true of all but one participant, who continued to experience mild nausea for approximately thirty minutes after taking the recommended morning dose throughout the trial.

Five out of fourteen (36%) participants experienced side effects which may have been related to the intervention. Two participants experienced nausea and three experienced gastrointestinal disturbances which were definitely related to the intervention. Another participant experienced gastrointestinal symptoms which may have been related to the

intervention. Three participants experienced agitation on the pills. This occurred in the first two weeks of the intervention. Reducing the dosage then slowly increasing over the next three to four weeks remedied this symptom, which was probably related to the intervention, given the number of participants who experienced agitation and its proximity to the beginning the intervention. Dry mouth, sleep disturbance and nose bleeds were also experienced at some point in the trial by a participant. These results are presented in Table 3.

Nine (64%) of the participants were compliant in terms of adherence to the treatment protocol. These participants were those who took the micronutrients at the recommended dose and did not miss a significant number of doses during the trial, which was defined as a compliance rate greater than 80%. Of the nine compliant participants, three (33%) took the micronutrients at a lower dose than eight pills per day (from four to six pills per day). This was either because they could not manage the number of pills which needed to be taken or experienced side effects at the recommended dose and thus stayed at a lower dose with fewer side effects. These participants are referred to as *compliant – low dose* in the following sections.

Non-compliant participants were those who achieved a compliance rate of less than 80%. This was either through forgetting to take a number of doses or having spent the majority of the trial going on and off the micronutrient for various reasons such as illness, taste of the powder and lack of effect (and so low motivation to be compliant). Furthermore, two participants opted to take the powder form of EMP+: one after trialling the pills and finding the quantity too difficult to take, while another participant refused to try the pills. One of these participants took the powder at a lower dose but was compliant, and the other participant was non-compliant. Another two participants opted to try the powder after some time on the pills, but found it more convenient to take the pills and so switched back to the capsule form.

Table 3: *Treatment-emergent adverse effects reported by at least 5% of participants during the trial*

Adverse effect	Definitely related		Possibly related	
	n	%	n	%
Gastrointestinal disturbance	3	21	1	14
Nausea	2	14		
Agitation			3	21
Headache			1	7
Dry mouth			1	7
Sleep disruption			1	7
Nose bleed			1	7

3.2 Brinley Plot Analyses

Data are presented below visually using modified Brinley plots (Blampied, 2007, 2014; Jacobson, et al., 1984; Sobell et al., 1995). Brinley (1965) introduced these plots as a way of presenting group mean data from cognitive psychology experiments. Mean group values were displayed as a scatter-plot, in such a way as to compare results within many conditions of the experiment with data in each condition categorised dichotomously, e.g., mean reaction times of men versus mean reaction times of women. If there was no systematic effect of the categorical variable (e.g., if male reaction times were the same as female reaction times) the condition data points lie on the diagonal (so long as the X and Y coordinates have the same origin and scale). If, however, the categorical variable did have a systematic effect, data points deviate from the diagonal. For a recent example see Dye, Green, and Bavelier (2009), who used Brinley plots to show that over many conditions and

experiments, experienced video-game players have systematically faster reaction times than novice video-game players.

In the case of modified Brinley plots, data from individuals rather than group means is plotted (Blampied, 2007; 2014; Rucklidge & Blampied, 2011). For each individual, a measurement made at Time 1 (T_1) is plotted on the X axis against a measurement on the same variable, for the same individual, at some subsequent time (T_x), which is plotted on the Y axis. If there has been no change in the measure between T_1 and T_x the data point will lie on the diagonal line, the line of no effect (or close to it if there has been measurement error without any intrinsic change in the variable measured). If, however, there has been change over time, the data point will lie somewhere off the line. If data from many individuals are thus plotted, systematic effects over time will be shown by systematic deviations from the diagonal line. To assist interpretation, lines showing clinically significant cut-off scores for the particular measure (Jacobson, et al, 1984) can be drawn (vertically to show the cut-off at T_1 , horizontally to show it for T_x) and the mean, confidence interval, and other measures of variance can also be shown. Capstick and Blampied (2004) and Blampied (2007) have proposed that Brinley plots are particularly useful and relevant for single-case research as they show the effect of an intervention, yet also preserve each individual's identity in the visual display.

Data for the study are presented as scores on a measure at one particular time-point plotted against scores on that same measure at another particular time-point. As described above, an effect is observed when scores deviate from the line of no effect. For the SCARED, PEDS, RCMAS, MYMOP, MFQ, CDRS and SDQ, points which fall below the line reflect a decrease in score and thus improvement, while those that fall above the line, show an increase in score and so some deterioration. However, on the CGAS the opposite is true, such

that points which fall above the line reflect an increase in score and thus an improvement in functioning. Points which fall below the line indicate a decline in functioning on the CGAS.

With clinical cut-off lines added, and when reduced scores indicate improvement, scores which fall below the line of no effect and below the horizontal clinical cut-off line indicate improvement and a non-clinical score at T_2 . In addition, scores which fall below the line of no effect and horizontal line as well as to the right of the vertical cut-off line show that the individual scored in the clinically significant range at the earlier time-point but was in the non-clinical range at the latter time-point.

Arrows are also displayed on the graphs and show the directional change which would be indicative of improvement. In addition, the crosses shown on each graph represent the mean and confidence intervals for each time-point. The point where the lines that form the cross intersect show the means for each time-point presented on each axis. The lengths of the lines themselves show the 95% confidence interval for each mean. This confidence interval represents the range in which we can expect the true mean to fall 95% of the time, if the trial was repeated multiple times. Thus, if the mean and confidence interval fall below the line of no effect we can infer that there is likely some effect of the intervention, as the mean is clearly different from the point prediction of the T_2 mean being equal to the T_1 mean. This is true of all measures, except the CGAS where the opposite would be true such that if the mean and confidence interval are above the line of no effect we can infer that there is likely some effect of the intervention, and that the post-treatment mean is different from the point prediction of no effect. Refer to Figure 1 below for an interpretation of modified Brinley plots.

The following figures show the same series of eight Brinley plots presenting the same comparisons for each of the main measures within the trial. These are: Baseline 1 (X axis) versus Baseline 2 (Y axis), Baseline 2 (X axis) versus Week 2 (Y axis), Baseline 2 (X axis)

versus Week 4 (Y axis), Baseline 2 (X axis) versus Week 6 (Y axis), Baseline 2 (X axis) versus End of Trial (Y axis), Baseline 2 (X axis) versus Follow-up (Y axis) and End of Trial (X axis) versus Follow-up (Y axis). The eighth plot compares Baseline 2 (X axis) versus End of Trial (Y axis) using an intent-to-treat analysis, such that for participants who did not complete the trial, their last data point was carried forward and used as the end of trial score, making for a more conservative comparison. Note also that Baseline 2 data were used as the primary baseline data, as opposed to Baseline 1 or an average of both sets of baseline data, given that it was common to see a trend toward a decrease in symptom severity over the baseline period. However, as demonstrated in Table 3, there was a statistically significant decrease over the baseline phase for only two measures, the SCARED and PEDS. Thus Baseline 2 was used as the primary baseline data as this also provides, along with using the intent-to-treat method, a more conservative measure to compare the intervention to.

In addition, this final plot also displays data separated by compliance level and the first plot (Baseline 1 [X axis] versus Baseline 2 [Y axis]) is split such that the baseline length is shown for each participant. This allows for any trends related to the length of baseline to be seen. In that first plot Group 1 refers to participants with a one week long baseline period, Group 2 refers to participants with a two week long baseline period and Group 3 refers to participants with a three week long baseline period.

The average increase or decrease in scores from Baseline 2 to End of Trial for each measure was calculated by determining the percentage change for each participant using the full sample of 14 participants and the intent-to-treat method detailed above, then calculating the mean of these percentage changes.

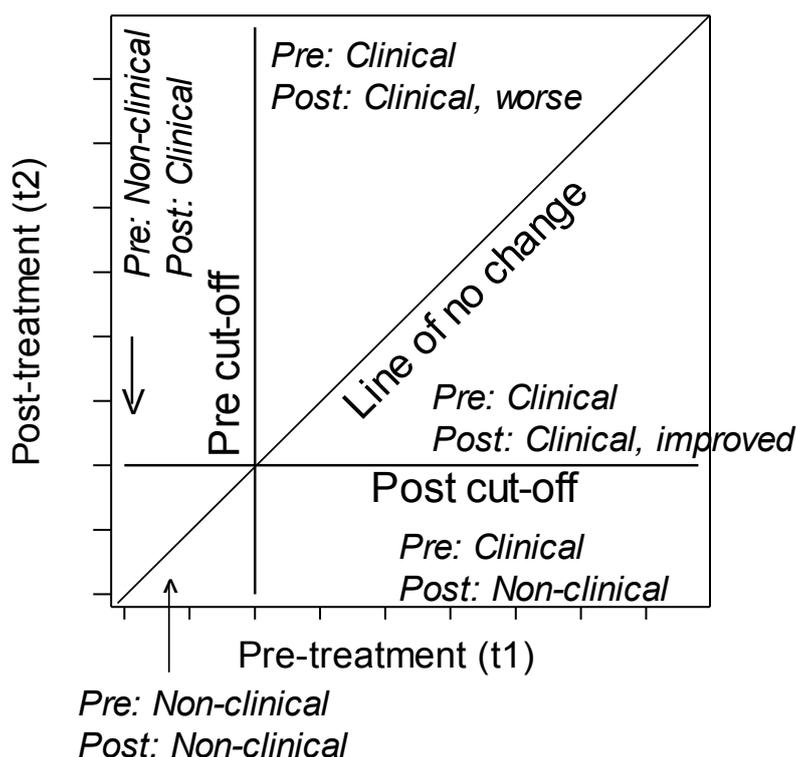


Figure 1. Modified Brinley plot interpretation (after Rucklidge & Blampied, 2011). Note that this interpretation applies where improvement is signalled by a **reduction** in score, indicated by the arrow to the right of the Y axis.

3.2.1 Primary measures. Figure 2 shows the effect of micronutrient intervention on the primary measure of anxiety, the parent-rated Screen for Child Anxiety Related Disorders (SCARED). The initial plot presenting Baseline 1 versus Baseline 2 shows a trend toward a decrease in anxiety level over the baseline period. It also shows that the majority of participants, nine out of 14 (64%), were over the clinical cut-off in terms of anxiety during the entire baseline period. Over the course of the next four plots, a steady decrease in scores is seen, until by the end of the trial, 10 of the 11 (91%) participants who completed the trial fall below the clinical cut-off in terms of anxiety level, including six out of seven (86%) of completers who were over the clinical cut-off at Baseline 2 and fell below the clinical cut-off at End of Trial. Furthermore, the mean and confidence interval for End of Trial was below

the clinical cut-off line and line of no effect. The Baseline 2 and End of Trial scores gave an average decrease in anxiety level of 58%. These gains continue to be seen at follow-up. However, there is little or no change seen in anxiety level from End of Trial to Follow-up as demonstrated on the plot comparing these time points.

The final plot presenting Baseline 2 versus End of Trial shows that overall, non-compliant participants demonstrate little change in anxiety during the course of the intervention as demonstrated by the means and confidence intervals for this group. This is in stark comparison to compliant and compliant – low dose participants who all showed improvement and fell below clinical cut-off following the micronutrient intervention, as seen by the individual data points and the means and confidence intervals for these groups. However, the non-compliant group did have a higher Baseline 2 score than the compliant groups.

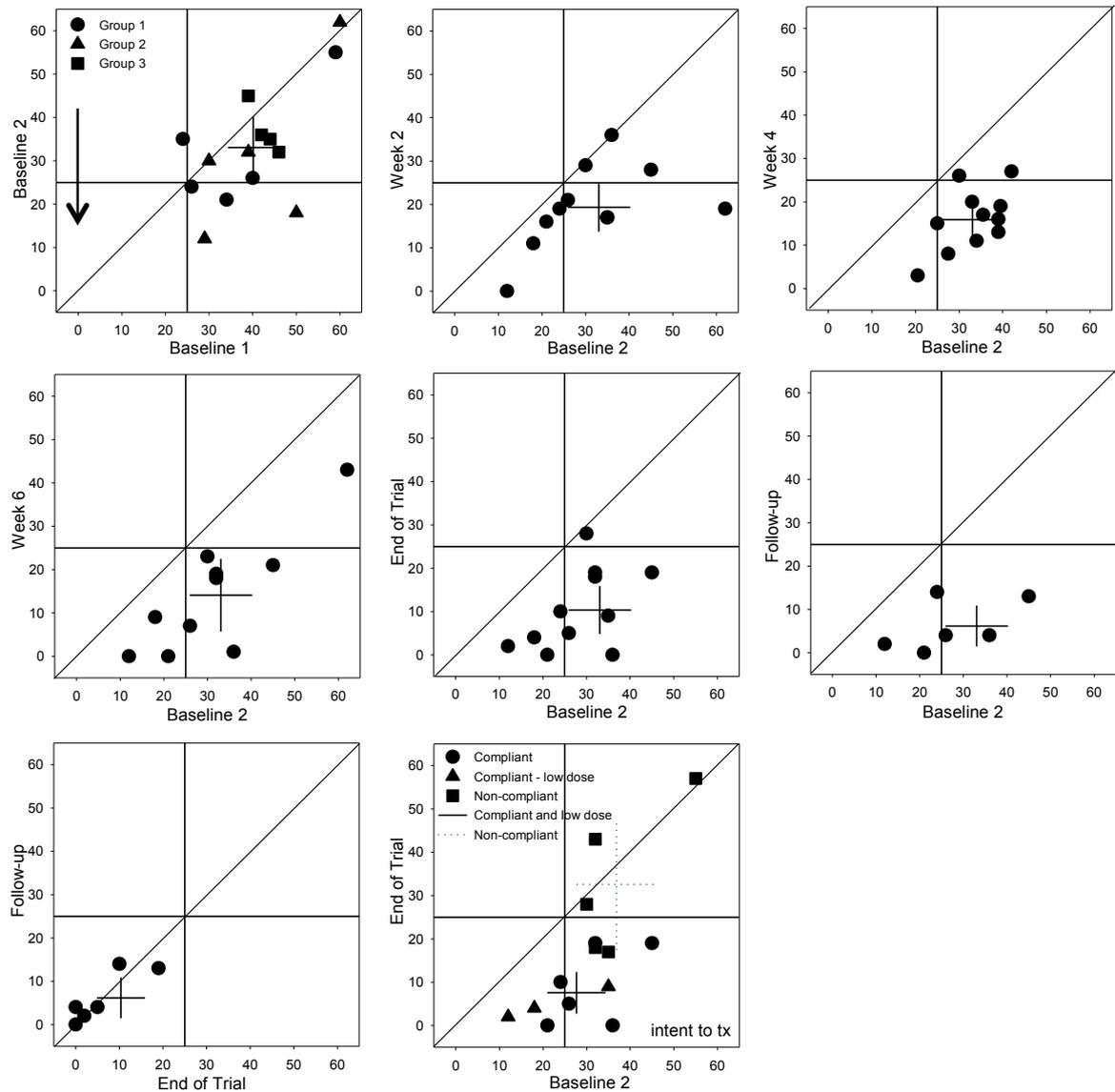


Figure 2. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the SCARED.

