An Investigation into the Effects of Micronutrients on Mood and Behaviour in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): A pilot study using a single case ABABA design with six-month follow-up

By

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This thesis is dedicated to my parents Cookie and Stephen Landau who I lost just months after each other while I was in the final stages of preparing this thesis.

I would not be where I am today without your unconditional, undying support. You both made me believe that I could do anything I put my mind to, and here I am proving you right. The last 18 months have been the hardest of my life and yet I have accomplished more than I had ever imagined I could. This is a tribute to you, as you have given me the strength to persevere and conquer. You will forever live on inside of me.

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood psychiatric disorders characterised by impairments in attention, hyperactivity and impulsivity. ADHD is a chronic disorder that can negatively impact many areas of a child's life and cause significant difficulties for the child, their family and the wider community. Pharmacological and behavioural treatments have been shown to be effective in treating ADHD. However, with 30% of the population that do not respond or respond poorly to pharmacological treatments, and the growing concerns over the long-term impact stimulants may have on the developing brain, investigation into alternative treatments for ADHD is necessary. More recently research has investigated the effectiveness of EMPowerplus (EMP+), a formula containing a wide range of vitamins and minerals in treating ADHD in adults.

The current research examined the effect of EMP+ in treating ADHD in children, following a single-case ABABA design, with a six-month follow-up. Fourteen children between 8 and 12 years of age diagnosed with DSM-IV ADHD took part in the study. Following the baseline assessment, participants took part in an open-label trial of EMP+ for eight weeks, after which EMP+ was withdrawn for four weeks, and then had a final eight weeks on EMP+ and a final four weeks off the micronutrients. A follow-up was conducted approximately six-months after the end of the study. Modified Brinley plots revealed decreased ADHD behaviours, improved mood and improvements in overall functioning during the intervention phases and a reversal in symptoms, decrease in mood and overall functioning during the withdrawal phases. Cohen's d effect sizes, 95% confidence intervals and t-tests confirmed statistically significant change between the intervention and withdrawal phases. Adjusted effect sizes, displaying the likely effect of the micronutrient intervention, ranged from 0.50 to 1.39, on the primary measures of ADHD, and medium to large effect sizes of 0.53 to 1.40 on secondary

measures of mood. Five of the 13 participants assessed at the six-month follow-up were taking the micronutrients and reported a greater decrease in ADHD symptoms, and increase in mood and overall functioning compared to those who discontinued taking EMP+.

The current study provides further evidence for the potential of micronutrient interventions as a treatment option for children with ADHD. Further research utilising double-blind placebo-controlled studies is warranted.

Table of Abbreviations

ABC	Aberrant Behaviour Checklist
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-IV	ADHD Rating Scale-IV
ALC	Acetyl-L-Carnitine
ALT	Alanine Aminotransferase
APA	American Psychiatric Association
APT	Activated Partial Thromboplastin
ASD	Autism Spectrum Disorder
AST	Aspartate Aminotransferase
CARS	Childhood Autism Rating Scale
CBCL	Child Behavior Checklist
CBT	Cognitive Behavioural Therapy
CD	Conduct Disorder
CDRS	Children's Depression Rating Scale
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impressions Scale
CHP	Compound Herbal Preparation
CI	Confidence Interval
CMRS-P	Child Mania Rating Scale, Parent Version
CNE	Cell and Nerve Essential nutrition
CPRS	Children's Psychiatric Rating Scale
CPRS-R:L	Conners' Parent Rating Scale-Revised: Long Form
CPT-II	Conner's Continuous Performance Test
CTRS-R:L	Conners' Teacher Rating Scale-Revised: Long Form
DEN	Daily Essential Nutrients
DHA	Docisahexaenoic Acid

DSM	Diagnostic and Statistical Manual of Mental Disorders
DSD	Daily Self Defense
EFA	Essential fatty acid
EMP+	EMPowerplus
EPA	Eicosapentaenoic Acid
ES	Cohen's *d* Effect Size
GAD	Generalised Anxiety Disorder
GGT	Gamma-Glutamyl Transpeptidase
HDL	High-Density Lipoprotein
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version
LD	Learning Disorder
LOCF	Last Observation Carried Forward
MTA	Multimodal Treatment Study of Children with ADHD
MYMOP	The Measure Yourself Medical Outcome Profile
NZSEI	New Zealand Socioeconomic Index of Occupational Status
OCD	Obsessive Compulsive Disorder
ODD	Oppositional Defiant Disorder
PBD	Pediatric Bipolar Disorder
PDD	Pervasive Developmental Disorder
PTSD	Post-Traumatic Stress Disorder
RDA	Recommended Daily Allowance
SDQ	Strengths and Difficulties Questionnaire
SES	Socio-Economic Status
TOVA	Test of Variables of Attention
TSH	Thyroid-Stimulating Hormone
WBC	White Blood Cells
YMRS	Young Mania Rating Scale

Chapter 1: ADHD

This chapter will give a brief overview of Attention Deficit Hyperactivity Disorder. This will include core ADHD features, diagnosis, prevalence, course, comorbidity, associated difficulties with ADHD and possible aetiologies. Finally, it will cover current empirically supported and alternative treatments for ADHD.

1.1 ADHD Defined

According to the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV-TR), Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder characterised by a persistent pattern of impairing levels of inattention and/or hyperactivity/impulsivity that are developmentally inappropriate (American Psychiatric Association [APA], 2000). Impairing levels of inattention include losing things, an inability to stay on task, difficulty listening and/or paying attention and difficulty organising. Impairing levels of hyperactivity include difficulties with over activity, unable to stay seated, and fidgeting. Impairing levels of impulsivity include difficulty waiting turn, interrupting or intruding on others and blurting out answers before questions have been finished. These impairments are at levels that are inconsistent with the developmental level or age. The DSM-IV classifies ADHD in three subtypes; 1) Predominantly inattentive type, with maintaining attention the core deficit; 2) Predominantly hyperactive-impulsive, with deficits in disinhibition or self-regulation; 3) Combined type, a combination of deficits in both maintaining attention and hyperactivity/impulsivity (APA, 2000).

A diagnosis of ADHD is assigned when there is a persistent pattern of inattention and/or hyperactivity-impulsivity displayed frequently and outside developmental level, the behaviours have been present before seven years of age, difficulties span across at least two settings, difficulties have persisted for at least six months, and the behaviour does not occur

exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder, and not better accounted for by another mental disorder. Six or more of the nine inattention symptoms must be present for a diagnosis of the Inattentive Type and six or more of the nine hyperactivity-impulsivity symptoms must be present for a Hyperactive-Impulsive Type diagnosis. If an individual presents with six or more symptoms of inattention and six or more of hyperactivity-impulsivity, they then meet criteria for the Combined Type (see Table 1 for a full list of DSM-IV diagnostic criteria). ADHD persists across the lifespan, displaying impairments of academic, occupational and social functioning in adulthood.

As illustrated in Table 2, the recently published DSM-5 (APA, 2013) consists of two categories of inattention and hyperactivity and impulsivity similar to that of the DSM-IV. However, a few changes have occurred including: ADHD symptoms must be present prior to age 12, compared to 7 years as the age of onset in the DSM-IV, examples and descriptions have been included in the DSM-5 to help clinicians better identify ADHD behaviours at multiple stages of a client's life, a decrease in symptoms required for those 17 years and older from six symptoms to five, making a greater effort to address adults affected by ADHD, and the exclusion criteria for those with autism spectrum disorder has been removed as both disorders can now co-occur.

The *International Statistical Classification of Diseases and Related Health Problems-Tenth Edition* (ICD-10) describe a pattern of symptoms similar to ADHD in the DSM-IV, as Hyperkinetic Disorder (World Health Organisation [WHO], 1992). A key difference is the requirement of both 'impaired attention' and 'overactivity' when diagnosing Hyperkinetic disorders in the ICD-10. The DSM-IV criterion for ADHD has been the most widely researched and so will be the basis for discussion throughout the present study.

Table 1
DSM-IV Diagnostic Criteria for ADHD (APA, 2000 p. 92).

A. Either (1) or (2)

(1). Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
(e) often has difficulty organising tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework).
(g) often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g. butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g. at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

Table 2
DSM-5 Diagnostic Criteria for ADHD (APA, 2013 p. 59-61).

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential task; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

a. Often fidgets with or taps hands or feet or squirms in seat
b. Often leaves seat in situations in when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
c. Often runs about or climbs excessively in situations in which it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless).
d. Often unable to play or engage in leisure activities quietly
e. Is often "on the go", acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
f. Often talks excessively
g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

1.2 Prevalence and Gender Differences

Prevalence rates of ADHD range from 3% to 7% of children in the United States, 11% of children in Australia and about 5% of children and 2.5% of adults worldwide (Root & Resnick, 2003; Sawyer et al. 2001; APA, 2013). ADHD represents one of the most common diagnoses in the mental health services given to children in New Zealand (Ministry of Health, 2001). In a New Zealand sample, the prevalence of ADHD has been reported as 6.7% (Anderson, Williams, McGee & Sila, 1987).

ADHD is more commonly diagnosed in males (2:1-9:1 estimated male to female ratio) (Rucklidge, 2008). However, studies suggest that females may have more internalising symptoms (i.e. depression and anxiety) and greater difficulty with verbal abilities (Rucklidge & Tannock, 2001) and on average display lower levels of hyperactivity than boys (Arnold, 1996). Gaub and Carlson (1997) found that girls exhibited greater intellectual impairment and fewer symptoms of hyperactivity. More recent research has found that there are more similarities than differences in males and females with ADHD, and the subtype in which they are diagnosed is a more critical feature of difference (Rucklidge, 2008; Gross-Tsur, Goldzweig, Landau, Berger, Shmueli & Shalev, 2006).

1.3 Course

Although once considered a childhood disorder, longitudinal research has shown that ADHD symptoms can persist into adulthood (Barkley, 1998; Murphy & Barkley, 1996). The

initial apparent decline in prevalence of ADHD may have resulted from the criteria list in previous DSM editions being largely applicable towards younger children (Barkley, 2003). The DSM 5 includes descriptions depicting the expression of the disorder at varying stages of one's life to try and capture those who may have been missed in the past (APA, 2013). An estimated 70% to 80% of children diagnosed with ADHD experience clinically significant symptoms of ADHD into adolescence (Barkley, 2006). Studies investigating the persistence of ADHD into adulthood have found that up to 65% of children with ADHD continue to experience symptoms into adulthood; however, it is important to note that the number varies depending on how ADHD is defined (Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2005).

1.4 Comorbidity

ADHD frequently co-occurs with at least one other psychiatric condition. The Multimodal Treatment Study of Children with ADHD (MTA) found that nearly two-thirds of children with ADHD met criteria for another diagnoses with only 31% of children having ADHD alone (MTA Cooperative Group, 1999). Kadesjo & Gillberg (2001) found as many as 87% of children who were clinically diagnosed with ADHD met criteria for at least one other disorder and 67% had two or more comorbid disorders.

Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are among the most common coexisting psychiatric disorders experienced by children with ADHD. Within the general population approximately half of those presenting with combined type ADHD would meet criteria for ODD and a quarter would meet criteria for CD (APA, 2013). Studies have shown that anxiety disorders co-occur in children with ADHD up to a third of the time (Biederman, Newcorn & Sprich, 1991; MTA Cooperative Group, 1999) and comorbid mood

disorders occur around 20% of the time (Cuffe, Moore & McKeown, 2005; Cuffe et al., 2001).

Studies looking at comorbidity between Learning Disorders (LD) and ADHD have found rates ranging from 10% to 92% (Biederman et al., 1991). Although LD have long been associated with ADHD, true comorbidity rates between the two disorders have been inconclusive (Jensen, Martin & Cantwell, 1997). Research has shown an elevated risk of tic disorders in children and adults with ADHD **(**Spencer, Biederman, Coffey, Geller, Wilens & Faraone, 1999; Peterson, Pine, Cohen & Brook, 2001; Spencer et al., 2001). Tic Disorders in those with ADHD appear to have a high probability of remission and do not appear to change the course or presentation of ADHD (Spencer et al., 2001).

The literature on the comorbidity of ADHD with Autistic Spectrum Disorders is limited due to the exclusion of children with Autism, Asperger syndrome or other Pervasive Developmental Disorders (PDD), when diagnosing ADHD using the DSM-IV. This exclusion criterion is based on the belief that the ADHD-like symptoms present in children with a PDD are often a consequence of their severe and pervasive disorder (Barkley, 2006). Goldstein and Schwebach (2004) found that 59% of their PDD sample (n=27) met diagnostic criteria for either combined type (26%) or inattentive type (33%) ADHD, which suggests the existence of comorbidity between ADHD and PDD.

1.5 Associated Difficulties

In addition to the increased risk of various psychiatric disorders, children with ADHD are more likely to experience a substantial amount of associated difficulties. Children with ADHD have a higher risk of learning, behavioural, and emotional problems. They have greater difficulty with social interactions and family members; this is especially true when

co-occurring conditions are present (Kollins, Barkley, & DuPaul, 2001; Miranda & Presentacion, 2000). Some of these difficulties will be discussed in the following section.

1.5.1 Social Difficulties

In the DSM-IV ADHD is classified as an attention-deficit and disruptive behaviour disorder due to the disruptive effect that ADHD symptoms have on overall functioning. The interpersonal problems that children with ADHD experience are among the most salient and debilitating of their associated difficulties (Hinshaw, 1992). In their paper identifying behavioural characteristics, Gaub and Carlson (1997) found, that children with ADHD were identified as having poorer social functioning compared to their control group peers, regardless of subtype. The children with ADHD, Combined type, were rated highest on the peer dislike variables and total problem scale compared to predominantly Inattentive or predominantly Hyperactive/Impulsive types (Gaub & Carlson, 1997).

Children with ADHD appear to be more prone to making errors when processing social cues and emotional cues from others, even when they show an understanding of the cues (Barkley, 2003). Demaray and Elliot (2001) found that children with ADHD behaviours perceived less overall social support from classmates, close friends and teachers. In social interactions with peers, children with ADHD have fewer friendships, are less liked, and, as a consequence, are rejected (Erhardt & Hinshaw, 1994). Although children with ADHD have an increased risk of social difficulties, some children experience more severe social deficits than others. A longitudinal study found that boys with ADHD and a co-occurring social disability had greater rates of disruptive behaviours, substance use and mood and anxiety problems at a four year follow-up compared to boys without ADHD or with ADHD alone (Greene, Biederman, Faraone, Sienna & Garcia-Jetton, 1997).

Studies have found that although children with ADHD are quicker to accept other children as playmates and talk more than those without, they are more disorganised and less efficient in communicating information (Hinshaw & Melnick, 1995; Barkley, 2006). These children express less reciprocity in their exchanges and are less likely to respond to questions or verbal interactions with their peers (Stroes, Alberts, & van der Meere, 2003).

1.5.2 Family Functioning

There are greater levels of family adversity when a child is diagnosed with ADHD (Counts, Nigg, Stawicki, Rappley, & Von Eye, 2005). Research has found that families who have children with ADHD have greater marital difficulties and family conflict, which is particularly evident in parent-child interactions (Murphy & Barkley, 1996; Kaplan, Crawford, Field, & Simpson, 1998; Johnston & Mash, 2001). When compared to interactions between parents and children without ADHD, there is an increase in negative interactions and controlling behaviour, a decrease in responsiveness, and fewer rewards for good behaviour in parents who have children with ADHD (Danforth, Barkley, & Stokes, 1991; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Lange et al., 2005). Parents of children with ADHD were less likely to seek support from relatives or friends and had poor adaptive coping styles (DuPaul et al., 2001).

Parents of children with ADHD report higher levels of parental stress (Breen & Barkley, 1988; Johnston & Mash, 2001; DuPaul et al., 2001); an increase in alcohol consumption, especially evident in those with a family history of alcohol problems (Cunningham, Benness, & Siegel, 1988; Pelham & Lang, 1993; Molina, Pelham, & Lang, 1997; Pelham et al., 1998); greater maternal depression (Cunningham, Benness, & Siegel, 1988; Chronis et al., 2003); and a decrease in parenting satisfaction (Lange et al., 2005), compared to parents of children without ADHD.

There are even greater degrees of parental stress, parental psychopathology, marital discord, mood and anxiety disorders, and substance dependence in parents when the child has ADHD with comorbid oppositional defiant disorder (ODD) or conduct disorder (CD) (Barkley, Fischer, Edelbrock, & Smallish, 1991; Chronis et al., 2003; Shelton et al., 1998). Parents with ADHD symptoms may find it even more difficult to manage a child with ADHD (Weiss, Hechtman, & Weiss, 2000). This may affect the family functioning as a whole due to martial breakups, changes in occupation, frequent moves, and other behaviours associated with adult ADHD (Weiss, Hechtman, & Weiss, 2000).

1.5.3 Intellectual Functioning

In a meta-analysis conducted by Frazier, Demaree, and Youngstrom (2004), it was found participants with ADHD show poorer intellectual performance than controls without ADHD. This poorer performance affects a child's overall academic ability, with the majority of children clinically referred for ADHD performing poorly in school (Barkley, 2006). This is believed to be a result of their restless, impulsive and inattentive nature in the classroom along with a lack of organisational skills. When reflecting a difference between ADHD and control groups, Frazier and colleague's meta-analysis (2004) found a substantial reduction in academic achievement in participants with ADHD with an effect size of .61 of a standard deviation.

1.5.4 Overall Health

Children with ADHD are more accident prone than their peers. These accidents often include head injuries, broken bones, lacerations, burns and poisoning (Merrill, Lyon, Baker, & Gren, 2009; Hoare & Beattie, 2003; Mangus, Bergman, Zeiger, & Coleman, 2004). Bruce, Kirkland, and Waschbusch (2007) found that children with ADHD, when compared to a normal control group, were at an increased risk for minor injuries requiring physician care.

They also discovered that the risk of emergency room visits was 42% greater for children with ADHD; however, this increased significantly when ADHD was accompanied with conduct problems (Bruce, Kirkland, & Waschbusch, 2007). There was also a 43% increased risk of hospitalisation in the ADHD group relative to controls.

Adolescents and young adults with ADHD receive more traffic violations and are involved in a significantly greater amount of driving related accidents than their age-matched peers without ADHD (Barkley, Murphy, DuPaul, & Bush, 2002; Barkley, Guevremont, Anastopoulous, DuPaul, & Shelton, 1993). Consistent with this research, a New Zealand study found that adolescents with increasing attentional difficulties had an increase in driving risks that included: motor vehicle accidents, drink driving, and an increase in traffic law violations (Woodward, Fergusson, & Horwood, 2000).

Barkley and colleagues (2002) found the estimated cost of the first motor vehicle accident in those with ADHD to be more than twice as high as the control group. The increase in amount of accidents and injuries in children and adolescence with ADHD results in significant financial costs to both the family and the community. Burd, Klug, Coumbe, and Kerbeshian (2003) found the overall annual cost of care for children with ADHD was 31% higher than the cost of care for children without ADHD. A review investigating the economic cost of ADHD found children with ADHD had higher annual medical costs, greater indirect costs to their families (require more time and energy from family, parents miss work to attend meetings with teachers or time at doctors, etc.), significantly higher rates of juvenile and adult arrests, a significant increase of work-related problems in adulthood (due to poorer job performance, lower occupational status, less job stability and more days absent), and limited long-term cost effective treatments (Matza, Paramore, & Prasad, 2005).

1.6 Aetiology of ADHD

1.6.1 Neurobiology

Research using neuropsychological testing has found deficits in executive functioning in participants with ADHD (Frazier, Denmaree, & Youngstrom, 2004). Executive functions are neurocognitive processes that attain a future goal by upholding the appropriate problem solving set (Welsh & Pennington, 1988). Results of neuropsychological testing in participants with ADHD often suggest a disinhibition of behavioural responses, difficulty with working memory, planning, verbal fluency, motor coordination and other frontal-striatal-cerebellar functions (Barkley, 2006). A meta-analysis investigating executive function and ADHD found that ADHD is associated with weaknesses in executive function domains; with effect sizes in the medium range on all of the executive function measures (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). They found the most affected areas were spatial working memory, response inhibition, vigilance and planning (Wilcutt et al., 2005). Although executive function deficits are not the cause of ADHD, the difficulties they represent are seen to be one of the important weaknesses comprising the overall neuropsychological etiology of ADHD (Wilcutt et al., 2005).

Brain imaging studies have found an overall reduction in brain size and a reduction of brain region dimensions (Bush, Valera, & Siedman, 2005; Swanson et al., 2007). Carmona et al. (2009) researched the region most commonly associated with processing of rewards, the ventral striatum, and found reductions in both right and left ventral striatum. The volume of the right ventral striatum was negatively correlated with maternal ratings of hyperactivity/impulsivity (Carmona et al., 2009). Functional magnetic resonance imaging (fMRI) is a technique used to study brain activation in participants with ADHD while they complete specific cognitive and behavioural tasks. The use of fMRI techniques have shown a

reduction in the responsiveness to rewards in the ventral striatum of ADHD participants (Scheres, Milham, Knutson, & Castellanos, 2007; Plichta et al., 2009). A study by Scheres et al. (2007) found, using an fMRI, that participants with ADHD had no significant anticipatory activation of striatal regions when cues signalling gain were presented compared to a control group where the opposite occurred.