Figure 3 shows the effect of micronutrient intervention on the parent-rated Pediatric Emotional Distress Scale (PEDS). The initial plot presenting Baseline 1 versus Baseline 2 shows a trend toward a decrease in anxiety level over the baseline period, as demonstrated by the means and confidence intervals for these time-points. It also shows that all participants were over the clinical cut-off in terms of anxiety during the baseline period.

Over the course of the next four plots a decrease in scores is seen, until by the end of the trial five out of 11 (46%) of participants who completed the trial fall below the clinical cut-off in terms of anxiety level. The mean for the End of Trial lies about the clinical cut-off line, although the lower bound of the confidence interval for this mean is below the clinical cut-off line. The Baseline 2 and End of Trial scores gave an average decrease in anxiety level of 25%. The gains made at End of Trial continue to be seen at Follow-up, with the mean falling below the clinical cut-off at follow-up. However, there is only a small further decrease in anxiety level seen from End of Trial to Follow-up as demonstrated on the plot comparing these time points.

The final plot presenting Baseline 2 versus End of Trial shows that overall, compliant and non-compliant participants demonstrated a similar level of change in anxiety over the course of the intervention, as illustrated by the means and confidence intervals for the two different compliance groups. However, compliant participants started and finished the study at a lower level of anxiety, with the mean falling below the clinical cut-off, although the confidence interval for the end of trial overlapped this line.

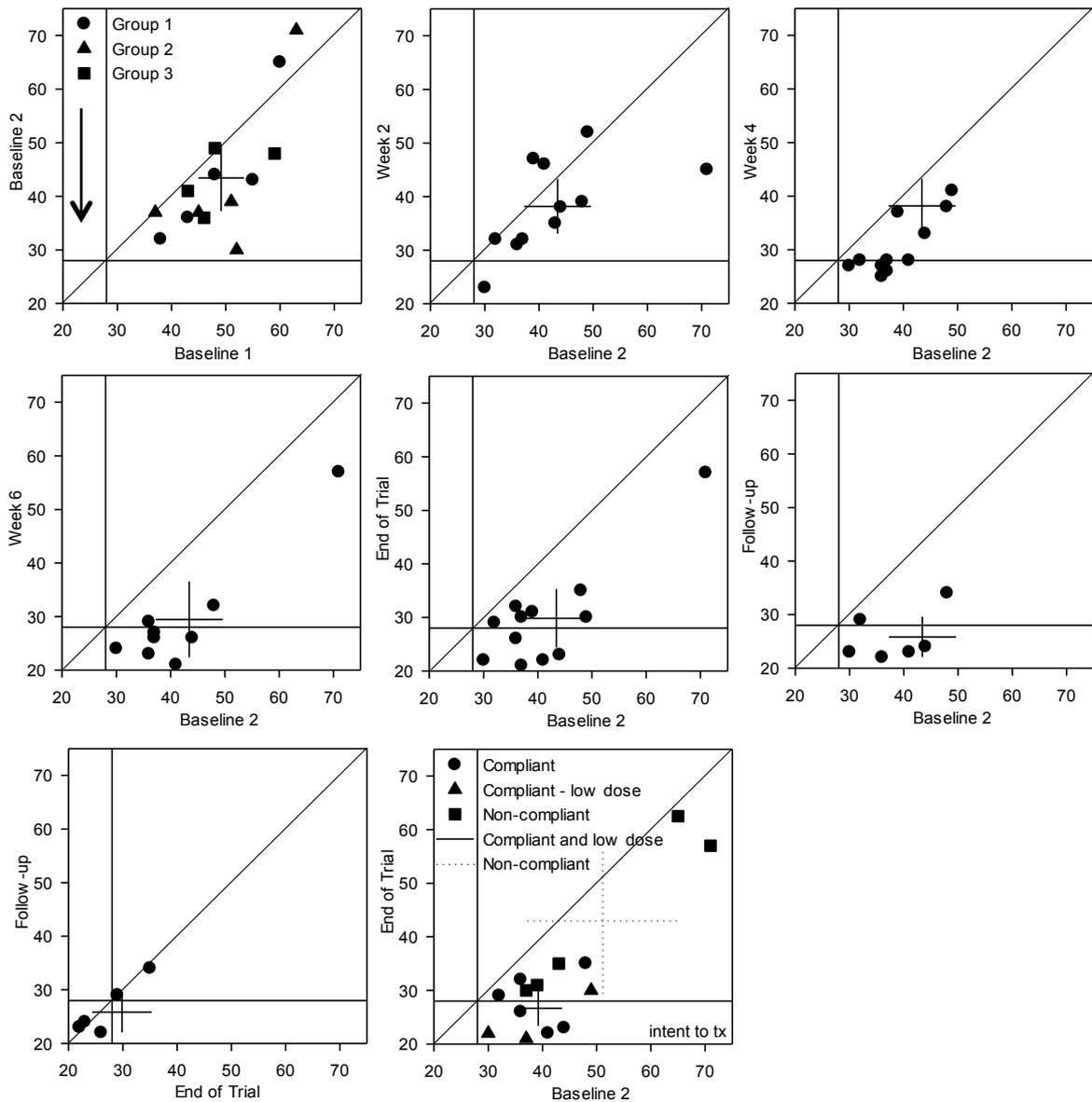


Figure 3. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the PEDS.

Note. The possible range of scores for the PEDS is 21 to 84.

Figure 4 shows the effect of micronutrient intervention on the Children’s Global Assessment Scale (CGAS), a clinician-rated measure of functioning. The initial plot presenting Baseline 1 versus Baseline 2 illustrates that level of functioning remained

consistent over the baseline period. Over the following four plots a steady increase in scores is seen, indicating improvement in functioning, such that by the end of the trial 10 out of 11 (91%) participants had moved above the line of no effect. The Baseline 2 and End of Trial scores gave an average increase in functioning of 18%. The plot presenting End of Trial versus Follow-up demonstrates that participants whose follow-up data were collected, tended to continue to improve, as shown by the mean and confidence interval for Follow-up, although the lower bound of the confidence interval overlapped the line of no effect and some data points fell below the line.

The final plot presenting Baseline 2 versus End of Trial shows that overall, non-compliant participants demonstrate a small, if any, increase in functioning over the course of the intervention, as shown by the means and confidence intervals for this group. In comparison, the compliant and compliant – low dose participants improved more than the non-compliant group, as seen by the individual data points and the means and confidence intervals for these groups. Of note is that the mean and confidence intervals for the compliant group fall above the line of no effect, although it is also noted that this group was slightly higher functioning at Baseline 2 than the non-compliant group.

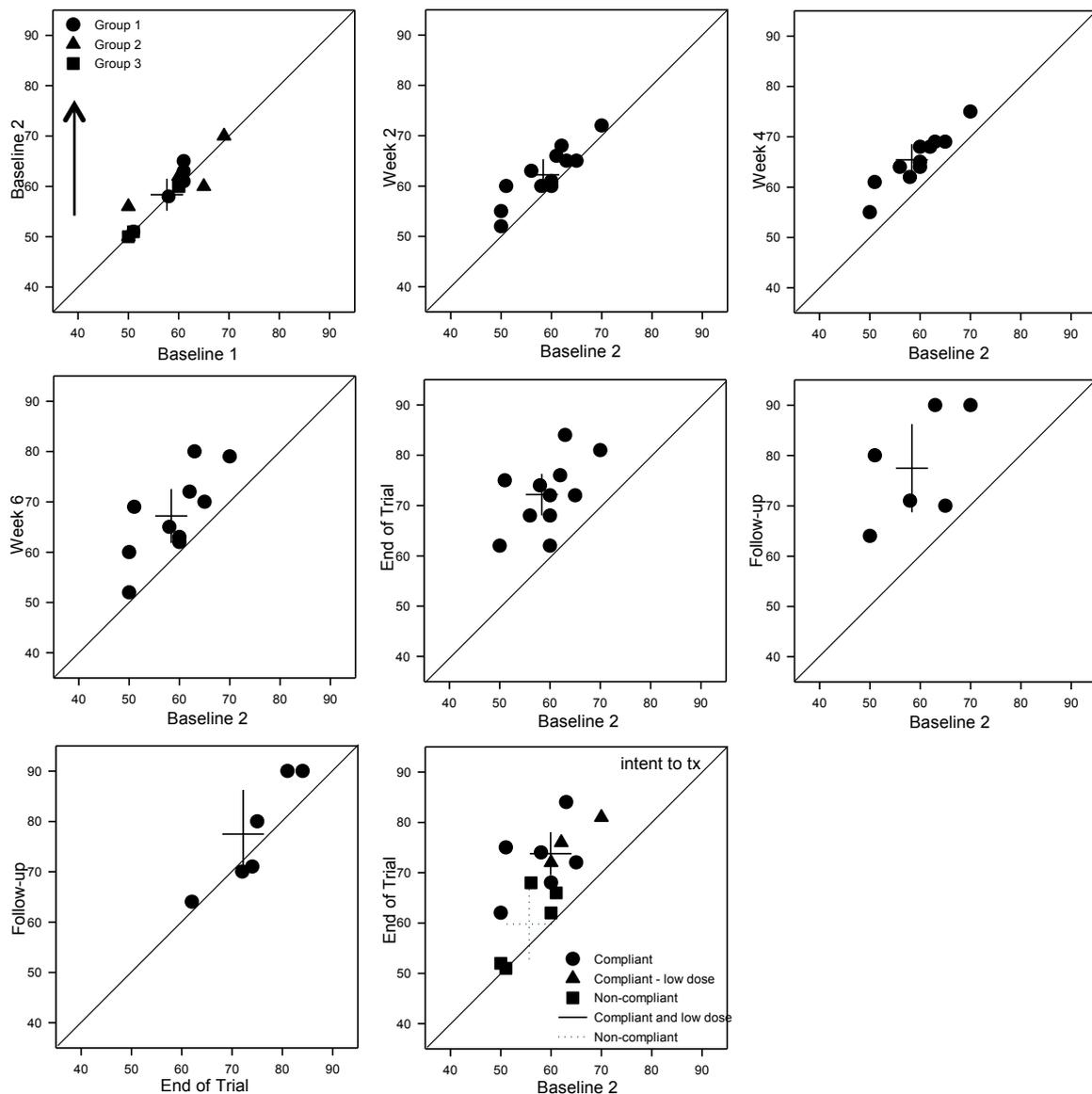


Figure 4. Modified Brinley plots showing the effect of micronutrient intervention on functioning as measured by the CGAS.

Note. The range of scores for the CGAS is 0 to 100.

3.2.2 Secondary measures. Figure 5 shows the effect of micronutrient intervention on the child-rated Revised Children’s Manifest Anxiety Scale (RCMAS). The initial plot presenting Baseline 1 versus Baseline 2 shows a large scatter among the individual data points around the line of no effect, indicating a large range of change in the baseline period,

with some participants improving and some participants worsening in terms of anxiety. While it appears that four out of five (80%) participants in Group 1 (one week baseline period) saw an increase in anxiety over the baseline period, the overall means and confidence intervals show there was little to no change in anxiety over the baseline period for this measure. It also shows that three out of 14 (21%) participants were over the clinical cut-off at the end of the baseline period and two out of 14 (14%) throughout the entire baseline period.

Over the course of the next four plots there is a general trend toward a decrease in anxiety. By the end of the trial nine out of 11 (82%) participants who completed the trial fell below the clinical cut-off in terms of anxiety level, including two out of the three (67%) completers who were over the clinical cut-off at Baseline 2. Also, the mean and confidence interval for the end of the trial fell below the line of no effect, indicating significant improvement. The Baseline 2 and End of Trial scores gave an average decrease in anxiety level of 43%.

These gains continue to be seen at Follow-up; however, there is little or no change seen in anxiety level from End of Trial to Follow-up as demonstrated on the plot comparing these time points. The final plot presenting Baseline 2 versus End of Trial shows that overall, both non-compliant and compliant groups decreased in anxiety throughout the intervention. However, the compliant group decreased more than the non-compliant group despite having similar Baseline 2 scores, as can be seen by the means and confidence intervals for both groups.

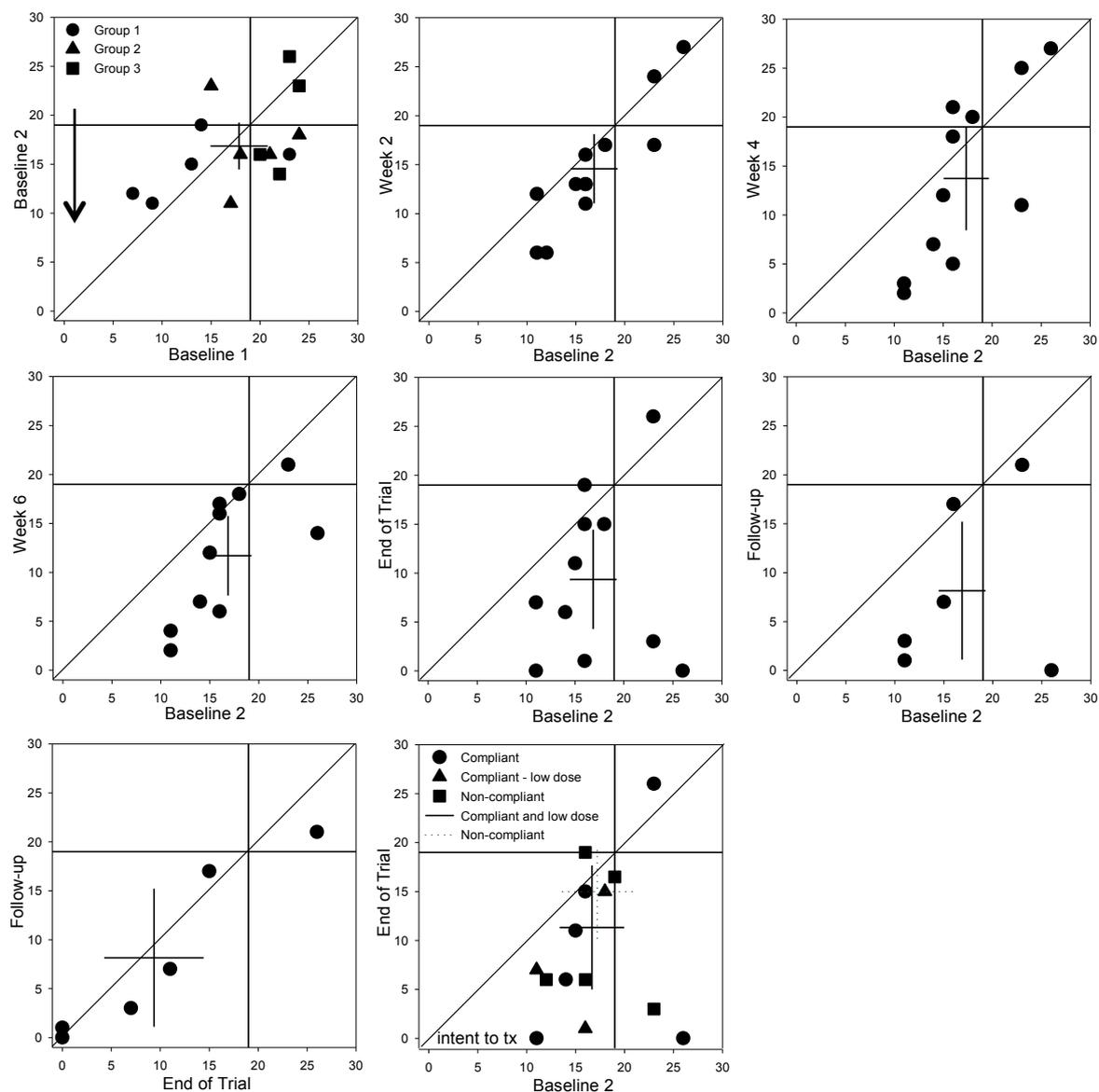


Figure 5. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the RCMAS.