The behavioural concept of reinforcement in children with ADHD has been extensively researched with advances in the understanding of the neural mechanisms involved (Tripp & Wickens, 2009). The neurotransmitter dopamine has been implicated in mediating the brain's reinforcement signal and some of the structures implicated in ADHD (Tripp & Wickens, 2009). Tripp and Wickens (2008) propose that some ADHD symptoms may be explained by a failure of the dopamine cell response to the cue that predicts reinforcement. The dopamine transfer deficit (DTD) assumes that, in children without ADHD, the dopamine cell response to positive reinforcement transfers to previous cues that predict reinforcement, providing immediate reinforcement at a cellular level when there is a delay in behavioural reinforcement (Tripp & Wickens, 2008). In children with ADHD, the transfer fails to occur and this leads to delayed reinforcement at a cellular level if there is a delay in behavioural reinforcement, explaining the sensitivity to delay in reinforcement compared to children without ADHD (Tripp & Wickens, 2008).

1.6.2 Astrocytes, Oxidative Stress, and Mitochondrial Dysfunction

Russell and colleagues (2006) propose that in individuals with ADHD there are inefficient and inconsistent neuronal transmissions of information due to deficient lactate production (energy supply) by the astrocyte (the major non-neuronal component of the central nervous system) which leads to variability in responding to external stimuli. Astrocytes play a crucial role in giving energy (lactate) to rapidly firing neurons, provide

nutrients and modulate the release and uptake of by-products of neural activity, as well as providing lactate to oligodendrocytes. This lactate is then used as a substrate for the synthesis of myelin, enabling neurotransmission at a 10-fold increased rate compared to unmyelinated axons (Russell et al., 2006). Russell and colleagues (2006) hypothesise that ADHD may be caused by these inconsistencies and inefficiencies in the astrocytes.

Ceylan, Sener, Bayraktar and Kavutcu (2010) found children and adolescents with ADHD have higher oxidant levels compared to a control group, suggesting the increase in oxidants may play a role in ADHD by impairing the structure and functions of dopamine. Further research conducted by Ceylan and colleagues (2012) argues that oxidative metabolism and cellular immunity might contribute to the prevalence of ADHD by injuring neuronal cells, resulting in corruption of dopamine synthesis and neurotransmission. Ceylan and colleagues (2012) link their findings to previous research on maternal smoking and nicotine's action on the production and function of neurotransmitters with the pathology of ADHD, as smoking produces an increase in oxidative stress and inflammation.

Mitochondrial disorders have been implicated in the pathophysiology of some mental health disorders (Rucklidge & Kaplan, 2013). Mitochondrial disorders affect the energy metabolism of neurons and glia cells, consequently impairing their ability to function optimally (Rucklidge & Kaplan, 2013). Young (2007) discussed the role mitochondrial dysfunction has on neurodegenerative disorders and the possible role it may play in bipolar disorder due to the neural damage that may occur if energy metabolism is reduced. Research has also discussed the role that oxidative stress plays on the pathophysiology of schizophrenia (Tosic et al., 2006). The treatment of mitochondrial disease is typically through the use of a combination of nutrients to increase mitochondrial function (Parikh et al., 2009).

1.6.3 Genetics

Research from twin, family and adoption studies indicates a significant genetic link, with estimated heritability rates of 76% (Faraone et al., 2005), and an increased likelihood of parents or siblings meeting criteria for ADHD (Faraone & Biederman, 2000). Minde and colleagues (2003) found that 43% of the children of adults with ADHD met criteria for ADHD, and Smalley and colleagues (2000) found that 55% of families with at least two children with ADHD, also had at least one parent with ADHD. The high heritability of ADHD is thought to be due to the small effect size of a number of genes, instead of a major effect of one or a few specific genes (Sagvolden, Johansen, Aase & Russell, 2005).

Although the evidence for one specific gene to play a major role in ADHD has not been discovered, a review of all molecular genetic studies of ADHD between 1991 and 2004 found significant associations for four genes in ADHD: the dopamine D4 and D5 receptors, and the dopamine and serotonin transporters (Bobb, Castellanos, Addington, & Rapoport, 2006). Dopamine beta-hydroxylase (DBH), HTR1B (a serotonin receptor) and synaptsosomal-associated protein 25 (SNAP25) genes have also been shown to be associated with ADHD (Faraone et al., 2005). Research continues to investigate specific genes and their role in ADHD; however, a multifactorial polygenic etiology is thought to characterise ADHD, as well as most other psychiatric disorders (Gizer, Ficks, & Waldman, 2009; Sagvolden et al., 2005).

More recently a polygenic hypothesis has been suggested as a more plausible view of the genetic role of ADHD; where multiple risk genes contribute to the aetiology of the disorder (Hawi et al., 2015; Faraone & Mick, 2010). Genes involved in biological processes, such as catecholamine metabolic processes, synaptic transmissions, cell migration and G-protein signalling pathways were over-represented in those with ADHD (Hawi et al., 2015).

However, there have been a limited number of functional genomic studies performed in ADHD, further research is required to investigate the importance of the variants in genetic targets and the mechanisms they may influence in the development of ADHD. Much larger sample sizes (10,000-20,000 individuals) are required to detect significant effects of genes at the genome-wide level (Cortese, 2012).

There is an increase in the recognition of the interaction that genes, plus environmental risk factors, play in the behavioural and neuropsychological characteristics of ADHD (Swanson et al., 2007). There have been a number of environmental risk factors identified that may increase the risk of ADHD (Banerjee, Middleton, & Faraone, 2007; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). Kahn, Khoury, Nichols, and Lamphear (2003) found children who were exposed to prenatal smoking and had the DAT 480 genotype had significantly higher hyperactive/impulsive and oppositional scores compared to those without the gene or exposure to prenatal smoking alone. Another study investigating the association between prenatal exposure to smoke and ADHD found twins who inherited the DAT1 440 allele and had exposure to prenatal smoke were 2.9 times more likely to receive an ADHD combined subtype diagnosis than in twins that were unexposed without the DAT1 440 allele (Neuman, Lobos, Reich, Henderson, & Todd, 2007). These studies are suggestive of the interaction between genes and environment as an explanation for the phenotypic complexity of ADHD.

1.6.4 Pregnancy and Birth Complications

Epidemiological studies have shown that complications during pregnancy, labour, or neonatal complications, are more commonly found in children diagnosed with ADHD (Milberger, Biederman, Faraone, Guite, & Tsuang, 1997; Mick et al., 2002). An intrafamilial study found an increased level of neonatal complications in the children with ADHD

compared to their non ADHD siblings (Amor et al., 2005). During the neonatal period the child becomes more independent of the mother, compared to prenatal stages, so events experienced are more likely to be specific to that child, instead of shared factors (Amor et al., 2005). These events may include neonatal admission to the hospital, incubation, oxygen therapy, and surgery (Amor et al., 2005). Low birth weight has also been identified as a risk factor for ADHD (Milberger et al., 1997; Mick et al., 2002). However there are potential confounders when linking low birth weight and ADHD, for example socioeconomic status, parental education, parental ADHD, prenatal exposure to alcohol and cigarettes (Mick et al., 2002).

Mick and colleagues (2002) examined whether prenatal exposure to cigarettes, alcohol and other drugs had an effect on later development of ADHD. They found a two fold increase in risk of developing ADHD, after prenatal nicotine or smoke products exposure, and a two and a half fold increase for ADHD when prenatally exposed to alcohol (Mick et al., 2002). Although there was no association between drug use and ADHD, marijuana was the most prevalent drug of use, so the null finding may not be representative of prenatal exposure to substance use and the subsequent risk of ADHD. Thapar and colleagues (2003) investigated maternal smoking during pregnancy and genetic influences using a population sample of twins and found a significant association between maternal smoking during pregnancy and childhood ADHD that was additional to the effect of genes. As previously mentioned this could be due an increase in oxidative stress and inflammation in maternal smoking (Ceylan et al., 2012).

Ornoy, Michailevskaya, Lukashov, Bar-Hamburger and Harel (1996) found that children who were exposed to heroin, methadone and possibly other psychoactive drugs, in utero have a normal development potential if no neurological damage occurred. Children

were more at risk of developmental difficulties when raised in environments that were neglectful or abusive, than when born to heroin-dependent mothers (Ornoy et al., 1996).

A study conducted by Rodriguez and Bohlin (2005) investigated the influence that prenatal stress and smoking while pregnant had on later symptoms of ADHD and found a positive correlation, particularly for boys. Similarly, Motlagh and colleagues (2010) found that severe levels of psychosocial stress (i.e. home environment, emotional supports, parental interpersonal relationship, parental employment, financial status, parental physical health) and heavy maternal smoking during pregnancy were robustly associated with an ADHD diagnosis.

1.6.5 Psychosocial Factors

Almost 40 years ago, Block (1977) described the cultural environment as "frenetic"—fast paced, in a wild and uncontrolled way—and suggested that this is why children may have become more hyperactive compared to the past when the cultural tempo was slower. However, theories for an environmental cause of ADHD have not been very well supported. Past research indicated maternal education, solo parenting, and socioeconomic class as important adversity factors for ADHD, and found that maternal communication with children with ADHD consisted of more negative interactions compared to control groups (Barkley, 1990). Research has found that when children with ADHD are given stimulant medication maternal warmth increases, and maternal commands and negative interactions decrease, suggesting the negative behaviour of the mother to be in response to the difficult behaviour from the child (Schachar, Taylor, Weiselberg, Thorley, & Rutter, 1987; Barkley, Karlsson, Pollard, & Murphy, 1985). Chronis and colleagues (2003) suggest that, although stimulant medication may result in more positive interactions between parent and child, it is likely insufficient in treating the multitude of mental health needs of the families.

Although the current literature has shown that ADHD is not caused by parenting, the quality of the interactions and responsiveness of the parent can play a role in the development of oppositional and conduct problems in children with ADHD (Johnston & Jassy, 2007). Studies implicating psychosocial causes of ADHD using measures of adversity like socioeconomic status, marital discord and family conflict may be measuring the effects of the genes implicated in ADHD rather than independent causes of ADHD (Faraone & Biederman, 1998).

1.6.6 Toxins

Exposure to heavy metals (i.e. lead) can cause motor, sensory, and cognitive impairments; when exposed at high levels it causes a full neurobiological syndrome that is distinct to ADHD (Nigg, 2006). It has been documented that blood lead levels of 80 micrograms per decilitre (mcg/dl) are fatal; encephalopathy is caused at 60 mcg/dl; and the safe level was 25 mcg/dl until 1991 when it was decreased to the current level of 10 mcg/dl (Nigg, 2006). Research has investigated the impact of exposure to heavy metals, which are below the high levels that cause neurobiological disorders, and the relationship this exposure has with ADHD.

A study by Braun and colleagues (2006) found that children with blood lead levels greater than 2.0 µg/dL had a fourfold increased risk of ADHD. Blood lead levels have been associated with hyperactivity but not inattention when using DSM-IV ADHD ratings (Nigg et al, 2008, Nigg et al, 2010). A study of Romanian children investigated blood concentrations of lead, mercury and aluminium and found significant associations between blood lead levels and ADHD but no association with the other metals assessed (Nicolescu, 2010). Research has shown an association between exposure to toxins and ADHD behaviours. However, the direction of this relationship has not been determined: whether children with predominantly

hyperactive-impulsive ADHD ingest more lead, or whether the increased lead is pre-existing and leads to increased hyperactivity remains unclear.

1.6.7 Diet

The Western diet has been linked to a variety of health risks (i.e. obesity, diabetes etc.), and over the years there has been an increase in interest in the role that diet has on behavioural and mental health disorders, including ADHD. Howard and colleagues (2011) found that adolescents who scored high on the "Western" dietary pattern—which included a higher intake of sodium, saturated fat, total fat, refined sugars and a lower intake of omega-3 fatty acids, fibre and folate—were more likely to have been diagnosed with ADHD than those that scored high on the "Healthy" dietary pattern (higher intake of omega-3 fatty acids, folate and fibre and a lower intake of sodium, saturated fat, total fat, refined sugars). This finding suggests that those who have a greater consumption of foods that fit the Western dietary pattern may have poorer nutrient intake, which could lead to changes in neurotransmitter functioning and result in an increase in ADHD symptoms (Howard et al., 2011). However, the relationship between the Western dietary pattern and ADHD symptoms may have been mediated by poor family functioning. Families with children who have ADHD experience greater parental challenges and an increase in emotional distress, which could lead to self-soothing strategies such as craving fat-rich foods, suggesting a bidirectional relationship between diet and ADHD.

Research investigating childhood malnutrition in people who were subsequently rehabilitated nutritionally, found a greater frequency of attention difficulties on the Conners' Adult ADHD Rating Scales (CAARS) and omission and commission errors on the Conners' Continuous Performance Test (CPT) in those who had been malnourished in childhood compared to the control group (Galler et al., 2012). Another study found that children who

experienced growth retardation, or stunting, due to malnourishment during the first two years of life, experienced greater problems with hyperactivity, compared to the control group, but not attention (Walker, Chang, Powell, Simonoff, & Grantham-McGregor, 2007).

Diet may not be the only cause for a lack of ingestion of vitamin and mineral content necessary for optimal functioning. Research investigating the mineral content of fruit and vegetables grown in the 1930s compared to the 1980s found several significant reductions in mineral content, an increase in water content and a decrease in dry matter in the vegetables grown in the 1980s, compared with those grown in the 1930s (Mayer, 1997). Further research found the following reasons for the decline of nutrients in vegetables during the last 50 to 100 years. First, the "dilution effect", food grown through use of fertilization, irrigation and other environmental means contain larger absolute amounts of minerals than those grown without fertilizer; however, these amounts are significantly diluted by the increased dry matter found in the plants. An overall decline in food composition has also been identified, when comparing some minerals in groups of vegetables to historical data of the same vegetable. A genetic dilution effect, where plantings of low and high yield cultivars are grown side by side and only the genetics of the cultivators being the difference may also be another reason for the deterioration of nutrient content (Davis, 2009). The significant reductions found in vitamin and mineral content of food may play a similar role, changing neurotransmitter functioning and increasing ADHD behaviours, to that found in studies investigating malnourishment and hyperactivity and attention difficulties.

1.6.8 Food Additives and Artificial Food Colouring

Food additives and artificial food colouring have also been implicated in the development of ADHD. In 1975, Feingold published a paper linking artificial food flavours and colours to behavioural difficulties and learning disorders. However, a meta-analysis

investigating the effectiveness of the Feingold diet, found that the composite effect size (d = 0.11) was too small to have been important (Kavale & Forness, 1983). In 2004, a meta-analysis found an effect size of d = 0.28 for the relationship of artificial colours and parent-rated ADHD symptoms, and this effect was not found for teacher or observer ratings (Schab & Trinh, 2004). A more recent meta-analysis found the restriction of artificial food colours was beneficial for some ADHD populations, particularly on parent-rated measures (Nigg, Lewis, Edinger, & Falk, 2012).

There has been some support for the impact that malnutrition, particularly early in life, has on later functioning and ADHD behaviours. It has also been shown that the quality and content of vitamins and minerals found in the food being consumed has decreased over time, which may also play a role in the development of ADHD through the disruption of neurotransmitter functioning. Research on artificial colour additives and the role they play on ADHD behaviours is mixed. It is possible that the elimination of such additives may result in the reduction of ADHD behaviours; however, this evidence does not identify food additives as a cause of ADHD. Further research is required in order to identify the strength and direction of the possible association between diet and the development of ADHD.

1.7 Treatment

Due to the potential for widespread difficulties in multiple areas of functioning, effective treatment of ADHD is vital. There have been three general approaches to treatment for ADHD: pharmacological (i.e. drug treatment); behavioural/psychosocial; or a combination of these approaches (Dogget, 2004, Barkley, 2006, Chronis et al., 2004). Currently, multimodal interventions are recommended for ADHD, as there is no single risk factor that explains ADHD (Thapar, Cooper, Eyre, & Langley, 2013). There has been an increase in literature investigating the effects alternative treatments have on ADHD, this

section will end by summarising what has been found so far. The following chapter will go into greater detail about the use of micronutrients in the treatment of psychological disorders, particularly ADHD.

1.7.1 Pharmacological Treatments

Pharmacological treatments have been found to be the most effective treatment for ADHD to date, with a response rate of around 70% (Zachor et al., 2009). Stimulant medications have the most efficacy data from hundreds of controlled trials and are the most commonly prescribed as the first line of treatment for ADHD (Vaughan, March, & Kratochvil, 2012). Over the past decade there has also been an increase in data supporting the use of non-stimulant medications for treating ADHD (Vaughan et al., 2012). Some of the major classes of drugs used in the pharmacotherapy of ADHD, as listed by Biederman and colleagues (2004), are: stimulants, such as dextroamphetamine (Dexedrine), mix salts of L and D-amphetamine (Adderall, Adderall XR), methylphenidate (Ritalin, Methylin, Focalin, Concerta, Ritalin LA, Metadate CD); norepinephrine specific reuptake inhibitors (NSRI), such as atomoxetine; anti-depressants, such as, tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, citalopram, bupropion, venlafaxine, nefazodone, mirtazapine; and noradrenergic modulators such as Alhpa-2 agonists (clonidine, guanfacine); and beta blockers (propanolol).

There has been extensive literature on the short-term effectiveness of stimulant medications on the core symptoms of ADHD (Biederman, Spencer, & Wilens, 2004). Stimulant use in the treatment of ADHD has shown an increase in attention to school work, and a decrease in disruptive and non-compliant behaviours. The decrease in disruptive and non-compliant behaviours in children treated with stimulants has resulted in more positive interactions with parents and teachers (Schachar et al., 1987; Barkley et al., 1985; Chronis et

al., 2003; Vaughan et al., 2012). Stimulant medication has also shown broader therapeutic effects, such as becoming increasingly socially appropriate, compared to unmedicated children with ADHD (Granger, Whalen, Henker, & Cantwell, 1996). Short-term data showed some promise, with an increase in academic performance and productivity in children with ADHD receiving stimulant treatment, compared to children with ADHD who were not medicated; however, children still performed below the level of children without ADHD (Powers, Marks, Miller, Newcorn, & Halperin, 2008).

A Multimodal Treatment Study of Children with ADHD (MTA) completed a 14-month randomised clinical trial investigating the effect of medication alone, behavioural treatment, a combination of medication and behavioural treatment, and a standard community care treatment, on ADHD behaviours (MTA, 1999). Although all groups showed a reduction in symptoms over time, medication alone and combined medication and behavioural therapy showed the greatest improvement at the end of the study (MTA, 1999). However, at a three year follow up, they found no difference in ADHD symptoms across the different groups and found 71% of the medication alone and combination group taking high levels of medication compared to 62% of the community care group and 45% of the behavioural treatment group (Jensen et al., 2007). They also found that medication use between year two and year three was associated with an *increase* in ADHD symptomology during that period, compared to those not taking medication (Jensen et al., 2007).

Greenhill and colleagues (2006) conducted the first controlled study investigating the safety and efficacy of methylphenidate in treating pre-schoolers, aged three to five and a half. They found that the optimal dose was lower than that used in the MTA study investigating school age children (Greenhill et al., 2001). Children who received methylphenidate had a greater decrease in ADHD symptoms than those in the placebo group; however the effect sizes from both parent and teacher ratings were smaller than those found in the MTA study

investigating the same medication on older children with ADHD (Greenhill et al., 2006; Greenhill et al., 2001).

A meta-analysis of 74 studies found larger effects for pharmacological treatment compared to psychosocial, parent-training and educational interventions; however the pharmacological interventions show little impact on educational outcomes (Purdie, Hattie, & Carroll, 2002). Medication alone as treatment for ADHD tends to relieve some symptoms by increasing attentiveness and decreasing over activity; however, it tends to be palliative and provides only short-term benefits (Sterman, 2000). Purdie and colleagues (2002) found that although medication decreased inattention, hyperactivity and impulsivity, there was no flow-over effect to learning or achievement, and no improvement in emotional well-being or school-based achievement.

Although pharmacological treatments for ADHD have been shown to be effective, all stimulant medications have similar side effects such as delayed sleep onset, decrease in growth, weight loss, increased heart rate and blood pressure, decreased appetite, and increased irritability and emotional outbursts (Greenhill, et al., 2002; Swanson et al., 2007; Wigal, et al., 2006). Due to the adverse side effects, the percentage of people with ADHD who either do not respond to medication or do not respond as intended (Doggett, 2004; Sterman, 2000; Chabot, Merkin, Wood, Davenport, & Serfontein, 1996), and the concerns over the long-term impact of stimulants on the developing brain (Andersen, 2005), continued research into the treatment of ADHD is needed.

1.7.2 Psychosocial Treatments

In the search for effective, evidence-based, psychosocial treatments for ADHD, a few techniques have been identified as well-established treatments for children with ADHD. Behavioural parent training and behavioural contingency management, in the classroom, have

been shown to be well-established treatments for children with ADHD (Pelham, Wheeler, and Chronis, 1998; Pelham & Fabiano, 2008; Kaiser & Pfiffner, 2011). The more cognitive focused interventions (cognitive behavioural therapy, play therapy, social skills training, etc.) appear to be less effective in treating children with ADHD (Pelham et al, 1998; Pelham & Fabiano, 2008).

Although stimulant medications have been shown to be effective in treating ADHD symptoms, the MTA study reported that parents had a preference for the groups that included behaviour management over medication (MTA, 1999). Modification of poor parenting skills as a way to increase positive interactions and improve outcomes of children with behavioural problems, has been shown to be effective in treating ADHD (Pelham et al., 1998; Chronis, Chacko, Fabiano, Wymbs, & Pelham, 2004; Fabiano, Pelham, Coles, Gnagy, Chronis-Tuscano, & O'Connor, 2009). Behavioural parent training interventions are based around teaching children with ADHD socially acceptable behaviour by working with the primary caregivers in contingency management strategies, behaviour modifications, consequence and reward systems and the role of discipline (Chronis et al., 2004). Studies have shown positive treatment outcomes in social behaviour and acceptance (Pelham et al., 1998), parental reported problem behaviour, and negative parent-child interactions (MTA, 1999; Fabiano et al., 2009). Behavioural parent training offers an alternative, effective treatment when children with ADHD do not respond to medication, or when parents are looking for an alternative to medication (Pelham et al., 1998). Behavioural treatments for adolescents with ADHD is lacking research, and as adolescents with ADHD are a difficult population to treat, further research is required (Barkley, Anastopoulos, Guevremont, & Fletcher, 1992; Smith, Waschbusch, Willoughby, & Evans, 2000).