Figure 6 shows the effect of micronutrient intervention on the Measure Yourself Medical Outcome Profile (MYMOP), a child-rated measure of anxiety symptoms. The initial plot presenting Baseline 1 versus Baseline 2 shows a trend toward a small decrease in anxiety symptoms over the baseline period. However, the confidence intervals for the mean do overlap with the line of no effect and the individual data points show a range of scatter above

and below this line. Over the course of the next four plots, the means and confidence intervals for the intervention phase time-points drop below the line of no effect, until by the end of the trial seven out of 11 (64%) participants who completed the trial fall below the line of no effect. The Baseline 2 and End of Trial scores gave an average decrease in anxiety level of 34%. These gains continue to be seen at Follow-up, although there is a further small decrease in anxiety symptoms as indicated by the means on the plot comparing End of Trial to Follow-up. However, the confidence intervals do overlap with the line of no effect and there is also some scatter either side of this line.

The final plot presenting Baseline 2 versus End of Trial shows that overall, non-compliant participants demonstrate little change in anxiety over the course of the intervention, as illustrated by the means and confidence intervals for this group. In comparison, the means and confidence intervals for the compliant and compliant – low dose group fell below the line of no effect, with six out of nine (67%) participants from the compliant groups also falling below this line. However, the non-compliant group also began the intervention phase with a higher mean score than the compliant groups.

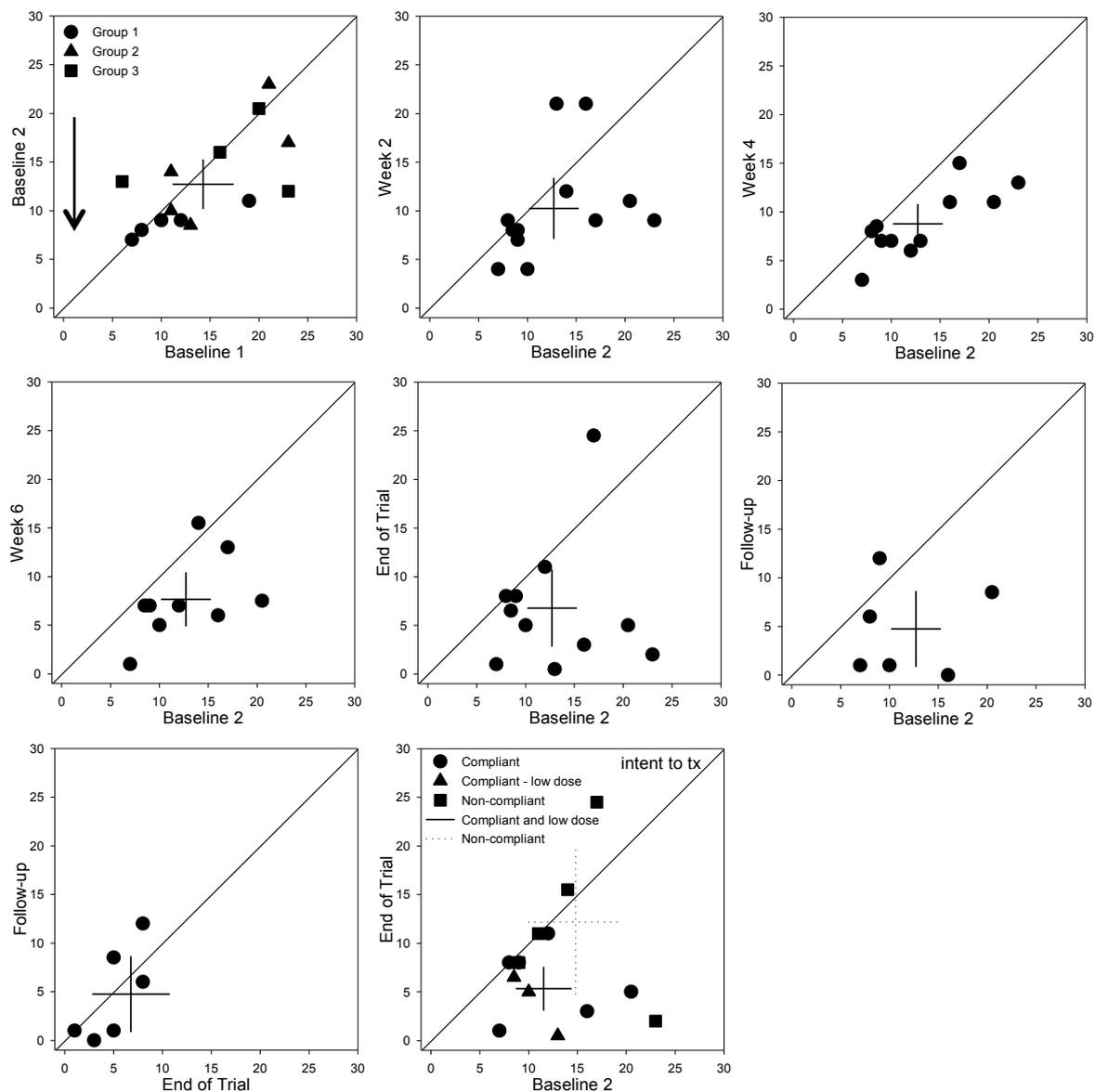


Figure 6. Modified Brinley plot's showing the effect of micronutrient intervention on anxiety as measured by the MYMOP.

Figure 7 shows the effect of micronutrient intervention on the Mood and Feelings Questionnaire (MFQ), a parent-rated measure of mood. The initial plot presenting Baseline 1 versus Baseline 2 shows an overall trend toward little change in mood over the baseline period, with a range of scatter above and below the line of no effect, and the means falling very near this line. It also shows that three out of 14 (21%) participants were over the clinical

cut-off in terms of mood during the entire baseline period and four out of 14 (29%) by the end of the baseline period. Over the course of the next four plots there is a decrease in scores until by the end of the trial, all participants fall below the clinical cut-off in terms of mood, with 10 out of 11 (91%) participants who completed the trial falling below the line of no effect. The Baseline 2 and End of Trial scores gave an average decrease in mood of 54%. These gains continue to be seen at follow-up. However, there was no change seen in mood from End of Trial to Follow-up as demonstrated on the plot comparing these time points.

The final plot presenting Baseline 2 versus End of Trial shows that overall, compliant and compliant – low dose participants tended to improve and remain under the clinical cut-off by the end of the trial, while non-compliant participants moved from being over the clinical cut-off to under it, as seen by the means for the two groups. However, the confidence intervals for the non-compliant group did overlap the clinical cut-off lines and line of no effect. This final plot also demonstrates a similar degree of improvement among both the compliant and non-compliant groups, though the non-compliant group had more symptomatology at Baseline 2 and remained more symptomatic than the compliant group at the end of the trial.

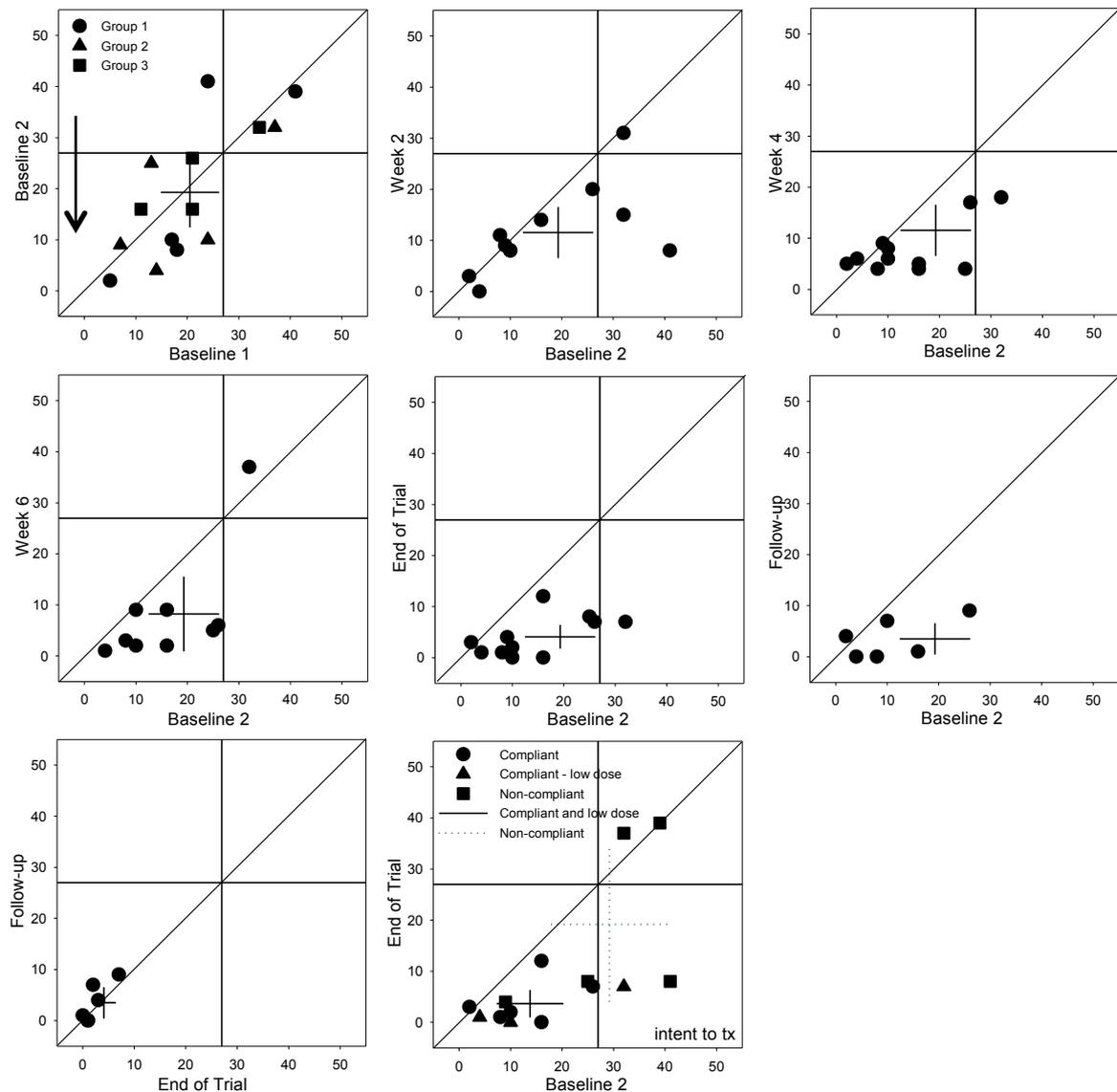


Figure 7. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the MFQ.

Figure 8 shows the effect of micronutrient intervention on the Children’s Depression Rating Scale (CDRS), a clinician-rated measure of mood. The initial plot presenting Baseline 1 versus Baseline 2 shows a trend toward a small decrease in mood over the baseline period, as demonstrated by the mean and confidence intervals for this plot. It also shows that by Baseline 2, all participants were under the clinical cut-off in terms of mood symptoms. Over

the next four plots a decrease in scores is seen until by the end of the trial the mean and confidence intervals are very close to the minimum possible score (16) and all participants remain under the clinical cut-off. The Baseline 2 and End of Trial scores gave an average decrease in mood symptomatology of 13%. These gains continue to be seen at Follow-up, although there is little or no change seen in mood symptoms from End of Trial to Follow-up as demonstrated on the plot comparing these time points.

The final plot presenting Baseline 2 versus End of Trial shows that overall, the non-compliant group remained more symptomatic in terms of mood symptoms than compliant participants; however, the non-compliant group began the trial with a higher mean score. Despite this, both groups were under the clinical cut-off at End of Trial. This is demonstrated by the means and confidence intervals for both groups.

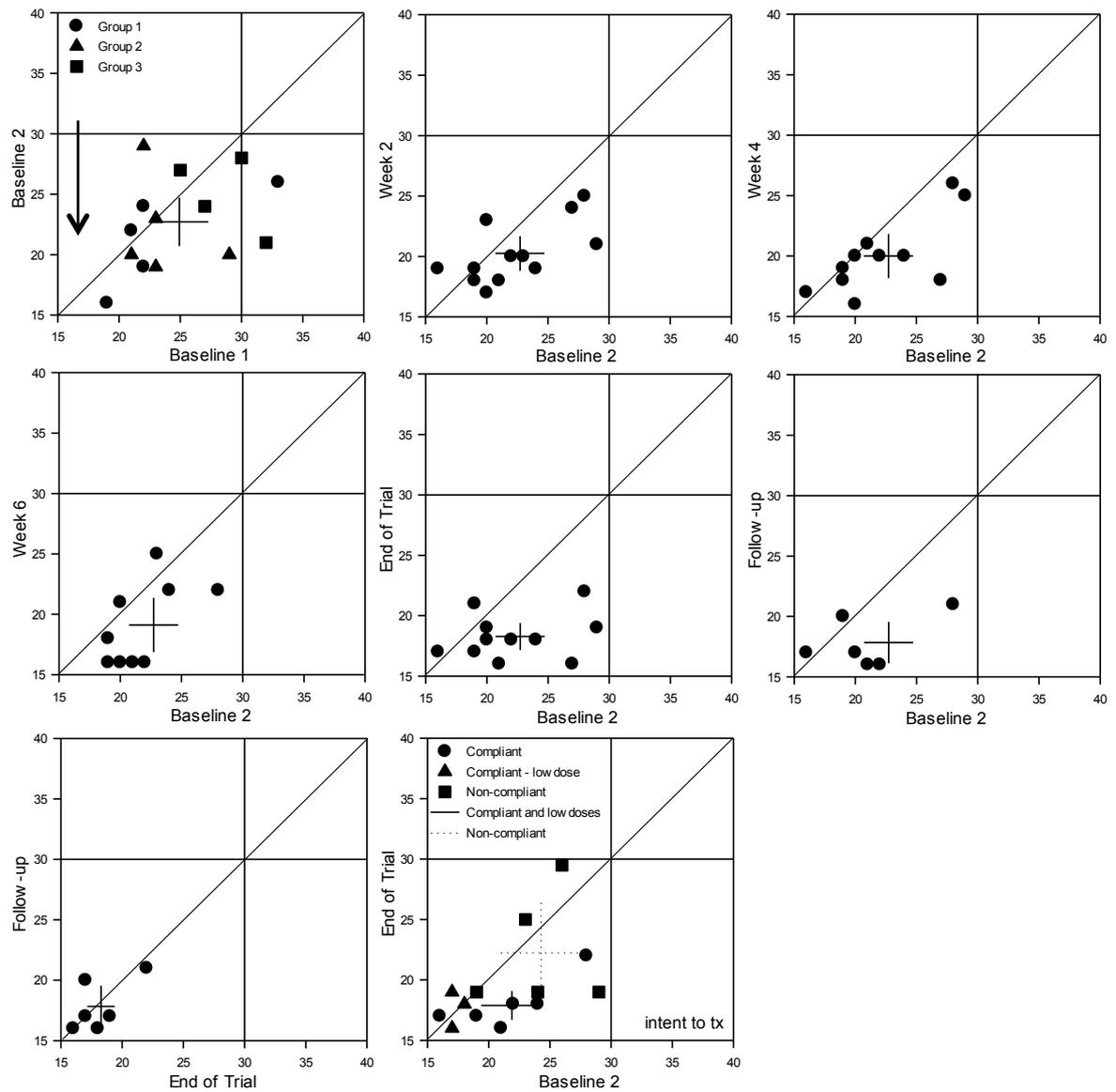


Figure 8. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the CDRS.