Behavioural classroom management, or contingency management, techniques have shown to be well-established treatments for children with ADHD (Pelham et al., 1998;

Pelham & Fabiano, 2008; Fabiano et al., 2009). These techniques include point/token economy systems, response-cost, teacher implemented reward programs, and time-out. Although these techniques have proven to be a well-established treatment option, difficulty with generalisation of the treatment effects to other settings, as well as a regression of gains once treatment has ceased has been found (Barkley et al., 2000; Pelham & Fabiano, 2008). However, the MTA follow-up data showed no regression of gains after the behavioural intervention (Jensen et al., 2007), suggesting maintenance over time due to the comprehensive and intensive nature of the intervention (Pelham & Fabiano, 2008).

The results of reviews and meta-analyses investigating behavioural treatments for children with ADHD have found behavioural techniques to be an effective form of treatment (Pelham et al., 1998; Pelham & Fabiano, 2008; Fabiano et al., 2009), and highlight the need to shift the focus from the effectiveness of behavioural interventions to employing, enhancing and refining behavioural intervention use across settings (Fabiano et al., 2009).

1.7.3 Combined Treatments

Randomised control trials, such as the National Institute of Mental Health multimodal treatment study of children with ADHD (MTA study) and the New York and Montreal Multimodal treatment study, investigating the effectiveness of treatment strategies for children with ADHD, have suggested that medication alone is more effective than behavioural interventions in treating the symptoms of ADHD (MTA, 1999; Klein, Abikoff, Hechtman, & Weiss, 2004). Further analyses of the MTA study found that children with ADHD and comorbid anxiety were particularly responsive to all treatment types in all areas except academically, due to the adverse effects that medication may have on learning (Jensen et al., 2001). They found that children with combined ADHD, anxiety and ODD/CD, had the greatest benefits from the combined treatment of medication and behavioural interventions,

compared to the ADHD alone group, and the ADHD with ODD/CD group (Jensen et al., 2001). Wells and colleagues (2000) found, when examining parent and family stress outcomes of the MTA study, that combination medication and behavioural interventions were associated with significant decreases in parent-rated measures of negative parenting and negative/ineffective discipline, compared to the community care group.

1.7.4 Alternative Treatments

As not all children respond to medication or behavioural interventions, or experience significant side effects from medication use, research has begun to investigate possible alternative treatments for children with ADHD.

Essential fatty acid (EFA) supplementation has been one of the more widely researched alternative treatments. Controlled trials investigating the efficacy of EFAs in children with ADHD have found subgroups, particularly inattentive type, of participants who show a significant decrease in ADHD symptoms when compared to the control group (Johnson, Ostlund, Fransson, Kadesjo, & Gillberg, 2009; Belanger et al., 2009). A meta-analysis of randomised placebo-controlled studies comparing omega-3 fatty acid to placebo found small, but significant benefits compared to placebo (Bloch & Qawasmi, 2011). Their meta-regression also found a significant association between omega-3 dose and efficacy (Bloch & Qawasmi, 2011). Randomised control trials conducted with the omega-3 EFA, docisahexaenoic acid (DHA), found no significant differences in ADHD symptoms in children, when comparing DHA supplementation to the placebo group (Voigt, Llorente, Jensen, Fraley, Berretta, & Heird, 2001; Hirayama, Hamazaki, & Terasawa, 2004). Recent research has found omega 3 fatty acids eicosapentaenoic acid (EPA) and DHA produce different effects, as EPA has neuroprotective actions, and has shown positive effects in treating depression, and DHA may have damaging effects on the nervous system (Martins,

2013). This may be due to the oxidative derivatives of EPA having an anti-inflammatory effect, where oxidized derivatives of DHA have pro-inflammatory effects (Bloch & Qawasmi, 2011). More research is needed in the area of EFAs and their effectiveness as a treatment for ADHD.

Research investigating one ingredient at a time for the treatment of ADHD has shown some modest effects (Hurt, Arnold, & Lofthouse, 2011). A review of nutrient supplementation as treatment of ADHD found 27 human studies investigating single vitamins, such as pyridoxine (B6); single minerals, such as iron, magnesium, zinc; amino acids; essential fatty acids; and botanicals, such aspine bark extract; as well as multi ingredient formulas (Rucklidge, Johnstone, & Kaplan, 2009). Zinc, based on two randomised control trials of varying doses, was the individual nutrient with the most evidence of treatment efficacy, however more research is needed (Rucklidge et al., 2009). Kaplan and colleagues (2007) highlight that single-nutrient interventions for psychiatric symptoms have undergone 100 years of research and have found modest results. This finding is not surprising as most diseases are multi-factorial (Mertz, 1994). Overall, although some single nutrient treatment show promise, the research to date has showed mixed findings and requires further investigation. Nutrient treatments will be discussed in more detail in Chapter 2.

Elimination or restriction diets as a treatment for children with ADHD have found mixed results. In 1975, Feingold reported that approximately 50% of children with hyperkinesis (now known as ADHD) responded to elimination diets that excluded all artificial colours and flavours. However a meta-analysis in 1983, regarding the Feingold diet, concluded that the effects of dietary interventions were too small to be important, and considered diet modification a questionable efficacious treatment (Kavale & Forness, 1983). A more recent meta-analysis found that about 30% of children with ADHD had a reduction in symptoms when adhering to a restriction diet, suggesting that food additives can influence

ADHD behaviours (Nigg et al., 2012). Nigg and colleagues (2012) acknowledge that although current research is limited in this area, the impact that food restriction diets have on ADHD symptoms, and the potential importance of this, is too substantial to dismiss.

Neurofeedback is an alternative treatment that trains the brain (through operant conditioning) to improve self-regulation, by providing real-time audio/video information about the electrical activity of the brain obtained from electrodes on the scalp (Barabasz & Barabasz, 1995; Sterman, 2000; Arnold et al., 2013). The theory behind neurofeedback is that one's brainwaves can be consciously modified. Although results of neurofeedback as a treatment for ADHD show promise, results are inconclusive due to the inconsistencies in study design. Pilot feasibility trials have been completed warranting a large double blind randomised control trial (Arnold et al., 2013).

1.8 Summary

ADHD is a neurobiological disorder that is characterised by a persistent pattern of developmentally inappropriate levels of inattention, hyperactivity and impulsivity that interfere with functioning and development. ADHD is a chronic disorder that begins in childhood and causes significant difficulties for the child, the family and the community. ADHD usually manifests as hyperactivity in preschool, with inattention becoming more prominent during primary school years. ADHD has been classified as a neurodevelopmental disorder, suggesting that biological and family factors may contribute to the maintenance and/or exacerbation of ADHD symptoms. Children with ADHD may have difficulties with social functioning, and many experience comorbid externalising or internalising disorders.

Empirically supported treatments for children with ADHD include stimulant medication, behavioural interventions and a combination of the two. Alternative treatments continue to show some promise, however to date have shown mixed results and require

additional research. Research on the use of broad based micronutrients to treat children with ADHD is a promising area for future research. The following chapter will discuss previous research investigating the use of micronutrients as a possible alternative treatment for mental health disorders and the rationale for their use in children with ADHD.

Chapter 2: Micronutrients

This chapter will explore the rationale for the use of nutrient supplementation in treating mental health disorders, and some of the possible mechanisms of action behind this application. The literature on the use of both single- and multi-nutrient supplements for ADHD will then be outlined, followed by a review of the formula used in the current study (EMPowerplus) and its applications in mental health.

2.1 Why Micronutrients?

Micronutrients_vitamins and minerals—are important in both physical, and mental health functioning. Micronutrients are required for promoting physical growth, sexual maturation and neuromotor development (Singh, 2004). Micronutrients are necessary for many brain functions, from maintaining blood supply to brain tissue, to energy metabolism of the nerve cells (Haller, 2005). For example, glucose, the primary energy source for the brain, is dependent on vitamins such as thiamine to be metabolised, and B-vitamins are important in maintaining optimum blood supply to the brain (Haller, 2005). Vitamins and minerals are also important cofactors in the synthesis of many neurotransmitters, and more than a third of enzymes also require a vitamin or mineral cofactor (Haller, 2005).

There is increasing evidence that micronutrients may be beneficial in the treatment of mental health disorders. Inborn errors of metabolism—abnormalities in the biological capacity to metabolise nutrients that may be the cause of low blood levels of micronutrients in some individuals (Kaplan et al., 2001; Kaplan et al., 2007)—have been implicated in brain functioning, and the use of high doses of vitamins and minerals may be effective in treating those with inborn errors of metabolism (Kaplan et al., 2007). Some studies have suggested that inborn errors of metabolism are evident in psychiatric illness. For example, Suboticanec, Folnegovic-Smalc, Korbar, Mestrovic, and Buzina (1990) found that patients with

schizophrenia had lower levels of fasting plasma vitamin C, and 6-hour urinary vitamin C excretion, than a healthy control group. The group difference in plasma levels of vitamin C was removed by supplementation of vitamin C, but supplementation did not affect the levels in urinary excretion, suggesting that these patients with schizophrenia had a higher metabolic requirement for vitamin C (Suboticanec et al., 1990).

Mitochondrial dysfunction, resulting from an alteration in the biochemical cascade and damage to the electron transport chain, has been implicated as a possible factor in the pathogenesis of mental health disorders (Rezin, Amboni, Zugno, Quevedo, & Streck, 2008; Rucklidge & Kaplan, 2013). Mitochondria are involved in essential processes, such as apoptosis, calcium homeostasis and energy metabolism. Research has found that abnormalities in energy metabolism result in cellular degeneration, which has been implicated in neurodegenerative diseases, such as Parkinson's disease (Calabrese, Scapagnini, Stella, Bates, & Clark, 2001). A multinutrient formula known as a "mitochondrial cocktail" is often used in the treatment of physical mitochondrial disorders. This cocktail most frequently includes coenzyme Q10 (a substance very similar to a vitamin that is synthesised by the body), riboflavin (B2), and at least one antioxidant (Gardner & Boles, 2011). Although this formula has only been tested as an intervention for physical expressions of mitochondrial dysfunction so far, a high prevalence of psychiatric comorbidity has been found in those with mitochondrial disorders, which may have etiological implications for mental health (Fattal, Link, Quinn, Cohen, & Franco, 2007). This suggests a possible mechanism by which micronutrients can improve mental health symptomatology: if underling mitochondrial dysfunction is an etiological factor in some psychiatric disorders, then correcting this underlying abnormality in energy metabolism with nutrients is a possible way forward.

Ames (2006) proposed that the body uses a triage mechanism for the allocation of nutrients, a system that has evolved to help the body cope with times of micronutrient shortages: the triage theory. When there is inadequate availability of a micronutrient, this system places priority on short-term survival at the expense of long-term health. The triage theory proposes that the stress response, and short-term survival, require an increasing nutritional content, and that these short-term biological needs take precedence over longer term needs, acting as a survival mechanism (McCann & Ames, 2009). As psychological well-being is not part of the initial fight-flight response required for immediate survival it is likely to be neglected in the triage mechanism, and so stress could be a factor in the development of mental disorders due to the triage mechanism of nutrients.

Stress has also been shown to reduce numbers of beneficial bacteria in the gut flora (Knowles, Nelson, & Palombo, 2008), which can affect the absorption of nutrients (Holzapfel, Haberer, Snel, Schillinger, & Huis in't Veld, 1998; Kaplan et al., 2007). Inadequate absorption may negatively affect the nutrients required for the synthesis of neurotransmitters, and any functions that use these neurotransmitters (Kaplan et al., 2007). Research has found a relationship between patients with either gluten sensitivity or Celiac's disease, and neurologic and psychiatric complications (Jackson, Eaton, Cascella, Fasano, & Kelly, 2012). A study investigating the association of Celiac disease with ADHD-like symptoms found a significant decrease in ADHD-like symptoms following 6 months of a gluten-free diet (Niederhofer & Pittschieler, 2006). A recent review suggests that the promotion of healthy gastrointestinal functioning can improve absorption of nutrients and therefore improve neurological and psychological well-being (Jackson et al., 2012).

Micronutrients appear to serve great purpose in normal brain functioning, and one's overall well-being. Due to the possible role of the mitochondria, inborn errors of metabolism, and the triage allocation mechanism in the pathophysiology of mental health disorders, it is

reasonable to consider the application of nutrient supplementation in mental health. This is of particular interest in ADHD given the widespread prevalence of the chronic neurodevelopmental disorder, the lack of long-term efficacy of stimulant medication, the limited research on the effect of stimulant use on the developing brain, and the negative side effects experienced by a large portion of people treated with stimulant medication.

2.2 Research on the Use of Single Ingredient Interventions for ADHD

There is a long history of using single nutrients to treat ADHD. Some of the more widely researched single nutrient interventions for ADHD will now be discussed.

2.2.1 Minerals

The mineral zinc is essential for neurological development, immune functioning and normal growth. Zinc is also an important trace element for biogenic amine metabolism, and this is thought to play a part in ADHD (Yorbik, Ozdag, Olgun, Senol, Bek, & Akman, 2008). Research has indicated that zinc deficiencies may lead to cognitive impairment and affect information processing in children with ADHD (Yorbik et al., 2008). A 6-week double-blind randomised control trial using zinc sulphate as an adjunct treatment with methylphenidate, compared to placebo with methylphenidate, found those in the zinc group were rated as significantly better, by both parents and teachers, than those in the placebo group (Akhondzadeh, Mohammadi, & Khademi, 2004). This suggests the application of zinc alongside medication may further reduce ADHD symptoms. A 12-week double-blind randomised control trial comparing zinc sulphate to placebo, using children with ADHD, found that those in the zinc sulphate group had a significant reduction in hyperactivity, impulsivity and socialisation scores, compared to the placebo group (Bilici et al., 2004). However, there was a high drop-out rate, 52.9% of the zinc group and 50.5% of the placebo group, and a strict inclusion criteria (no comorbid illness), which may affect the

generalizability to the ADHD population. Arnold and colleagues (2005) found that ratings of ADHD inattention behaviours, by both parent and teacher, were negatively correlated with zinc serum. This finding is in contrast to the reduction of hyperactivity/impulsivity ADHD behaviours but not inattentive behaviours that Bilici and colleagues (2004) found. This could be due to a number of factors, such as difference in diet between study sites (Turkey and the United States), and a number of differing inclusion/exclusion criteria.

A three phase placebo-controlled double blind pilot study investigated the effect of zinc glycinate (compared to zinc sulphate) on ADHD behaviours, both alone and when combined with amphetamine (Arnold et al., 2011). Phase one consisted of random assignment to zinc supplement or placebo for eight weeks and phase two added an open-label fixed dose (based on weight) of amphetamine to the double-blind zinc and placebo groups for two weeks. Phase three continued with the double-blind zinc and placebo; however, in this phase they openly titrated the amphetamine to optimal clinical effect by closely monitoring parent and teacher ratings. They found that, when compared to placebo, there was no significant effect of zinc on ADHD symptoms and there was no significant difference in ADHD behaviours when zinc was combined with amphetamine, compared to placebo and amphetamine. Their finding suggests no effect of zinc on the treatment of ADHD. However, a significantly lower optimal dose of amphetamine, with a reduction of more than a third, was found for those taking the zinc supplement compared to those taking placebo (Arnold et al., 2011). Although zinc has shown some promise in the area of reducing ADHD symptoms in children, there have been mixed results in the use of zinc alongside medication, and limited research on zinc alone as a treatment for ADHD.

Iron deficiency has also been implicated in contributing to the pathophysiology of ADHD, as symptoms of iron deficiency can include a decrease in attention, arousal and responsiveness, which are similar to the symptoms of ADHD (Konofal, Lecendreux, Arnulf,

& Mouren, 2004). Iron is a coenzyme of dopamine synthesis, and iron deficiency has been shown to alter dopamine receptor density and activity in animal trials (Erikson, Jones, Hess, Zhang, & Beard, 2001). Konofal and colleagues (2004) found serum ferritin (iron is bound to ferritin) levels to be twice as low in children with ADHD, compared to the healthy control group, suggesting that low ferritin levels may alter brain dopaminergic activity, thereby contributing to ADHD behaviours (Konofal et al., 2004). They found that the level of serum ferritin was inversely correlated with the severity of ADHD symptoms: the most inattentive, hyperactive and impulsive children were also the most iron deficient (Konofal et al., 2004). The ADHD symptoms of inattention and distractibility were significantly correlated with low ferritin levels on the Conners Parent Rating Scale, and there was also a trend toward a correlation between hyperactivity and serum ferritin levels although this result was not significant (Konofal et al., 2004).

Konofal and colleagues (2008) conducted a double-blind randomised control trial using iron, in the form of ferrous sulphate tablets, as a treatment of ADHD symptoms in children who were not anaemic but iron deficient. They found a significant reduction in scores on the clinician rated scales (ADHD Rating Scale and Clinical Global Impression-Severity), but not on the Conners' Parent Rating Scale or the Conners' Teacher Rating Scale (Konofal et al., 2008). Overall, the research to date has shown iron supplementation alone as a treatment for ADHD may show some benefits for those who are iron deficient; however, generally, results are weak.

2.2.2 Amino Acids

A few amino acids have been researched individually as possible treatments for children with ADHD. A double-blind, randomised, placebo-controlled, double-crossover trial with ADHD boys, that consisted of three 8-week phases (either carnitine—placebo—

carnitine or placebo—carnitine—placebo), found carnitine treatment was associated with significantly better scores on both parent and teacher Conners' Rating Scales (Van Oudheusden & Scholte, 2002). They found that, compared to baseline, children with ADHD had a decrease in attention difficulties and aggressive behaviours when treated with carnitine. The authors suggest that carnitine stimulates the synthesis of acetylcholine and DHA in certain areas of the brain in children with ADHD.

Arnold and colleagues (2007) conducted a 16-week multi-site, placebo-controlled pilot study investigating Acetyl-L-Carnitine (ALC) in children with ADHD. The dose of the strawberry flavoured powder was dependent on the weight of the child, with doses ranging from 500mg to 1500mg. The main analyses found no group differences, with only small mean changes on ADHD scales. However, children in the ALC group, who were predominantly ADHD inattentive type, showed a greater decrease in inattention items compared to the placebo group; this is in contrast to those who were ADHD combined type who showed an inclination in the opposite direction (Arnold et al., 2007). Although ALC has been shown to be a safe alternative to standard ADHD medication, its effectiveness for the treatment of ADHD symptoms is negligible when treating inattentive type, and ineffective on the combined type ADHD population.

This comprehensive review of the most widely researched single nutrients for the treatment of ADHD found a limited number of published studies with mixed results. Of the single ingredient interventions investigated, zinc has shown the greatest promise but there is limited research on the use of zinc alone as treatment for ADHD. Iron may show some benefit, particularly for those who are iron deficient prior to treatment, but the results to date are weak. Mixed results have been found for amino acids: carnitine showed some promise on inattention and aggressive behaviours and ALC showed a minor benefit on inattention. Due to the complexity of the presentation of ADHD, a single nutrient intervention may be too

simplistic an approach. It is also important to keep in mind the potential dangers of supplementing a single nutrient alone. Vitamins and minerals work together to optimise absorption and break down excess. An excess of zinc can be harmful: 50-150 mg/day may cause headaches and gastrointestinal problems, 300 mg/day can suppress immune function (Arnold & DiSilvestro, 2005). Hemosiderosis is a serious health problem caused by an overload of iron (Rucklidge et al., 2009).

2.3 Research on the Use of Multi Ingredient Interventions for ADHD

The use of multi-ingredient supplements is based on the assumptions that micronutrients serve as essential co-factors for manufacturing neurotransmitters required for optimal brain functioning, and that individuals with mental illness may have higher nutritional requirements than those without mental illness (Kaplan, Crawford, Field, & Simpson, 2007). It has been argued that, due to the complex brain functioning and complexity of psychiatric illnesses, a broad-based micronutrient intervention may be more effective than a single nutrient intervention (Kaplan et al., 2007). Two decades ago, a leading international authority on human nutrition argued that the concept of "one-disease—one-nutrient" was outdated (Mertz, 1994). He described the potential risk of imbalances and deficiencies if a dietary intervention was designed with only one nutrient in mind (Mertz, 1994). Currently, there is not a single nutrient intervention that has shown greater therapeutic potential than others, suggesting that the single nutrient approach may be too narrow (Kaplan et al., 2007; Mertz, 1994). Pauling (1995) stated that the functioning of the brain is affected by the presence of molecular concentrations of multiple substances, and that the optimal concentration of these substances for a person may differ significantly from what is provided by the diet and "genetic machinery". He suggested that providing optimal concentrations of these important micronutrients, which are imperative for the brain's functioning, may be a preferred method of treatment for mental health patients (Pauling, 1995).