Note. The range of scores for this measure is 16 to 62

Figure 9 shows the effect of micronutrient intervention on the parent-rated Strengths and Difficulties Questionnaire, a measure of functioning difficulties in daily life. Because this measure was only completed at the beginning and end of the intervention phase and follow-

up, there are only four Brinley plot comparisons made. In addition, data was missing for two participants, resulting in a sample of nine participants who completed the trial. The initial plot presenting Baseline 2 versus End of Trial shows a trend toward a decrease in total difficulties a child has with everyday life, as shown by the mean and confidence interval for End of Trial. By the end of the trial, all participants who completed the trial fell under the clinical cut-off, with seven out of nine (78%) participants seeing some decrease in total difficulties. These gains are maintained at Follow-up. However, there was no change from End of Trial to Follow-up as demonstrated on the plot showing these time points. Of note is that one participant was above the clinical cut-off at Follow-up, having previously been below the clinical cut-off at the end of the trial, despite continuing to take a micronutrient compound (Daily Essential Nutrients, a newer version of EMP+ with very similar ingredients), albeit at a lower dose than in the trial. This converts to 17% of participants at Follow-up worsening between End of Trial and Follow-up.

The final plot presenting Baseline 2 versus End of Trial showed that the overall, non-compliant participants demonstrated little or no change in level of difficulties with everyday life over the course of the intervention, as illustrated by the means and confidence intervals for this group. In addition, the mean for this group at Baseline 2 and End of Trial is above the clinical cut-off throughout the trial. This is in comparison to the compliant groups, who experienced a decrease in level of everyday difficulties, such that all participants fell below the clinical cut-off following the micronutrient intervention, including the two participants who had been above the cut-off at Baseline 2. This is illustrated by the mean and confidence intervals for the compliant group.

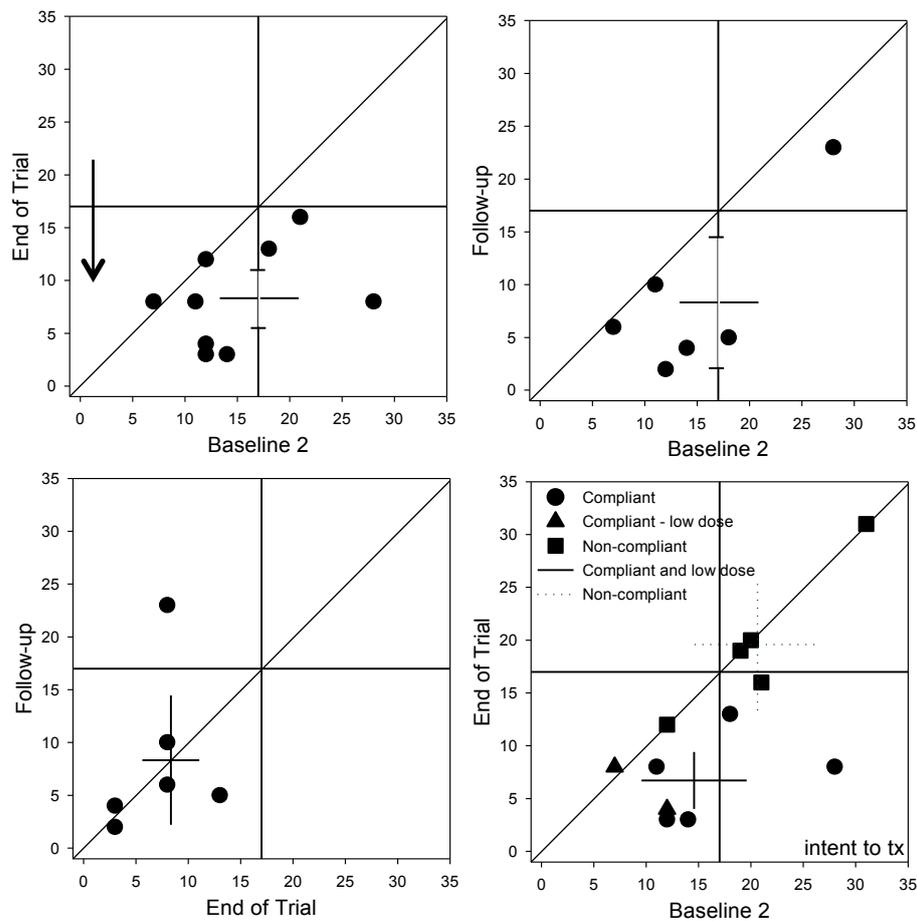


Figure 9. Modified Brinley plots showing the effect of micronutrient intervention on anxiety as measured by the SDQ.

3.3 Comparison of Change over Time in Group Mean Data

Tables 4, 5 and 6 present the group mean, standard error of the mean (SEM), the mean difference between the respective experimental phases, the 95% Confidence Interval (95% CI) for the mean difference, the t value for non-independent samples and the Effect Size (Cohen’s *d* for non-independent samples) for the SCARED, PEDS, CGAS, RCMAS, MYMOP, MFQ, CDRS and SDQ.

3.3.1 Baseline comparisons and multiple baseline analyses. A multiple baseline design allows researchers to examine any differences in symptom stability between groups with different length baseline periods over the entire baseline period. In doing this the researcher can determine if there was a decrease in symptoms prior to the intervention and how this decrease compares to decreases seen during the intervention phase.

Analysis of stability over the baseline period. Table 4 compares initial baseline scores with final baseline scores to assess stability over the baseline period. Participants tended to have elevated scores in terms of clinical cut-offs throughout the baseline period on the primary measures (SCARED and PEDS). Scores on measures of mood (MFQ and CDRS) tended to be below the clinical cut-offs and remain so throughout the baseline period. Paired sample t-tests revealed that for the CGAS, RCMAS, MYMOP, MFQ and CDRS there were no statistically significant changes in scores over the baseline period. However, there were statistically significant decreases in anxiety over the baseline period on the SCARED and the PEDS. This somewhat compromises the multiple baseline design, given the SCARED and the PEDS are the primary measures of anxiety within the study, because it shows that there was a trend in baseline that was in the direction expected during treatment. However, as shown below in the pre-post treatment mean comparisons and demonstrated in the above modified Brinley plots, there was a clear change evident during the treatment phase that was considerably greater than the observed changes in baseline, and the treatment effect was replicated across participants, and across all dependent variables, providing strong evidence that the micronutrients did alter the children's symptoms.

Confidence intervals for the mean difference between initial and final baseline scores do range from approximately one point in difference to approximately 13 and nine points for the SCARED and PEDS respectively. This indicates that the true difference could be as little as one point between initial and final baseline for each of these measures. Furthermore, the

mean difference 95% CI's for the SCARED and PEDS are both large, indicating large variability amongst participants' scores during the baseline period. All 95% CI's for the mean difference between initial and final baseline on the other measures shown in Table 3 include 0 and thus the true mean difference may be 0, or a worsening in score over the baseline period. The effect sizes for the changes on the SCARED and the PEDS fell in the moderate range using Cohen's (1992) criteria of 0.2 for a small effect, 0.5 for a medium effect and 0.8 for a large effect size.

Baseline length comparisons. There were no notable trends in terms of differences between baseline scores when comparing the three different baseline length groups (group 1=1 week baseline, group 2=2 week baseline and group 3=3 week baseline). Between group comparisons of the means and 95% CI's for measures completed during baseline assessments were made at each time point and the mean and 95% CI for group one at initial baseline was compared to the mean and 95% CI for group two at initial baseline and these both then compared with the mean and 95% CI for group three at initial baseline. On the child rated RCMAS and MYMOP there was a tendency toward a difference between scores for group 1 compared to group 3. There was no overlap between 95% CI's for group 1 and group 3 on the RCMAS at initial baseline. This indicates that the true mean for these groups cannot be the same and thus that group 3 was more severe in terms of child-rated anxiety compared to group 1 at initial baseline. On the MYMOP there was no overlap in the 95% CI's for group 1 compared to group 3 at final baseline. This indicates that the true mean for these groups cannot be the same and thus that group 3 was more severe in terms of child-rated symptoms of anxiety when compared to group 1 at final baseline.

Table 4
Means, SEMs, Paired Sample t-tests and Effect sizes for Baseline 1 and Baseline 2 comparisons for Primary and Secondary Outcome Measures

Variable	Baseline 1 (n=14)		Baseline 2 (n=14)		Comparing baseline to post-trial				
	Mean	SEM ^a	Mean	SEM ^a	Mean difference	Difference (95% CI) ^b	t-test	p-value	Effect size ^c
Primary outcomes									
SCARED	39.93	2.98	33.07	3.66	6.86	0.78-12.93	2.438	.030	0.65
PEDS	47.00	2.12	41.86	2.95	5.14	1.14-9.14	2.778	.016	0.74
CGAS	57.64	1.65	58.36	1.63	-0.71	-2.14-0.71	-1.085	.298	0.29
Secondary outcomes									
RCMAS	17.86	1.49	16.86	1.22	1.00	-1.99-3.99	.723	.482	0.19
MYMOP	14.29	1.59	12.71	1.30	1.57	-1.11-4.25	1.267	.227	0.34
MFQ	20.50	2.90	19.29	3.49	1.21	-3.79-6.22	.524	.609	0.13
CDRS	24.93	1.20	22.71	1.02	2.21	-0.51-4.93	1.759	.102	0.47

Note. SCARED = Screen for Child Anxiety Related Disorders, PEDS = Pediatric Emotional Distress Scale, CGAS = Children's Global Assessment Scale,

RCMAS = Revised Children's Manifest Anxiety Scale, MYMOP = Measure Your Medical Outcome Profile, MFQ = Mood and Feelings Questionnaire,

CDRS = Children's Depression Rating Scale.

- a. SEM = standard error of the mean, $SEM = \frac{\sigma}{\sqrt{n}}$
- b. 95% CI = 95% confidence interval
- c. Cohen's d measured as the mean difference pre-post/mean SD of the difference.

3.3.2 Baseline versus post-intervention comparisons. Table 5 compares final baseline and post-trial means for the same set of variables as Table 4, as well as the SDQ. Each participant's final baseline data point was used for these baseline-to-treatment phase comparisons (as noted above, baseline measures were taken at the start and then again either one, two or three weeks later, prior to the intervention). Paired sample *t*-tests were completed using intent-to-treat analysis and final baseline data points (due to the trend in reductions seen over the baseline period and illustrated in Table 4), making for a more conservative analysis as discussed above (3.2). The average participant tended to improve to a point where they were no longer within the clinically significant range over the treatment phase on the SCARED and PEDS. There was an average improvement of 10 points on the CGAS over the intervention phase as well as further decreases in scores on all secondary measures, although the mean score for each of these measures was not elevated at final baseline.

Paired sample *t*-tests revealed statistically significant improvements on all nine outcome measures (Table 5). Of particular note are the changes observed on the primary measures of the study. These are the parent-rated measures of anxiety (SCARED and PEDS) and the clinician-rated measure of level of functioning (CGAS). While the paired sample *t*-tests for the primary measures were all statistically significant, the effect sizes for these measures were also large, confirming clinically meaningful change. The effect sizes for the secondary measures range from moderate to large in size, also indicating clinically meaningful change from final baseline to post-intervention.

Table 5
Means, SEMs, Paired Sample t-tests and Effect sizes for Final Baseline and Post-trial comparisons for Primary and Secondary Outcome Measures

Variable	Final Baseline (n=14)		Post-trial (n=14)		Comparing baseline to post-trial				
	Mean	SEM ^a	Mean	SEM ^a	Mean difference	Difference (95% CI ^b)	t-test	p-value	Effect size ^c
Primary outcomes									
SCARED	33.07	3.66	16.00	4.31	17.07	11.90-22.24	7.138	<.001	1.91
PEDS	41.86	2.95	31.57	2.94	10.29	5.99-14.59	5.168	<.001	1.38
CGAS	58.36	1.63	68.79	2.59	-10.43	-14.50- -6.36	-5.538	<.001	1.48
Secondary outcomes									
RCMAS	16.86	1.22	10.14	2.17	6.71	1.77-11.66	2.931	.012	0.78
MYMOP	12.71	1.30	7.79	1.71	4.93	0.12-9.44	2.361	.034	0.63
MFQ	19.29	3.49	9.43	3.37	9.86	3.62-16.09	3.416	.005	0.91
CDRS	22.71	1.02	19.29	0.83	3.43	0.98-5.88	3.027	.010	0.81
SDQ	17.08	2.07	12.08	2.41	5.00	1.05-8.95	2.783	.018	0.80

Note. Abbreviations as for Table 4. SDQ = Strengths and Difficulties Questionnaire

a. SEM = standard error of the mean, $SEM = \frac{\sigma}{\sqrt{n}}$

- b. 95% CI = 95% confidence interval
- c. Cohen's *d* measured as the mean difference pre-post/mean SD of the difference.

3.3.3 Post-intervention versus follow-up comparisons. Table 6 compares post-trial and follow-up means for the same set of variables as Table 5. Table 6 illustrates that, based on the six participants followed for three months post-trial, there were no significant changes found between the end of trial and three month follow-up on any measure. This indicates that although participants did not continue to improve, on average they also did not lose the gains they had made by the end of the trial. Four out of six (66.7%) participants continued to take EMP+ (or Daily Essential Nutrients, a newer version of EMP+ with very similar ingredients) at follow-up. These participants took micronutrients at least every third day at a lower dose than during the intervention phase and more regularly during times of stress. In addition, one other participant had been taking EMP+ for the majority of the follow-up period. This participant was off the EMP+ at the time of follow-up and stated they were planning to resume taking it.

Table 6
Means, SEMs, Paired Sample t-tests and Effect sizes for Post-trial and Three Month Follow-up comparisons for Primary and Secondary Outcome Measures

Variable	Post-trial (n=6)		3 month follow-up (n=6)		Comparing post-trial to 3 month follow-up				
	Mean	SEM ^a	Mean	SEM ^a	Mean difference	Difference (95% CI ^b)	t-test	p-value	Effect size ^c
Primary outcomes									
SCARED	6.00	3.02	6.17	2.40	-0.17	-4.06-3.73	-0.110	.917	0.04
PEDS	25.33	1.45	25.17	2.21	0.17	-2.90-3.24	0.139	.895	0.06
CGAS	74.67	3.14	77.50	4.47	-2.83	-7.77-2.11	-1.47	.200	0.60
Secondary outcomes									
RCMAS	9.83	4.04	8.17	3.60	1.67	-1.49-4.83	1.356	.233	0.55
MYMOP	5.00	1.13	4.75	1.99	0.25	-3.29-3.79	0.182	.863	0.07
MFQ	2.83	1.01	3.50	1.57	-0.67	-3.83-2.49	-0.542	.611	0.22
CDRS	18.17	0.87	17.83	0.87	0.33	-1.62-2.29	0.439	.679	0.18
SDQ	7.17	1.54	8.33	3.13	-1.17	-9.17-6.84	-0.375	.723	0.15

Note. Abbreviations as for Table 5.

a. SEM = standard error of the mean, $SEM = \frac{\sigma}{\sqrt{n}}$

- d. 95% CI = 95% confidence interval
- e. Cohen's *d* measured as the mean difference pre-post/mean SD of the difference.

3.4 Further Analyses

Responder status demonstrates the percentage of participants who during baseline were above clinical cut-off for a measure and moved to below that clinical cut-off following intervention with micronutrients. These analyses were completed using the final baseline data in order to give an accurate representation of the impact of the micronutrient intervention.

Seven out of the 10 (70%) participants who were within clinical range at final baseline as measured by the SCARED responded positively to the intervention, such that their level of anxiety decreased from the clinical range to within normal range. Five out of the 14 (35.7%) participants who were within clinical range at final baseline as measured by the PEDS responded positively to the intervention, such that their level of anxiety decreased from clinical range to within normal range.

Two out of the four (50%) participants who were within clinical range at final baseline as measured by the RCMAS responded positively to the intervention, such that their level of anxiety decreased from clinical range to within normal range. Two out of the four (50%) participants who were within clinical range at final baseline as measured by the parent-rated MFQ responded positively to the intervention, such that their mood symptoms decreased to be within normal range. No participants were elevated in mood at final baseline or the end of trial as measured by the clinician-rated CDRS and thus responder status as determined by this measure cannot be calculated. All three (100%) of the participants who were within clinical range at final baseline as measured by the SDQ responded positively to the intervention, such that their level of difficulties decreased from clinical range to within normal range.

Further analyses show that nine (64%) of the full sample of participants improved moderately or markedly from baseline as measured by the clinician-rated Overall Clinical Impression measure.

4. Discussion

4.1 Summary of Findings

This innovative research points to a completely new approach to treating anxiety in children. It found micronutrient intervention resulted in clinically significant decreases in anxiety, as well as improvements in overall functioning, amongst a sample of children who were suffering from clinically elevated anxiety. This is consistent with other reports from the literature on micronutrient interventions for anxiety in adults and what little research has been published in terms of micronutrient interventions for anxiety in children. This study found there were statistically significant changes in favour of micronutrient intervention for all dependent variables, as demonstrated by modified Brinley plots and comparison of means. Eleven participants completed the trial, one participant withdrew following the final baseline assessment, another following week two of the intervention phase and another following week six of the intervention phase.

The current sample reflected a group of children with clinically significant levels of anxiety, many of whom experienced onset or worsening in anxiety following the Canterbury earthquakes. Ten of the final fourteen participants also met criteria for at least one DSM-IV anxiety disorder and all were experiencing clinically significant impairment in day-to-day functioning prior to starting the intervention.

As predicted, the hypotheses were generally supported. The primary hypothesis proposed that micronutrient intervention would be associated with improvements in anxiety. This hypothesis was supported such that ten out of eleven participants who completed the intervention experienced a clinically significant decrease (e.g. they dropped below the clinical cut-off) in anxiety on the SCARED. Furthermore, five out of eleven of these same participants experienced a clinically significant decrease in anxiety on the PEDS. The remaining six participants all experienced a decrease but remained in the clinical range on the

PEDS. Some quotes from participants illustrate the effect of the information in a qualitative way. For instance, at the end of the intervention phase, one caregiver commented that their child was “not reacting as much” and another caregiver that their child would “deal with things better without tantrums and tearfulness”. Another caregiver said their child was “happier and more animated”.

Though the current study found there was a tendency for a slight decrease on some measures over the baseline period, with statistically significant decreases on the two primary measures of anxiety, there was a much steeper change in anxiety and overall functioning during the intervention phase. The fact that multiple replications of a treatment effect were seen across all dependent variables and consistently across participants reinforces this, particularly when considering the impact of compliance on improvement, such that compliant participants (those accurately following intervention protocol) improved more than those participants who did not follow the protocol. This demonstrates an effect of the intervention above that of regression to the mean or a natural tendency for people to improve over time.

The second hypothesis, that micronutrient intervention would be associated with improvement in overall functioning and in mood where mood was elevated at baseline, was also supported. Ten out of the eleven participants who completed the intervention experienced an improvement in every day functioning as measured by the CGAS. Only one participant was elevated in terms of mood at baseline (as measured by the MFQ) and this participant experienced a clinically significant decrease in mood following the intervention phase, such that they dropped to below the clinically significant cut-off on the MFQ.

Intervention with micronutrients was associated with mild to moderate side-effects in five out of fourteen participants. The majority of adverse effects during the intervention were mild (e.g. gastrointestinal disturbance and nausea), with one participant experiencing side effects at a moderate level (gastrointestinal disturbance and nausea). All side effects were

transitory or able to be remedied with small changes in diet or dosage, except for one participant who continued to experience mild nausea after taking the morning dose throughout the trial. No participant withdrew because of adverse effects.

In terms of compliance, most participants (92%) were able to swallow the pills at the trial dose. Three participants took EMP+ at a lower dose (four to six pills per day) than recommended in the treatment protocol, but still achieved improvement in anxiety and overall functioning. Over half of the sample achieved at least an 80% compliance rate. Two participants who were non-compliant struggled to remember to take the pills regularly. Another could not swallow the pills but did not like the taste of the powder and thus took the micronutrient intermittently. Another did not experience a significant effect and so was not motivated to continue with what was seen as a “hassle”. The fifth participant who struggled with compliance developed glandular fever and missed a number of doses as a result of this illness.

Despite documented benefit for participants, compliance was a struggle for some, highlighting the challenges associated with such a treatment. However, no participant withdrew because of problems associated with taking the actual micronutrients. One participant withdrew prior to week two of the intervention phase because of family illness, another following the week two appointment due to the trouble of visits and another following week six of the intervention phase due to family stress.

It was observed that those participants with lower levels of anxiety initially found it easier to comply with the study protocol, as was demonstrated in the modified Brinley plots within the results section. These showed that compliant participants had lower levels of anxiety at baseline, as well as lower symptomatology on all measures but one (the RCMAS), when compared to non-compliant participants. These also showed that although there was sometimes a similar level of improvement between compliant and non-compliant

participants, the non-compliant participants completed the study with more symptomatology than the compliant participants. There are many factors that could influence compliance such as SES, family stress and parental anxiety. A study by Dean, Wragg, Draper and McDermott (2011) investigated factors affecting poor compliance with psychotropic medication regimes in children. The authors found that lack of parent involvement, use of commentary medications and difficulty remembering doses all negatively affected adherence. Future research should investigate compliance and factors which make it more likely an individual will have difficulty with adherence. Future research should also aim to monitor and remove those factors, both before participants engage in an intervention and during the intervention phase, in order to make treatment effective for as many individuals as possible.

The final hypothesis, that improvements would be maintained over the follow-up period if participants remained on EMP+, was also supported. Overall, little or no further improvement was seen between the end of the intervention phase and the three month follow-up for the six participants who attended follow-up. Four of the six participants who attended follow-up continued to take EMP+ at least every third day at a lower dose than during the intervention phase, with continued positive effect. Another participant had been taking EMP+ for the majority of the period between the end of the trial and follow-up but had stopped prior to follow-up.

The findings of the present study are consistent with previous reports investigating the effect of micronutrient intervention with EMP+ on anxiety in children and adults. Furthermore, this study replicated findings from a number of studies internationally which have demonstrated the positive effect of EMP+ on mental health problems such as OCD, bipolar disorder and ADHD (Gately & Kaplan, 2009; Kaplan et al., 2001; Kaplan et al., 2002; Kaplan et al., 2004; Kaplan et al., 2007; Mehl-Madrona et al., 2010; Popper, 2001; Rucklidge, 2009; Rucklidge et al., 2010; Rucklidge et al., 2011; Rucklidge et al., 2014).

These studies have demonstrated a positive treatment response and side effects which are minor and transitory when compared to pharmacological treatment approaches. Furthermore, other studies investigating the impact of micronutrient formulas which are not EMP+ on anxiety and stress have also found a positive treatment response. It is difficult to compare these studies to each other and to those investigating the impact of EMP+ given the different formulas and dosages which are utilised in them. Even so, the overall findings indicate strong potential for the use of multi-ingredient micronutrient formulas, including EMP+, in the treatment of anxiety and stress in children, as well as adults.

The current recommended protocol by the National Institute of Health and Care Excellence (NICE) for treating high anxiety and anxiety disorder in children is to trial psychotherapy followed by pharmacotherapy as a final resort treatment and only in cases where symptoms are moderate to severe (NICE, 2005). Furthermore, New Zealand guidelines published by The Werry Centre for Child and Adolescent Mental Health Workforce Development state there is an overall lack of efficacy about the use of selective serotonin reuptake inhibitors (SSRI; the main pharmacological medication utilised) for the treatment of child anxiety disorders, except in the case of OCD, where it is considered a “promising treatment” (Dunnachie, 2007). In addition, it is well documented that pharmacotherapy is associated with side effects which are sometimes severe and distressing for the child (Birmaher et al., 2003). Furthermore, there is also very little research documenting the long term effect of psychiatric medication administration to children with anxiety disorders. Many drug trials only monitor participants for three months to one year, which is not enough time to be sure the drug does not negatively impact the child in anyway, particularly his or her development. Admittedly, there is also no research on the long-term efficacy and safety of micronutrients; however, it also may be, as was shown in the current study that children are able to reduce their dosage or take EMP+ intermittently, while stilling maintain a therapeutic

effect, unlike with psychiatric medication. The current research suggests that micronutrient intervention has a less severe side effect profile than psychiatric medications and yet, is also effective at relieving anxiety. Thus, further research into the impact of micronutrient intervention on anxiety in children appears to be warranted.

Furthermore, it is noted that micronutrients may actually have a quicker therapeutic effect than psychiatric medications for the treatment of child anxiety, as well as a similar length of therapeutic effect as psychotherapy. As discussed in the introduction, both Rynn et al. (2001) and Walkup et al. (2001) reported a general trend toward improvement in their medication trials but that it took nine weeks for there to be a difference between symptom severity for those taking fluoxetine compared to those taking placebo. This is the same length as a recommended course of psychotherapy. While the current study had no placebo group to compare the course of the intervention too, and thus cannot rule out these effects (the contribution of placebo effects to treatment effect found is discussed below), it may be that micronutrient intervention provides symptom relief at a rate equal to psychotherapy (i.e. approximately eight weeks to clinically significant effects) and quicker than pharmacotherapy. Future studies might examine these trajectories of improvement in terms of symptom relief between treatments, including placebo, in more detail.

An explanation for the effect of multi-ingredient formulas may lie in the fact that nutrients do not work in isolation, but rather in combinations which lead to optimal functioning within the brain and body. Indeed, as discussed in the introduction, Mertz (1994) has argued that single-nutrient interventions may actually lead to deficiencies given the intertwined and complex nature of the role of micronutrients within bodily systems. Kaplan and colleagues' (2007) review suggests that the multi-ingredient approach to nutritional supplementation is gaining support within the field of mental health. There have been a number of studies investigating the role of multi-ingredient formulas in the treatment of

psychiatric disorders, such as the recently published double-blind randomised control trial by Rucklidge, Frampton, Gorman and Boggis (2014).

As examined in the introduction, Kaplan and colleagues (2007) have discussed four conceptual frameworks for how micronutrients may act within the brain to alleviate the symptoms of mental health disorders, particularly of mood disorders. The authors propose that these models are not mutually exclusive or exhaustive but rather that they are compatible (Kaplan et al., 2007). The first model suggested that unstable mood may be the result of inborn errors in metabolism, which might affect enzyme or coenzyme reactions and thus brain function (Kaplan et al., 2007; Ames, 2004). Another model suggests problems with methylation processes that lead to deficient methylation rates. While methylation is essential to a number of processes within the brain, it may particularly affect neurotransmitter synthesis (Kaplan et al., 2007). B-vitamin deficiencies could have a role within this model via homocysteine metabolism, which can affect levels of SAMe within the brain, ultimately affecting neurotransmitter synthesis (Camfield et al., 2013; Papakostas et al., 2003).

It has been well established that nutrient status can alter gene expression. Thus, nutrient deficiencies could result in alterations in the expression of genes involved in certain mental health disorders, of which a number have high heritability and therefore some genetic basis (Kaplan et al., 2007; Kaplan & Leung, 2011). Another model proposes that long-term deficiencies eventually lead to disorder over time (Kaplan et al., 2007). This model is based on Ames's (2010) triage hypothesis which suggests the body naturally diverts nutritional resources to those functions necessary for survival when the body experiences nutrient deficiency, even if this is sometimes at the expense of long term health, which may eventually lead to disorder.

Mitochondrial dysfunction has also been implicated via negatively affecting the energy metabolism of neurons and glial cells and thus having a flow on effect to other processes, such as synaptic communication (Rucklidge & Kaplan, 2013).

These models and theories propose possible mechanisms behind the positive effect on psychiatric symptoms that is being observed in mental health and nutrition research using multi-ingredient micronutrient formulas. It may be that these models are all intertwined; indeed there is overlap among them. Furthermore, the consequence of the models is that some individuals may require more nutrients than available through diet, and at higher rates than recommended daily allowance, in order to function optimally. Furthermore, within this group of individuals, some people may need more nutrients than others. Perhaps this is why those in the compliant – low dose group within the present study experienced a treatment effect equivalent to those taking the recommended dose of EMP+, despite consuming a lesser amount of the intervention. This difference may be because of biological individuality in the amount of nutrients a person requires to function optimally, as has been acknowledged by Rucklidge and Kaplan (2013).

Another consideration is that it may be that some individuals are more vulnerable to the depletion of nutrients in soils and foods which has occurred over previous decades (Mayer, 1997; Thomson & Robinson, 1980; Ekholm et al., 2007), and thus require supplementation, perhaps because of one of the problems illustrated in the above models.