There is a growing body of literature showing some promising results using broad-based micronutrients in the treatment of ADHD, from open label trials (Kaplan, Crawford, Gardner, & Farrelly, 2002; Kaplan et al., 2001), database analyses (Rucklidge, Gately, & Kaplan, 2010) and randomized controlled trials (Rucklidge et al., 2014a; Katz et al., 2010). A study by Harding and colleagues (2003) compared 20 children with ADHD, 10 in the dietary supplement group and 10 in the Ritalin group, over a four week period. The supplemented group received multiple vitamins, multiple minerals, phytonutrients, EFAs and phospholipids, probiotics, and amino acids; the Ritalin group received prescribed doses of 5-15mg two to three times daily (Harding, Judah, & Grant, 2003). There were no post measures of behaviour to compare to pre-treatment ADHD behaviours; however, both groups showed significant improvement on the neurocognitive tests—auditory response control, visual response control, auditory attention and visual attention—and the nutrient group did as well as the Ritalin group (Harding et al., 2003).

Katz and colleagues (2010) conducted a randomised, double-blind, placebo-controlled trial investigating the effect of a Compound Herbal Preparation (CHP) on children with ADHD over four months. The CHPs primary ingredients included Paeoniae Alba, Withania Somnifera, Centella Asiatica, Spirulina Platensis, Bacopa Monieri, and Mellissa Officinalis. One hundred and twenty children were either randomised into the CHP (n=80) or placebo (n=40) group. Ninety-one percent of the CHP group finished compared to 48% of the placebo group. Participants in the CHP group showed significant improvement on all four subscales of the Test of Variables of Attention (TOVA) at the end of the four months. There was an unequal withdrawal between the groups, which could potentially lead to selection bias; however, both groups had similar baseline characteristics. The treatment group performed significantly better than the placebo group on the TOVA, an objective neuropsychological measure of attention, suggesting that CHP may be effective in treating inattention in children

with ADHD (Katz et al., 2010), but further research investigating the effects of CHP on other areas of ADHD (hyperactivity/impulsivity) is warranted. It is important to note, however, that the exact combination and dose of nutrients in the CHP compound is unknown, making replication impossible.

An open-label, observational study looked at a multidimensional treatment plan that involved: nutrition, environmental control, chelation and behavioural, educational, physical and speech therapy, and their treatment effects on children with autism spectrum disorder and ADHD (Patel & Curtis, 2007). The 10 children were treated for three to six months with: vitamins, minerals, coenzyme Q10, amino acids and peptides, omega 3/6 fatty acids, milk thistle, probiotics, digestive enzymes and α-lipoic acid. Parents were given extensive instructions on controlling environmental factors such as, mite and mould control, toxic chemicals (i.e. tobacco smoke, pesticides, and cleaning products) and ensuring that their child ate an organic diet (i.e. low in refined sugars and food additives). Children were also given gastrointestinal support (probiotics to improve leaky gut), antigen injection therapy (addressing allergies to dust mites, moulds, foods, and chemicals), chelation therapy, and glutathione and methylcobalamin (B12) injections one to three times a week. The children continued their usual behavioural therapies throughout the study. Significant reductions in urinary lead levels and significant clinical improvements were found in all the children (Patel & Curtis, 2007). The authors report an 'average' improvement in attention and concentration and decrease in hyperactivity related problems; however, they did not describe the measures they used or the analyses used to come to these results. As the study involved many levels of treatment, it would be hard to approximate the effect that the supplements had on the results.

Although there are some promising results using micronutrients in combination for the treatment of ADHD, the studies are few and the need for further investigation into the effect of micronutrients across both varying ages and varying diagnoses is warranted.

2.4 Literature on EMPowerplus (EMP+)

Due to increasing evidence showing mental health benefits through micronutrient interventions, and the promising results found with ADHD in particular, the current study investigates the effectiveness of a particular micronutrient formula, EMPowerplus, which has been extensively researched in the context of a variety of mental health disorders. This literature base will be reviewed here.

EMPowerplus (EMP+) is a 36 ingredient broad-based micronutrient formula that contains 16 trace minerals, 14 vitamins, three amino acids and three antioxidants. See Appendix A for the full ingredient list. EMP+ was formulated by David Hardy and Anthony Stephan, initially for the treatment of bipolar disorder, based on agricultural knowledge concerning the treatment of aggressive livestock. EMP+ is the most researched formula, with 25 peer reviewed publications. These include a systematic review on the safety and tolerability of the formula, as well as randomised control trials and case studies. EMP+ has been revised since its initial development. In 2002, the processing method was changed, pulverising the mineral particle size, in order to reduce the daily dose from 32 capsules to 15 capsules a day. Research using EMP+ prior to 2002 will be on the older formula but with the same ingredients (Kaplan et al., 2007). An additional formula, equivalent to EMP+, was released for the general population called CNE (cell and nerve essential nutrition). Two formulas, providing a similar amount of the same nutrients as EMP+, were developed and are meant to be less irritating to the gut, for those who experienced gastrointestinal side effects on EMP+. They are, Daily Essential Nutrients (DEN), marketed towards those with mental or physical health difficulties, and Daily Self Defense (DSD), which is marketed more to the general population. More recently, EMPowerplus Advanced has been created, using the same ingredients but formulated using a unique process called Apex Biosynthesis Conversion

Technology. EMP+ is currently still available in pill form, and as a powder which can be mixed into a blended beverage for those who have difficulty swallowing pills.

In 2011, due to the widespread use of EMP+, and because the recommended dosage of EMP+ exceeds some of the RDAs (recommended daily allowance) for vitamins and minerals, a systematic review was conducted investigating the safety and tolerability of EMP+ for the use within the mental health field (Simpson et al., 2011). The researchers assembled the data from both published and unpublished studies of EMP+ and found no abnormalities in the blood tests or clinically meaningful negative outcomes due to toxicity. Minor, transitory adverse events, were identified, namely headaches and gastrointestinal problems (Simpson et al., 2011). They acknowledge that, although the results support the safety and tolerability of taking EMP+ on its own, combining the formula with psychiatric medications may result in complex interactions and should be monitored closely (Simpson et al., 2011; Popper, 2001).

2.4.1 EMP+ and ADHD

An open-label case series, consisting of 11 children with varying psychiatric disorders, (ADHD, bipolar disorder, anxiety, oppositional behaviours and Asperger's disorder) was conducted investigating the use of EMP+ (Kaplan, Fisher, Crawford, Field, & Kolb, 2004). Five of the nine completers were diagnosed with ADHD, and at the end of at least eight weeks of treatment, significant improvements in attention difficulties and mood were found in all nine completers. The two participants, one with ADHD, who were both on concurrent psychiatric medications, did not complete the trial due to symptom exacerbation (Kaplan et al., 2004); which is consistent with the warning of combining micronutrient formulas with psychiatric medications (Simpson et al., 2011; Popper, 2001).

More recently, there have been studies investigating the effect of micronutrients on psychiatric symptoms in adults with ADHD. A single case study using EMP+ as a treatment for a medication-free 21-year-old female, with bipolar II disorder and ADHD, found significant improvements in mood, anxiety and ADHD symptoms after eight weeks on the micronutrients (Rucklidge & Harrison, 2010). They found that her mood returned to baseline scores and ADHD symptoms worsened when the participant decided to come off the micronutrient, and when EMP+ was reintroduced, the symptoms gradually improved once again. Rucklidge, Taylor and Whitehead (2011) conducted an eight week open-label trial with 14 medication-free adults with ADHD and Severe Mood Dysregulation (SMD). There were significant improvements in inattention, hyperactivity/impulsivity, anxiety, mood, stress and quality of life. Effect sizes were within the medium to very large ranges, and the means of hyperactivity/impulsivity and mood were normalised; however, inattention remained within the clinical range. Follow-up data showed the means across all the primary measures were lower for those who decided to stay on EMP+ compared to those who stopped; those who chose to stay on the micronutrient maintained the changes or displayed further improvements (Rucklidge et al., 2011).

Recently, the first double-blind, randomised, placebo-controlled trial was conducted to investigate the effectiveness of EMP+ on adults with ADHD, who were not currently taking any psychiatric medication, over an eight week period (Rucklidge, Frampton, Gorman, & Boggis, 2014a). A total of 80 participants were randomised to either the EMP+ group (n=42) or the placebo group (n=38); four of the EMP+ and two of the placebo group did not complete the study. The study employed three primary outcome measures to cover the range of ADHD symptoms and included multiple raters (self, observer—someone they lived with—and clinician). There was a significant decrease in ADHD symptoms for those in the EMP+ group, on both self- and observer-rated measures, compared to those in the placebo group.

The EMP+ group had greater overall improvement on the clinician-rated global functioning and ADHD symptoms. Those in the EMP+ group who were moderately to severely depressed at baseline had a greater increase in mood compared to the placebo group (Rucklidge et al., 2014a). A one year follow-up found that participants continued to confer benefits of treatment if they were persistent and stayed on the micronutrient, while the benefits dissipated for those who discontinued use of the supplement (Rucklidge, Frampton, Gorman, & Boggis, 2014b). Although 57% of participants stopped taking the micronutrients, of those who stayed on the micronutrients, 64% fell within the normal range of inattention and hyperactivity/impulsivity at follow-up. This study provides strong evidence for the effectiveness and potential use of micronutrients in the treatment of ADHD in adults; however, replication is required to ensure it is an empirically supported treatment before being recommended to clients.

2.4.2 EMP+ and Mood

Popper (2001) reported utilising EMP+ with a 10 year old boy with bipolar disorder in a naturalistic A-B-A-C-B design. He described the severe temper tantrums significantly improving after two days on the micronutrient and irritability and reported that outbursts were absent after five days. When the micronutrient ran out at two weeks, within 48 hours the temper tantrums had returned. A similar supplement was trialled with moderate improvement, and complete response returned when EMP+ was restarted. Full stabilisation was achieved with EMP+ without the adjunct of psychiatric medication, and no adverse events were observed. Popper (2001), in his clinical practice, investigated the use of EMP+ in 22 preadolescents, adolescents, and adults with bipolar disorder. He found that, among the 22 patients, 19 responded positively to EMP+, with 10 of those showing marked improvement, and that 11 of the 15 patients who had originally been on psychiatric medication when they started taking EMP+ were stable off their medication for six to nine months. Simmons (2002)

found marked clinical improvement in 12 patients, moderate improvement in three patients and mild improvement in one patient, after using EMP+ in adults with treatment-resistant bipolar disorder. 13 patients remained stable on EMP+ alone and, after several weeks, were able to discontinue psychiatric medication (Simmons, 2002).