In the 1920's, the Western world was accepting of the idea that “imperfect” nutrition was very important in the expression of mental illness, with treatment usually involving improvements in diet (Kaplan & Leung, 2011). Yet today this idea seems foreign to many scientists and clinicians who dismiss it. What the literature is showing is that multi-ingredient formulas may be a viable way forward in terms of providing another treatment for mental illness.

4.2 Limitations

One limitation of the current study is the open label nature of the trial, making participants, caregivers and clinicians susceptible to expectancy effects. Although a placebo response cannot be ruled out given participants knew they were taking an active intervention, there are several reasons why it is unlikely to explain the therapeutic effects found.

There were no therapeutic benefits seen for participants until at least two weeks after beginning EMP+, although more commonly at four weeks. Placebo effects are less strong when the illness has been present for some time, as is the case in the present study, where all participants had been experiencing problems with anxiety for some months at least (Cohen et al., 2010). Furthermore, 79% of the participants had undergone some type of treatment prior to entering the trial and had not experienced a significant treatment effect. It should also be considered that the follow-up data collected suggest changes in anxiety were maintained over at least three months. Cohen and colleagues (2010) also reported less of a placebo effect in samples which are predominantly Caucasian, as is true of the present study.

Children with anxiety disorders, including OCD, have been shown to be less susceptible to placebo effects than those with major depression (Cohen et al., 2008). Furthermore, it was stressed to participants that the researcher did not know if the treatment would work. The literature on placebo effects in children demonstrates that children are more susceptible to the placebo effect than adolescents and adults, although this is not always true (Rutherford, et al., 2011). So while placebo effects cannot be ruled out, a number of reasons suggest these effects are unlikely to be responsible for the positive effect of the micronutrient intervention. As the current study is a pilot trial, the promising results do highlight the need for future placebo-controlled research into the effect of multi-ingredient micronutrient intervention for anxiety in a larger sample of children.

Spontaneous remission should be considered, but given so many of the sample of participants experienced a positive effect and had been ill for so long, it is unlikely this is responsible for the treatment effect observed.

Participation in research trials involves regular therapeutic input through contact with the researcher, including assessment of symptoms, empathic responses and assistance with remaining treatment compliant. The therapist effect could have contributed to the improvements seen in this current study. Again, most participants had undergone some type of previous treatment with a health professional without significant improvement. Yet it cannot be ruled out that the participant, and/or the caregiver, may have felt there was some improvement in anxiety simply through contact with the researcher. There was a significant decrease in anxiety on the SCARED and PEDS over the baseline period, which may indicate some susceptibility on the caregivers' behalf to the therapist effect. However, this is unlikely to explain the strength of the changes in symptoms seen throughout the intervention, as contact with the researcher was kept to a minimum, occurring fortnightly unless there were other issues which necessitated contact more frequently and appointments were generally short (less than thirty minutes). Changes were also maintained over the follow-up period when there was no contact with the researcher. Furthermore, appointments were focused purely on assessment and improving compliance. Participants were not given psychological strategies to cope with their anxiety.

Experimenter bias should also be considered as a potential contributor to the positive findings seen in the current study. However, this study utilised multi-informant data, with two of the three primary measures being parent-rated.

Other factors which may explain some of the positive findings include improved daily routine and diet through needing to eat an adequate breakfast and evening meal, as well as drink plenty of water, in order to take the micronutrient correctly. These changes may have

influenced mood and/or anxiety. Diet was not assessed however, so the extent of influence these changes may have had on the outcome cannot be determined.

The small sample size is another limitation of the study. Such a sample size limits the generalizability of any results. Thus, further studies utilising a much larger sample, with a double-blind randomised controlled design, will be important in investigating whether these results do generalise to other samples and therefore potentially the population of children with anxiety.

It should also be considered that this particular sample was unique in that previous treatments had not been effective at alleviating symptoms for eleven of the fourteen participants, including traditional treatments. This may actually be a strength of the study given the majority of participants did respond positively.

Lastly, as noted above, the unanticipated reductions in symptom severity over the baseline period are another limitation of this study. However, it has been established that the changes seen in symptom severity over the intervention phase were much greater than any baseline changes. Kratochwill et al. (2010) suggest any fewer than three baseline data points cannot be used to show there was no effect on symptom severity over baseline. Thus, this should be remedied in any further research. Having a minimum of three probe points during the baseline phase is recommended to capture any systematic and natural fluctuations in anxiety, such that there would be an even clearer difference between baseline and intervention phases (Cooper et al., 2007; Kratochwill, et al., 2010). This would also determine if any reactivity to assessment levelled out of the course of the baseline period or if it continued over the whole baseline period. This could affect conclusions drawn about the effect of the intervention, such that if the level of reactivity reduced we could be much more confident in the effect of the intervention given this shows there would be less of an influence of assessment on the data collected.

4.3 Feasibility

An important issue to consider in terms of feasibility is compliance with the treatment protocol. Difficulties with maintaining compliance included struggles with swallowing the pills, necessitating a move to using powder for two participants. This entails its own problems as it takes more time and effort to prepare the powder than for the child to drink it, than it does for the child to take four pills during the course of a meal. Other difficulties included remembering to take the pills and the after taste of the pills or powder. Also, another difficulty for some participants was adapting to taking the micronutrient with enough water and food so as not to cause stomach upsets. This sometimes required additional organisation on the caregiver's behalf, as well as the child's, in often already busy households.

The cost of continuing the micronutrient intervention of the end of the trial is another important factor to consider. However, it was generally found that even low income families made this a priority when they saw how much EMP+ helped their child. Furthermore, there is a large commitment required not just of participants, but their families as well, in order to help the child be compliant, attend appointments and answer questionnaires.

Challenges for the researchers included contacting caregivers to get them and their child to visit for appointments. Caregivers would often need to bring their other children with them or only be able to come on certain days because of children's extra-curricular activities or work commitments. Communication via phone and email, as well as via text, was very helpful in this respect.

Side effects associated with the intervention also impact on the feasibility of such research. Thirty-six per cent of participants experienced a side effect which may have been related to the intervention and for 80% of these participants the symptoms were mild. All side effects were transient, except for one participant. One issue with monitoring side effects in

this particular sample was distinguishing between the physiological symptoms of anxiety and potential side effects of EMP+. It is common for children with anxiety to experience physiological symptoms which are similar to those side effects sometimes observed when taking EMP+. Baseline information on these particular symptoms was collected for the majority of participants and it was observed that these symptoms decreased for three participants over the course of the trial. This suggests that EMP+ was not associated with side effects in these participants but rather remedied physiological symptoms of anxiety.

4.4 Further Research

As people seek alternative treatments for mental health problems because of the limited availability of publically funded psychotherapy, the expense of attending psychotherapy privately, the modest efficacy of medications and the concerns about the side effects or the long-term impact of medication, further options will be essential to the consumer (Rucklidge & Kaplan, 2013). These options deserve to be explored to provide patients and families with alternatives which might suit them better.

Further research on multi-ingredient micronutrient formulas should explore the long-term safety and impact of these formulas over years. This might determine if people who continue to use these broad-based micronutrient interventions maintain any benefits in terms of their mental health, but also experience benefits in terms of their general health or increased resiliency, as well as any potential adverse effects. It will be particularly important that randomised controlled trials are conducted investigating the impact of micronutrient intervention for a number of mental health problems and in numerous different samples. While it is difficult to compare different multi-ingredient formulas, further investigation of dosage rates and particular combinations of ingredients may also be important.

As Rucklidge and Kaplan (2013) stated in a review published in *Expert Review of Neurotherapeutics*, this type of intervention may not be appropriate for all people, just as doctors would not provide “insulin to someone whose pancreas produces sufficient amounts”. Rucklidge and Kaplan (2013) go on to propose that it would be better to know if an individual would be suited to micronutrient intervention before providing it, rather than administering the intervention to all, but that current scientific knowledge and tests are not able to determine a person’s individual metabolic needs as yet. Perhaps as this knowledge and the knowledge about how micronutrient formulas act to affect mental health advances this sort of testing will become possible. This might allow treatment, including specific formulas and dosage rates, to be tailored individually based on an individual’s unique biological and genetic make-up.

Future research trials should continue to investigate the risk/benefit ratios of micronutrient interventions and compare these to other treatment options. These trials might focus on comparing not only broad-based micronutrient formulas to placebo but also to standard psychopharmacological treatment as well as psychotherapy. An interesting comparison would be to provide micronutrient intervention as an adjunct to psychotherapy, compared with other treatment options, such as psychotherapy alone. Furthermore, it may be that micronutrients are suitable for some individuals in the short-term but not necessary in the long term, for instance those whose anxiety was triggered by an acute stressor such as an earthquake; but that different dosages and regimes are necessary for other individuals, such as those whose anxiety is chronic in nature or who have anxious temperaments. For instance, future research might find that psychotherapy, to teach individuals with chronic illness strategies to manage their anxiety, alongside micronutrients, increases the effectiveness of psychotherapy and the speed at which symptoms decrease. This group of individuals may require micronutrients at a higher dose or on a more long-term basis.

Investigating the effect of probiotic supplementation alongside micronutrient intervention and the effect of this combination on, in particular stress and anxiety, given their impact on the gut, but also for other mental health problems, may be another avenue for exploration. Rucklidge and Kaplan (2013) anticipate that gut health will become increasingly important within the field of nutrition and mental health in order to maximise treatment response through ensuring optimal absorption of micronutrients.

4.5 Conclusion

In conclusion, the results of the current study provide evidence that multi-ingredient micronutrient formulas have potential as a treatment option for children suffering from problems with anxiety. The results also give further support to studies which indicate that micronutrient treatment is associated with improvements in a range of psychiatric symptoms and overall functioning. It is important that clinicians and researchers remain open to other treatment options, such as micronutrient intervention, in order to provide the best care for clients. Further studies investigating the effect of broad-based micronutrient interventions as a treatment for psychiatric disorders may provide more support for the use of micronutrients within mental health. This would afford clients another individual or additional treatment option. As physiological knowledge increases about the mechanisms of action for these formulas, treatments may be able to be tailored to individual's needs, furthering good client care.

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6. Appendices

Appendix A: Ingredient List of EMPowerplus

1 capsule	4 capsules	8 capsules	Ingredient
384.0 IU	1536.0 IU	3072.0 IU	Vitamin A
40.0 mg	160.0 mg	320.0 mg	Vitamin C
96.0 IU	384.0 IU	768.0 IU	Vitamin D
24.0 IU	96.0 IU	192.0 IU	Vitamin E
1.2 mg	4.8 mg	9.6 mg	Vitamin B1
0.9 mg	3.6 mg	7.2 mg	Vitamin B2
6.0 mg	24.0 mg	48.0 mg	Vitamin B3
1.4 mg	5.8 mg	11.5 mg	Vitamin B5
2.4 mg	9.6 mg	19.2 mg	Vitamin B6
96.0 ug	384.0 ug	768.0 ug	Vitamin B9
60.0 ug	240.0 ug	480.0 ug	Vitamin B12
72.0 ug	288.0 ug	576.0 ug	Vitamin H
88.0 mg	352.0 mg	704.0 mg	Calcium
0.9 mg	3.7 mg	7.3 mg	Iron
56.0 mg	224.0 mg	448.0 mg	Phosphorus
13.6 ug	54.4 ug	108.8 ug	Iodine
40.0 mg	160.0 mg	320.0 mg	Magnesium
3.2 mg	12.8 mg	25.6 mg	Zinc
13.6 ug	54.4 ug	108.8 ug	Selenium
0.5 mg	1.9 mg	3.8 mg	Copper
0.6 mg	2.6 mg	5.1 mg	Manganese
41.6 ug	166.4 ug	332.8 ug	Chromium
9.6 ug	38.4 ug	76.8 ug	Molybdenum
16.0 mg	64.0 mg	128.0 mg	Potassium

MICRONUTRIENTS AND ANXIETY IN CHILDREN

24.0 mg	96.0 mg	192.0 mg	dl-phenylalanine
12.0 mg	48.0 mg	96.0 mg	glutamine
16.0 mg	64.0 mg	128.0 mg	citrus bioflavonoids
3.0 mg	12.0 mg	24.0 mg	grape seed
36.0 mg	144.0 mg	288.0 mg	choline bitartrate
12.0 mg	48.0 mg	96.0 mg	Inositol
2.4 mg	9.6 mg	19.2 mg	ginkgo biloba
4.0 mg	16.0 mg	32.0 mg	methionine
1.4 mg	5.5 mg	11.0 mg	germanium sesquioxide
160.0 ug	640.0 ug	1280.0 ug	Boron
2.0 ug	7.8 ug	15.7 ug	Nickel
79.6 ug	318.4 ug	636.8 ug	vanadium
111.0	444.1	888.2	Proprietary Total

Appendix B: Screening Questionnaire for Participation in the Current Study

Child Anxiety and Stress Screening Questionnaire

Q52 This study aims to investigate the impact of taking a daily micronutrient formula on anxiety and stress in Canterbury children aged 8 to 11 years old. If you feel your child experiences a significant amount of stress or anxiety regularly then this study may be able help. The following survey is a screening questionnaire to determine if your child's difficulties make them eligible to take part in the study. This study has been approved by the University of Canterbury Human Ethics Committee and the Upper South A Regional Ethics Committee. If you would like to know more about the study you can contact the researcher at ellen.sole@pg.canterbury.ac.nz

Q1 Please provide your name and contact details below

- Name (1)
- Address (2)
- Address 2 (3)
- City (4)
- Contact number (5)
- Email (6)

Q4 Please provide the name and age of your child below

- Child's first name (1)
- Child's age (2)

Q56 The next questions pertain to the eligibility criteria which allow your child to take part in the study.

Q57 Does your child eat at least a snack two times a day?

- Yes (1)
- No (2)

Answer If Does your child eat at least a snack two times a day? No Is Selected

Q62 Participant's in the study must be able to eat at least a snack before taking the micronutrients. If the micronutrients are taken on an empty stomach they can cause nausea and other minor side effects. As such we require participants to be able to eat at least two snacks a day, one before each dose of micronutrients, which are taken as 4 pills twice per day. Is your child is able and willing to eat at least a snack two times a day?

- Yes (1)
- No (2)

Answer If Participant's in the study must be able to eat at least a... No Is Selected

Q75 Thank-you for taking this questionnaire. Your answers indicate one of the studies exclusion criteria has been met. Unfortunately this means your child is not eligible to participate in the trial. If you have any questions or concerns please contact the researcher at ellen.sole@pg.canterbury.ac.nz. Thank-you for your time.

If Thank-you for taking this q... Is Displayed, Then Skip To End of Survey

Q58 Does your child have a neurological disorder, serious medical condition that would require treatment throughout his/her time in the study or mineral metabolism abnormality?

- Yes (1)
- No (2)

Answer If Does your child have a neurological disorder, serious med... Yes Is Selected

Q76 Thank-you for taking this questionnaire. Your answers indicate one of the studies exclusion criteria has been met. Unfortunately this means your child is not eligible to participate in the trial. If you have any questions or concerns please contact the researcher ellen.sole@pg.canterbury.ac.nz. Thank-you for your time.

If Thank-you for taking this q... Is Displayed, Then Skip To End of Survey

Q59 Does your child have known allergies to any of the following? These are the ingredients within the micronutrient formula taken by participants in the study.

Vitamin A	Calcium	dl-phenylalanine
Vitamin C	Iron	Glutamine
Vitamin D	Phosphorus	Citrus bioflavonoids
Vitamin E	Iodine	Grape seed
Vitamin B1	Magnesium	Choline bitartrate
Vitamin B2	Zinc	Inositol
Vitamin B3	Selenium	Ginkgo biloba
Vitamin B5	Copper	Methionine
Vitamin B6	Managnese	Germanium sesquioxide
Vitamin B9	Chromium	Boron
Vitamin B12	Molybdenum	Nickel
Vitamin H	Potassium	Vanadium

- Yes (1)
- No (2)

Answer If Does your child have known allergies to any of the follow... Yes Is Selected

Q77 Thank-you for taking this questionnaire. Your answers indicate one of the studies exclusion criteria has been met. Unfortunately this means your child is not eligible to participate in the trial. If you have any questions or concerns please contact the researcher at ellen.sole@pg.canterbury.ac.nz. Thank-you for your time.

If Thank-you for taking this q... Is Displayed, Then Skip To End of Survey

Q60 Does your child take any medication?

- Yes (1)
- No (2)

Answer If Does your child take any medication? Yes Is Selected

Q67 Please provide details of the medication name, dosage and reason for prescription below.

Answer If Please provide details of the medication below. Text Response Is Displayed

Q68 Certain medications are known to interact with the micronutrients taken in the study. A researcher will contact you about eligibility to take part in the study after reviewing these medications. Please continue on with the remainder of the questionnaire.

Q61 Does your child take any nutritional or herbal supplements?

- Yes (1)
- No (2)

Answer If Does your child take any nutritional or herbal supplements? Yes Is Selected

Q69 Please provide details of the supplement consumption below. Include dosage, reason for taking and how long your child has been taking the supplement.

Q3 The questions below pertain to your child's everyday experiences. Please answer as truthfully and openly as possible.

Q5 When my child feels frightened, it is hard for him/her to breathe.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q6 My child gets headaches when he/she is at school.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q7 My child doesn't like to be with people he/she doesn't know well.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q8 My child gets scared if he/she sleeps away from home.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q9 My child worries about other people liking him/her.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q10 When my child gets frightened, he/she feels like passing out.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q11 My child is nervous.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q12 My child follows me wherever I go.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q13 People tell me that my child looks nervous.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q14 My child feels nervous with people he/she doesn't know well.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q15 My child gets stomachaches at school.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q16 When my child gets frightened, he/she feels like he/she is going crazy.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q17 My child worries about sleeping alone.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q18 My child worries about being as good as other kids.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q19 When he/she gets frightened, he/she feels like things are not real.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q20 My child has nightmares about something bad happening to his/her parents.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q21 My child worries about going to school.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q22 When my child gets frightened, his/her heart beats fast.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q25 He/she gets shaky.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q26 My child has nightmares about something bad happening to him/her.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q27 My child worries about things working out for him/her.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q28 When my child gets frightened, he/she sweats a lot.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q29 My child is a worrier.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q30 My child gets really frightened for no reason at all.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q31 My child is afraid to be alone in the house.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q32 It is hard for my child to talk with people he/she doesn't know well.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q33 When my child gets frightened, he/she feels like he/she is choking.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q34 People tell me that my child worries too much.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q35 My child doesn't like to be away from his/her family.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q36 My child is afraid of having anxiety (or panic) attacks.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q37 My child worries that something bad might happen to his/her parents.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q38 My child feels shy with people he/she doesn't know well.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q39 My child worries about what is going to happen in the future.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q40 When my child gets frightened, he/she feels like throwing up.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q41 My child worries about how well he/she does things.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q42 My child is scared to go to school.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q43 My child worries about things that have already happened.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q44 When my child gets frightened, he/she feels dizzy.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q45 My child feels nervous when he/she is with other children or adults and he/she has to do something while they watch him/her (for example: read aloud, speak, play a game, play a sport.)

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q46 My child feels nervous when he/she is going to parties, dances, or any place where there will be people that he/she doesn't know well.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

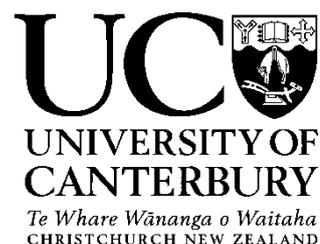
Q47 My child is shy.

- Not True or Hardly Ever True (0)
- Somewhat True or Sometimes True (1)
- Very True or Often True (2)

Q49 If there are any comments you would like to make, please do so below.

Q74 Thank-you for completing this questionnaire. The researcher will be in contact with you as soon as possible about whether your child meets eligibility criteria to allow them to participate in the study. If you have any questions in the meantime, feel free to email the researcher at ellen.sole@pg.canterbury.ac.nz.

Appendix C: Parent and Child Information Sheets and Consent/Assent Forms



INFORMATION SHEET: July 17th 2012

Title of research project: A pilot investigation into the effect of micronutrients on anxiety and stress in Canterbury children: a multiple baseline design.

Principal Investigator: Assoc Prof Julia Rucklidge
Department of Psychology, University of Canterbury
Private Bag 4800, Christchurch
Phone: 03 364 2987 ext 7959

Other investigators: Ellen Sole, Associate Professor Neville Blampied

What is the purpose of the study?

Your child is invited to participate in a study being run as a student Master's Thesis that will evaluate a nutritional supplement in the treatment of anxiety. There is much interest lately in complementary alternative medicines (CAM) to problems such as those your child is experiencing. The supplement we are studying has shown some promise in the treatment of mood instability and symptoms of anxiety, as shown in an open-label trial with adults experiencing stress conducted at the University of Canterbury. The supplement is called **EMPowerplus (EMP+)** and it contains 36 micronutrients. Your child is eligible for this study because he/she is struggling with anxiety and stress and is not presently on psychiatric medications. Approximately 15 children in Christchurch are being invited to take part in this study.

Background

It has been proposed that some vitamins and minerals might help people with anxiety and mood instability to improve symptoms and stabilize mood. When a new idea such as this comes along, it must be studied in a variety of people (referred to as case series). The case series that have been carried out in adults on EMP+ suggest that it might help to stabilize mood and help with symptoms of anxiety. Your child is now being invited to participate in a series of child case studies using EMP+.

What would I have to do?

First your child will be assessed for eligibility. This will involve an interview with you and other members of your child's family to ask about difficulties your child is experiencing. We will also ask you to complete some questionnaires about your child. If your child is eligible we will then proceed with the intervention phase. Your child will be randomised to one of three groups, each with a different start date and may need to wait until all 15 participants are recruited. This is a study design called multiple-baseline. This design allows us to see if changes in symptoms correspond with the period immediately after the intervention is given. This provides further evidence that it is the intervention which is improving symptoms rather than something else. Each group will start the intervention one week apart.

The preferred method for administration of the intervention is to have your child swallow the micronutrient formula in pill form. However, if this becomes too difficult for your child, the micronutrient formula is available in powdered form that could be incorporated into a smoothie or milkshake just prior to him/her taking it. It is up to your child how best to take the supplement. Before your child begins taking the capsules he/she will be shown a short video on different ways to swallow capsules. He/she will then practice swallowing by using hard lollies and recording which ways he/she prefers to have his/her head when swallowing. We will ask him/she to monitor preferred head positions over a number of days.

Once your child is ready to begin, your child will take 8 gelatin capsules per day, divided however you like, but preferably in 2 doses. Your child will begin by taking 4 capsules of EMP+ each day, increasing to 8 capsules on the 4th day. Attached to this consent form is a list of all the ingredients in EMP+. It will be important for your child to drink plenty of water every day to properly absorb these ingredients. Your child will take the supplement for 8 weeks. You will be responsible for making sure that your child takes the appropriate amount of supplement, as well as making sure that the supplements are not shared with others.

During the entire trial, which will be approximately 2-3 months, there will be weekly or fortnightly appointments with one of the primary investigators. At your appointments, this person will review the physical and mental health of your child, will ask about any problems he/she is having, and will complete a number of assessment tools evaluating his/her overall functioning. At every appointment, we will also ask you to complete questionnaires about your child regarding overall level of functioning. Your child will be asked to record in a daily diary how he/she is feeling each day and how much he/she worried that day. This will involve circling the appropriate picture for how he/she feels. You will also be asked to record here any unusual events in your child's life, and any capsules that you know have not been taken.

In addition to the above questionnaires, we will also measure cortisol. Cortisol is a hormone the body produces in response to stress and anxiety. Cortisol levels are higher in people with a lot of stress or anxiety. We will measure cortisol to determine if the supplement helps reduce your child's response to stress. We can measure cortisol in saliva. Your child will provide a total of 8 saliva samples. This procedure is easy and non-invasive. Children will use a method where they direct saliva through a straw into a tube. This method is called passive drooling. We need to collect samples over two consecutive days, in the morning before breakfast and evening before tea, both at the start and end of the trial.

Overall, the approximate time involved for initial interview and baseline assessment will be around two to three hours over two visits. There will be four to six hours for visits weekly or fortnightly to the University of Canterbury including completion of questionnaires by you and your child plus around 15 minutes for a follow-up call at week 1 and about one hour at three month follow up for a phone interview and completion of questionnaires. Daily your child will be expected to complete his/her feelings diary. This will take them less than five minutes. Each saliva sample will take five to ten minutes to collect, totally approximately one and one half hours over four days. A schedule can be found below detailing the order of assessment and visit time. Visits will take less time if questionnaires can be done at home beforehand and brought along.

If an antibiotic or antifungal agent must be taken orally for a health problem, it may be necessary for you to withdraw your child from the study for the time he/she needs to complete the course of the drug. If it is appropriate for your child to continue taking EMP+ while taking one of these agents he/she will be monitored closely. This is because antibiotics and antifungal drugs seem to interfere with the absorption of this nutrient supplement.

You will be asked to *not* have your child try any alternative medicines or other forms of therapy until he/she has completed his/her involvement in this study.

Members of all cultures will be encouraged to participate in the study. Respect for Maori customs and traditions are of the highest priority and if necessary, home visits with a cultural advisor can be conducted. 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 on te taha hinengaro (mental wellbeing), whanaungatanga (family relationships), taha wairua (spiritual wellbeing) and taha tinana (physical wellbeing).

Table 1.1 Schedule of Assessment

Assessment Number	Assessment Type	Time Involved
Initial interview	Initial visit for assessment and pill swallowing training. Also given saliva sample collection kit with samples to be collected during the week before baseline assessment.	1.5 – 2 hours and 40 minutes over 2 days for saliva collection
Baseline	Completion of questionnaires and given micronutrients	1.5 – 2 hours
Week 1	Phone follow-up	15 minutes
Week 2	Visit for fortnightly monitoring	1 hour
Week 3		
Week 4	Visit for fortnightly monitoring	1 hour
Week 5		
Week 6	Visit for fortnightly monitoring	1 hour
Week 7		
Week 8	Final visit and completion of study. During this week saliva samples will also be collected.	1 hour and 40 minutes over 2 days for saliva collection
3 month follow-up	Phone follow-up plus completion of mailed questionnaires	1 hour

What are the risks?

Although we have no reason to suspect that this supplement can harm a physically healthy individual in any way, we will monitor your child regularly. You will meet or have phone contact every other week with one of the investigators who will ask questions about your child's general physical and mental health and wellbeing.

In previous research at the University of Calgary in Canada, blood samples, heart rate, and blood pressure were monitored in 12 children, and no one was found to experience any problems while taking the supplement. This type of supplement has been used by many people for many years without any unpleasant results reported. More recently, 27 adults with bipolar disorder had their blood tested to determine whether they were all fine after taking Empowerplus for 1-3 years, and there were no health concerns in those test results that were attributable to the supplement. There

were some findings which the reviewing physician considered to be "incidental," but not attributable to any adverse effects of the supplement. In our trials conducted here at Canterbury, we have assessed to date 76 patients before taking EMP+ and 8 to 16 weeks after. There were no abnormal blood results that suggested that EMP+ was having an adverse effect on liver and kidney function. Further, any side effects reported by this sample were temporary and mild. Further, the dose we are using is half the dose used in our other trials which further reduces the chance of adverse effects.

Some of the ingredients in EMP+ are given at amounts higher than the recommended daily allowance (RDA) for that nutrient. This is because there is research suggesting that some people may need more than the daily allowance for optimal brain functioning. Although the doses are high, they are not being given in a level that is believed to be toxic to the system. Indeed, by consuming nutrients in combination, risks of toxicity are decreased. We will monitor your child closely for any sign of toxicity.

The most common 'side effects' are that previously-experienced constipation has been relieved and that the patient is sleeping better; i.e., positive side effects rather than adverse events. The patients who have stopped EMP+ have most commonly done so because of the indigestion type symptoms or due to problems with interactions with other medications (see below). Some of these difficulties can be avoided by taking the capsules **on a full stomach**, and so we suggest your child *always take their capsules with food*. Another way to prevent these side effects is increase the dose slowly over several days, so we begin with four capsules per day and increase gradually to the full dose. We will review side-effects with you and your child at each visit and make a referral to a medical practitioner if necessary. We are happy to provide you with copies of the studies that have been done to date on EMP+.

EMP+ has the potential to interact with other medicines or drugs so if possible, you should avoid having your child take other medicines whilst on this treatment. For this reason, we are only including individuals in the study who *are not being concurrently treated using prescribed psychiatric medications*. With respect to whether your child should take other medications, such as over-the-counter medications to treat colds, flu, stomach upset and sleep problems, because they may interact with EMP+, you should first discuss with us or your pharmacist before use. Pain killers such as Aspirin, Nurofen, Brufen or Voltaren (the NSAIDs or non-steroidal anti-inflammatory drugs) should be avoided whilst on EMP+ as they can affect the ability of your blood to clot, and hence stop bleeding from a cut, in a similar way to some of the ingredients of EMP+. So, for example, if your child needed a pain killer for a headache, it would be safer for him/her to take Paracetamol or Panadol than Nurofen whilst on EMP+. A list of appropriate medications that are acceptable to take during this trial is included as part of this information sheet.

Your child's safety is the most important thing. Thus, in the event of an emergency (e.g., if your child has thoughts of harming themselves or others), you should take your child to psychiatric emergency services. The emergency room personnel can call the number on your pill bottle to obtain information about the study and about the contents of the capsules your child is taking. The contents are also listed at the end of this information sheet.

If my child suffers a research-related injury, will I be compensated?

In the unlikely event of a physical injury as a result of your child's participation in this study, he/she may be covered by 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 might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. 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, contact your nearest ACC office or the investigator.

Will my child benefit if they take part?

There may or may not be a direct medical benefit to your child. His/her symptoms may be improved during the study but there is no guarantee that this research will help them. The information we obtain from this study may help us to provide better treatments in the future for people suffering from stress or anxiety.

Does my child have to participate?

If you or your child decide not to participate in this study, or if you decide part-way through that you want him/her to stop, you are certainly free to do so. This decision will not influence his/her ongoing health care in any way. Similarly, the study's investigators might choose to end your child's participation in the study at any time for any reason, for instance if we are concerned about safety. If new information becomes available that might affect your willingness to have your child participate in the study, you will be informed as soon as possible. There are many other treatments available for anxiety, including cognitive-behavioural and behavioural therapy and in severe cases, medication. We are happy to assist you with finding help if you would rather choose these evidence based treatments. You may also choose to go this route at the end of the trial and again, we will assist you in finding the services available in Christchurch.

Will I be paid for my child's participation, or do I have to pay for anything?

Arrangements will be made with each individual participant to ensure that your transportation costs are covered. At each visit, you will receive a petrol voucher to cover costs. The capsules that your child will take during the study will be provided at no cost.

Will my child's records be kept private?

All information about your child that is collected in this study will be held in the strictest confidence. 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; you can feel assured that all information you disclose concerning your child and your family will be kept in a confidential file which will be kept locked at all times. This data will be stored for 10 years after collection. With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health and Disability Ethics Committee. All information will be kept as group data. Therefore, forms will be coded and names removed such that you cannot be identified. Confidentiality will be respected and no material which could personally identify your child or family will be used in any reports on this study. However, in cases where we are concerned about your safety or the safety of others, we may decide to breach confidentiality.

The results of the tests described above will be used for research purposes only in the context of this study. We would need your permission and signed consent to send these test scores to another professional involved in your child's care. We recommend that a psychologist or physician interpret the results of these tests. During this study, it may be necessary for a member of the research team to look at your child's previous medical records. You are assured that this will also be handled in a confidential manner.

What happens after the study?

If you feel your child has benefited at the end of the trial, and want them to continue taking the supplement, it is commercially available. We can provide you with the contact information so that you can continue to obtain it.

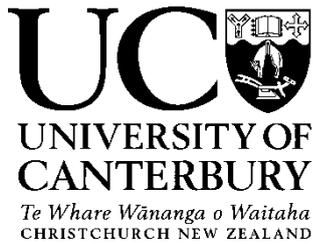
If you have any queries or concerns regarding your rights as a participant in the study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Telephone (NZ Wide) 0800 555 050, Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT), Email (NZ wide) advocacy@hdc.org.nz. You can also contact Dr. Julia Rucklidge, the principal investigator, 364-2987 ext7959, should you have any questions or concerns about this research. The Human Ethics committee at the University of Canterbury and the Upper South A Regional Ethics Committee have reviewed and approved this study. We have also consulted with The Maori Consultation Group at the University of Canterbury.

University of Canterbury Human Ethics Committee

Chair: **Dr Mike Grimshaw**

Telephone: 6390 or +64 3 364 2390

michael.grimshaw@canterbury.ac.nz



PARENTAL CONSENT FORM

Title of research project: A pilot investigation into the effect of micronutrients on anxiety and stress in Canterbury children: a multiple baseline design

Principal Investigators: Assoc Prof Julia Rucklidge, Ellen Sole, Assoc Prof Neville Blampied

I have read and I understand the information sheet dated April 26th 2012 for people taking part in the study designed to assess the impact of micronutrients on anxiety and mood in children with elevated anxiety. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I believe that [REDACTED] (participant's name) would have chosen and consented to participate in this study if he/she had been able to understand the information that I have received and understood.

I understand that taking part in this study is voluntary and that my child may withdraw from the study at any time if he/she wishes. This will not affect his/her continuing health care.

I understand that his/her participation in this study is confidential and that no material which could identify him/her will be used in any reports on this study.

I understand that the treatment will be stopped if it should appear to be harmful.

I understand the compensation provisions for this study.

I know whom to contact if my child has any side effects to the study or if anything occurs which I think he/she would consider a reason to withdraw from the study.

I understand that I can request for a karakia at the point of disposal of my child's tissue samples.

I know whom to contact if I have any questions about the supplement of the study.

This study has been given ethical approval by the both 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 following appropriate ethical procedures.

I consent to my child supplying saliva samples as indicated and to these samples being used to analyse cortisol level YES/NO

MICRONUTRIENTS AND ANXIETY IN CHILDREN

I agree to my GP or other current provider being informed of my child's participation in this study/the results of my child's participation in this study and be provided with any laboratory reports obtained for the purposes of this study YES/NO

I consent to being contacted approximately 8 weeks following the initial assessment for a review regardless of whether my child continued with the treatment. I understand we do not have to complete the assessment at that time. YES/NO

I consent to my child's name being placed in a separate database so that I can be contacted in the future should there be other studies for them to participate in with the understanding that I can choose whether they participate in such studies or not. YES/NO

I consent to the use of my child's data for future related studies, which have been given ethical approval from a Health and Disability Ethics Committee YES/NO

We would like a copy of the results of the study. YES/NO

Participants should be advised that a significant delay may occur between data collection and publication of the results.

Signed: Date:

Printed name:

Relationship to participant:

Address for results:

The person who may be contacted about the research is:

Dr. Julia Rucklidge, Principal Investigator, 364-2987 ext 7959

A signed copy of this consent form has been given to you to keep for your records and reference.

Ingredients of EMP+ attached.

EMPowerplus Capsule Ingredient List (Current)

1 cap		4 caps		8 caps	
384.0	IU	1536.0	IU	3072.0	IU Vitamin A
40.0	mg	160.0	mg	320.0	mg Vitamin C
96.0	IU	384.0	IU	768.0	IU Vitamin D
24.0	IU	96.0	IU	192.0	IU Vitamin E
1.2	mg	4.8	mg	9.6	mg Vitamin B1
0.9	mg	3.6	mg	7.2	mg Vitamin B2
6.0	mg	24.0	mg	48.0	mg Vitamin B3
1.4	mg	5.8	mg	11.5	mg Vitamin B5
2.4	mg	9.6	mg	19.2	mg Vitamin B6
96.0	ug	384.0	ug	768.0	ug Vitamin B9
60.0	ug	240.0	ug	480.0	ug Vitamin B12
72.0	ug	288.0	ug	576.0	ug Vitamin H
88.0	mg	352.0	mg	704.0	mg Calcium
0.9	mg	3.7	mg	7.3	mg Iron
56.0	mg	224.0	mg	448.0	mg Phosphorus
13.6	ug	54.4	ug	108.8	ug Iodine
40.0	mg	160.0	mg	320.0	mg Magnesium
3.2	mg	12.8	mg	25.6	mg Zinc
13.6	ug	54.4	ug	108.8	ug Selenium
0.5	mg	1.9	mg	3.8	mg Copper
0.6	mg	2.6	mg	5.1	mg Managnese
41.6	ug	166.4	ug	332.8	ug Chromium
9.6	ug	38.4	ug	76.8	ug Molybdenum
16.0	mg	64.0	mg	128.0	mg Potassium
24.0	mg	96.0	mg	192.0	mg dl-phenylalanine
12.0	mg	48.0	mg	96.0	mg glutamine
16.0	mg	64.0	mg	128.0	mg citrus bioflavanoids
3.0	mg	12.0	mg	24.0	mg grape seed
36.0	mg	144.0	mg	288.0	mg choline bitartrate
12.0	mg	48.0	mg	96.0	mg Inositol
2.4	mg	9.6	mg	19.2	mg ginkgo biloba
4.0	mg	16.0	mg	32.0	mg methionine
1.4	mg	5.5	mg	11.0	mg Germanium sesquioxide
160.0	ug	640.0	ug	1280.0	ug Boron
2.0	ug	7.8	ug	15.7	ug Nickel
79.6	ug	318.4	ug	636.8	ug vanadium
111.0		444.1		888.2	Proprietary Total



EMP+

Medication Management Information for the Study Participants

As you know from the intensive screening you went through prior to your child being invited to participate in this study, it is very important that participants avoid anything with known effects on the brain (alcohol, street drugs, and many medications). The following information will help guide you if your child develops a problem during the trial, such as a head cold.

Herbals, etc

Echinacea, chondroitin, and glucosamine are permitted with no restrictions on dose changes.

Over-the counter medications

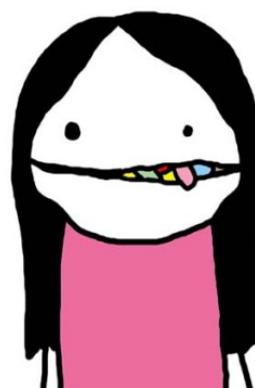
- If your child has trouble with **nausea**, please remember to take capsules with food. Please talk to the research clinician if this problem persists
- If your child has **diarrhoea**, please talk to the research clinician.
- If your child needs help with some type of **pain**, the preferred treatment is paracetamol
- If your child gets a **cold**, you may treat their cough with something like guaifensin (Plain Robitussin®). For a sore throat, you could use paracetamol.

A pilot study investigating the effect of micronutrients on anxiety and stress in children.

What is a Research Study? A research study is when someone collects a lot of information to learn more about something. You are being asked to be in this research study because we are trying to learn more about anxiety. There will be about 14 other children in the study.

If you join the study what will you have to do?

- You will visit the university for activities and questions every second week for about 3 months.
- You will take some vitamins and minerals every day for 2 months and fill out a daily feelings diary.
- You can choose to take the vitamins and minerals as pills or a powder to mix into a drink.
- You will need to give a small amount of saliva 8 times throughout the study.



You would never guess how many vitamins I can swallow at once. (hint: its about 28.)



Will the study help you?

- The pills in this study have helped some adults with anxiety and stress but it may or may not help you
- We don't know if your anxiety will get better because you take part in the study but we hope that it does
- This study may find out things that can help other children you feel like you

Who will see the information you give us?

- only people working on the study will see your information and it will all be kept in a locked cabinet.

Will any part of the study hurt?

- The vitamins and minerals **might** make upset your tummy or give you a sore head
- This is important to know and we will be able to help it so please tell your parent if you feel any of these things

Do you have to be in the study?

- NO. And nobody will be upset if don't want to be in the study
- If you want to be part of the research study, tell us that
- Remember you can say yes now and change your mind later. All you have to do is tell the person in charge, it is ok. It is up to you!



QUESTIONS???

- Do you have any questions?
- If you think of something you want to know about the study later you can ring us or get your parent to ring.

A Pilot Study Investigating the Effect of Micronutrients on Anxiety and Stress in Children

Principle Investigator: Assoc Prof Julia Rucklidge

Sign this form only if you:

- have understood what you will be doing for this study,
- have had all your questions answered,
- have talked to your parent(s)/legal guardian about this project, and
- agree to take part in this research

Your printed name

Your signature

Date

I have solicited the assent of the child.

Name of Parent(s)

Researcher explaining the study

Printed Name

Signature

Date

Appendix D: Instruction sheets for taking EPowerplus in capsule and powder form

How to Take your Pills

Week 1:

Day 1: Morning (take 2 pills), Tea time (take 2 pills)

Day 2: same as above

Day 3: same as above

Day 4: Morning (take 4 pills), Tea time (take 4 pills)

Day 5: same as above

Day 6: same as above

Day 7: same as above

Weeks 2 onwards: Morning (take 4 pills), Tea time (take 4 pills)

- Take your pills with **food and one large glass of water**. Drink plenty of water during the day. *The most common side effect of taking these pills is an upset stomach. This can be avoided by taking your pills with food and plenty of water.*
- If you miss a dose, take the dose when you remember but make sure that you leave **at least 2 hours** between doses.
- Try not to take your last dose later than 6pm because sometimes the pills can have an energising effect, which can make it difficult for you to get to sleep.

How to Take the Powder

Week 1:

Day 1: Morning (take half a scoop mixed with liquid), Tea time (take half a scoop mixed with liquid)

Day 2: same as above

Day 3: same as above

Day 4: Morning (take 1 scoop mixed with liquid), Tea time (take 1 scoop mixed with liquid)

Day 5: same as above

Day 6: same as above

Day 7: same as above

Weeks 2 onwards: Morning (take 1 scoop mixed with liquid), Tea time (take 1 scoop mixed with liquid)

- Take your powder shake with **food**. Drink plenty of water during the day. *The most common side effect of taking these pills is an upset stomach. This can be avoided by taking your pills with food and plenty of water.*
- If you miss a dose, take the dose when you remember but make sure that you leave **at least 2 hours** between doses.
- Try not to take your last dose later than 6pm because sometimes the powder can have an energising effect, which can make it difficult for you to get to sleep.
- The best way to make is shake is to blend it or to mix the powder into the shake then add the remainder of the liquid you are using.

Appendix E: Side Effects Questionnaire

Side Effects Questionnaire

YOUR name: _____

Today's date: _____
day/month/year

Please circle a face to indicate how severe this problem was in the past week.

1. Nausea/vomiting

*Major problem
this week*

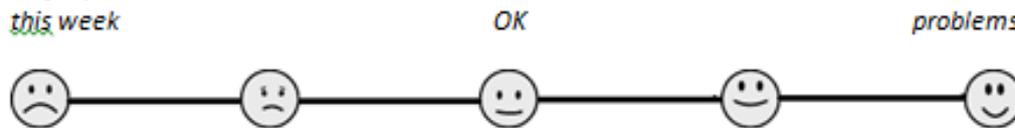
*Excellent – zero
problems!!*



2. Stomach aches

*Major problem
this week*

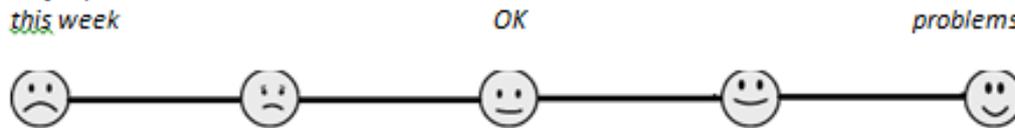
*Excellent – zero
problems!!*



3. Skin rash

*Major problem
this week*

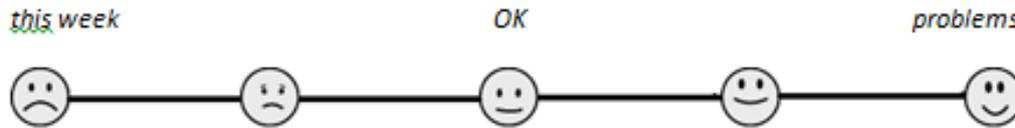
*Excellent – zero
problems!!*



4. Headaches

*Major problem
this week*

*Excellent – zero
problems!!*



5. Dry Mouth

*Major problem
this week*

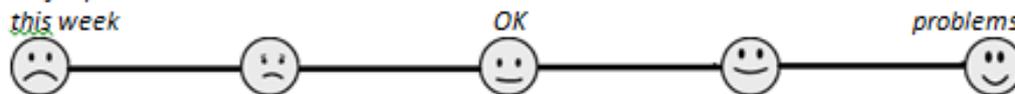
*Excellent – zero
problems!!*



6. Other- please describe _____

*Major problem
this week*

*Excellent – zero
problems!!*



7. Other- please describe _____

*Major problem
this week*

*Excellent – zero
problems!!*