A case study of a 12 year old boy, with treatment-resistant bipolar disorder, with psychotic features, Generalised Anxiety Disorder (GAD) and Obsessive Compulsive Disorder (OCD), found successful treatment with EMP+, after trying conventional medications for six years (Frazier, Fristad, & Arnold, 2009). After 19 days on EMP+, through slowly decreasing the medication amount, he was completely off all medications. They slowly titrated the micronutrient dose to the optimal 15 capsules a day and he experienced improvements across a number of domains, including overall global functioning, better sleep, and he became more calm and playful (Frazier et al., 2009). An open-label study was conducted to test the feasibility and therapeutic effects of EMP+ on children with bipolar spectrum disorders (Frazier, Fristad, & Arnold, 2012). Seven out of the 10 children completed the eight week study, which had a target dose of 12 capsules a day. Those who dropped out had all experienced difficulty swallowing the pills. Four of the participants took the maximum of 15 capsules a day and the rest reached the target dose of 12 capsules a day. The reported side effects were minor and transient. Intent-to-treat analyses were conducted which showed a decrease of 37% in depression scores and a decrease of 45% in mania scores from baseline to the end of the trial, suggesting the need for randomised placebo-controlled trials using EMP+ in the treatment of bipolar spectrum disorders to verify these initial positive effects (Frazier at al., 2012).

In 2009, a large database analysis investigating the effect of EMP+ on adults diagnosed with bipolar disorder was conducted (Gately & Kaplan, 2009). The database analyses of 358 adults with bipolar disorder showed there was a significant decrease in

symptom severity of 41% after three months and 45% after six months on EMP+, based on baseline severity. They found that reductions in symptom severity were associated with an increase in micronutrient dose and reduction of medication (Gately & Kaplan, 2009).

Rucklidge and colleagues (2010) conducted a database analysis of children and adolescents with Pediatric Bipolar Disorder (PBD) taking EMP+. Of the 120 children and adolescents with PBD, 24% also had ADHD. The data were analysed using Last Observation Carried Forward (LOCF), from three to six months of micronutrient use. At the LOCF, mean symptom severity of bipolar symptoms was 46% lower compared to baseline measures. Only 38% were still taking psychiatric medication at LOCF, compared to 79% at baseline, and at a much lower dose. Data for those with PBD and ADHD showed a 43% decrease in bipolar symptoms and a 40% decrease in ADHD symptoms. The use of EMP+ in the treatment of mood disorders has shown improvements in symptoms, an increase overall functioning, minimal side-effects and a good record of safety as monitored by blood pressure, weight, haematology and biochemistry (Rucklidge et al., 2010).

2.4.3 EMP+ and Anxiety

Kaplan and colleagues (2002) conducted an ABAB design case-study with a medication-free eight year old boy with atypical OCD (severe and pervasive obsessions without discernable compulsions), ADHD, mood lability and explosive rage. This involved a two week baseline phase, 17 week treatment phase, six week withdrawal phase and a five week reintroduction of treatment phase. The treatment phases included the original formulation of 32 capsules of EMP+ daily. Treatment phases were associated with virtually complete remediation of obsessional thoughts as well as significant improvements in mood lability (Kaplan et al., 2002).

Rucklidge (2009), using a similar ABAB design, found on-off control of OCD symptoms using EMP+, in a treatment-resistant medication-free 18 year old male. The author initially followed a standard cognitive behavioural therapy (CBT) approach that included exposure and response prevention, the development of hierarchies, thought challenging, talking back to the obsessive thoughts and developing rewards. This CBT approach originally resulted in a moderate decrease in symptoms; however, almost a year following termination of CBT, there was an increase in OCD symptoms, depressed mood and possible suicide ideation. After receiving information about possible treatment options, the family chose to trial EMP+. The client was up to the optimal dose of 15 capsules a day by the end of the first week and showed significant changes in symptoms within three weeks. By the end of eight weeks, there was a significant reduction in all measures of anxiety. When the client discontinued use of EMP+, to determine whether it was the cause of the reduction or just the passage of time that decreased his anxiety, the measures indicated that the severity of obsessions had increased, there was an increase in anxiety and a decrease in mood. It was recommended that some form of treatment was necessary and the client chose to resume EMP+. By week four his OCD was in remission. Six months later he was still taking EMP+, his OCD was still in remission, there were further improvements in his mood and his low anxiety was maintained (Rucklidge, 2009).

Research examined whether individuals with ADHD who were already taking EMP+ demonstrated more resilience to the stress and anxiety associated with experiencing a 7.1 magnitude earthquake, than those individuals with ADHD who were not taking EMP+ (Rucklidge & Blampied, 2011; Rucklidge et al., 2011). Participants who were already taking EMP+ reported significantly less stress and anxiety symptoms than those who were not taking EMP+, two weeks after the earthquake struck Christchurch, New Zealand on 4th September 2010. The difference between the groups could not be explained by other

variables, such as pre-earthquake emotions, age, gender, ethnicity, SES, personal loss and damage following the earthquake (Rucklidge et al., 2011).

Following the 6.3 magnitude aftershock that struck Christchurch, New Zealand on 22 February 2011, a randomised-control trial compared two different doses of CNE (a product formulated identically to EMP+ but marketed for general use), four or eight capsules daily, to Berocca Performance, one pill a day (Rucklidge et al., 2012). This study was unblinded, had a total of 116 participants that were randomised to one of the three groups, and each participant took the supplement for four weeks. At the end of the four weeks, all groups showed a significant reduction in anxiety, stress and PTSD (post-traumatic stress disorder) symptoms, regardless of the formula or dose. Those taking the higher dose of CNE, a broad-based formula, showed a greater benefit overall than those taking Berocca (Rucklidge et al., 2012). A naturalistic one-year follow-up compared those in the previous study to a nonrandomised control group from the same pool of volunteers (Rucklidge, Blampied, Gorman, Gordon, & Sole, 2014). Overall, there was a decrease in reported symptoms of depression, stress, anxiety, and PTSD symptoms in both groups, suggesting that people generally improve as time passes after a disaster. However, receiving acute nutritional treatment (micronutrients) directly following a disaster may enhance recovery, as those who were treated reported lower stress levels, fewer earthquake related intrusions, and better overall mood and energy levels as compared to the control group (Rucklidge et al., 2014). Research on EMP+, or the equivalent CNE, has shown some positive effects on anxiety. Currently, research investigating the effectiveness of EMP+ on anxiety in children is being conducted by the Mental Health and Nutrition Research Group at the University of Canterbury, New Zealand.

2.4.4 EMP+ and Autism Spectrum Disorder

Mehl-Madrona and colleagues (2010) conducted a naturalistic case-control study comparing two management styles, micronutrient versus standard medication, in 88 children and young adults with Autistic Spectrum Disorder (ASD). Forty-four families wished to avoid pharmaceutical treatment, and were therefore assigned to the micronutrient group, and the other 44 families, identified through file reviews as a match to the micronutrient group, had requested optimization of conventional medication. Both treatment groups saw a significant reduction on the Children's Psychiatric Rating Scale (CPRS), improvements on the Childhood Autism Rating Scale (CARS), and significant decreases in the total scores on the Aberrant Behaviour Checklist (ABC). The micronutrient group showed a greater change on the activity level scale items on the CARS, and exhibited a greater change compared to the medication group on the ABC, specifically statistically significant improvement on irritability and hyperactivity. Although there was no difference in the frequency of self-injurious behaviours for the two groups, the intensity of these behaviours was significantly lower in the micronutrient group at the end of the study as compared with the medication group. The micronutrient group showed significantly greater improvement on the Clinical Global Impressions scale, compared to the medication group which remained constant. Overall, the micronutrient group results showed significant advantages over the medication group in: activity level, social withdrawal, anger, spontaneity with the examiner, irritability, self-injurious behaviours, weight gain and adverse events. Although micronutrients resulted in several statistically significant advantages, the authors highlight three advantages for the medication group: insurance coverage, a fewer number of pills, and less frequent dosing (Mehl-Madrona, Leung, Kennedy, Paul, & Kaplan, 2010). Although there may be a potential bias due to the clinician being un-blinded to the treatment conditions, this study shows

potential in the use of EMP+ to manage behaviours associated with ASDs, and warrants further research as a possible treatment for ASD.

2.4.5 EMP+ and Other Applications

EMP+ has also been investigated for its effectiveness in other applications. Harrison, Rucklidge, and Blampied (2013) proposed, following a single case study, the usefulness of EMP+, and other micronutrient formulas like it, for the treatment of substance dependence and abuse. They found a clear on-off control of cannabis and nicotine use during the micronutrient treatment of ADHD (Harrison et al., 2013). The efficacy of EMP+ has also been researched in childhood psychosis. Rodway and colleagues (2102) reported a significant reduction in anxiety and obsessions, and a complete remission of psychosis, in a case study of an 11 year old boy with a three year history of mental illness. At a four year follow-up the improvements were sustained. They also reported that the cost of the micronutrient treatment was less than 1% of his inpatient mental healthcare (Rodway et al., 2012). EMP+ is a widely researched micronutrient supplement that shows great potential as a treatment option in a variety of mental health disorders.

2.4.6 Summary

ADHD is a debilitating and chronic condition for which current treatments are not effective for at least 30% of those affected. Although there has been an increase in research showing the effectiveness of EMP+ on the reduction of ADHD symptoms in adults with ADHD, research in children is currently limited. With growing popularity of alternative methods, it is essential that we provide the public with treatments that have been empirically tested. By assessing across multiple informants (clinician, self, observer), as well as investigating neurocognitive functioning before and after treatment, we can more clearly evaluate the effect of a nutritional approach to the treatment of this condition. Despite almost

90 years of scientific literature demonstrating the relevance of dietary nutrients for mental health (see Kaplan et al., 2007), less is known about multi-ingredient formulae as compared with conventional medicines. The current study aims to evaluate the effectiveness of EMP+ in treating psychiatric symptoms in children. If positive results are found, we begin to open up another option for families affected by these conditions, as well as beginning to document the importance of nutrition in the treatment of mental health conditions.

2.5 The Current Study

The main purpose of this study is to determine whether it is feasible to use micronutrients with children who suffer from ADHD. The current study set out to determine whether children, between 8 and 12 years old, could take the large number of pills per day required, remember to take them, and be compliant with study protocol. The study is also investigating whether the treatment has an effect on psychiatric symptoms. A single case ABABA design was employed to maximise the time spent on treatment versus off, and to gather replication of treatment within the course of the experiment. A single case design allows the experiment to be more flexible in time, by lengthening the number of data points collected during each phase. The current study aims to establish first, whether the treatment has an impact on symptoms, and also whether any improvement is reversed when the treatment is withdrawn. Micronutrients have not been studied extensively in children with ADHD and it is important to first establish the feasibility alongside effectiveness before launching (and investing) into a randomized, double-blind, placebo-controlled trial. As this study is examining the effectiveness of micronutrients in children, while much of the previous ADHD research has been in adults, identifying the optimal dose is important.

It was hypothesised that this study will find the following:

1. The micronutrient formula would be associated with a decrease in ADHD behaviours, and there would be improvements in overall general functioning associated with taking the micronutrient
2. ADHD behaviours would return to baseline, or near baseline symptom severity when the micronutrients were withdrawn, and there would be a regression in overall functioning
3. Improvements with overall general functioning, and a decrease in ADHD behaviours, would occur when the micronutrient formula is reintroduced, replicating the improvements found during the initial on phase
4. There would only be minor, if any, side effects related to taking the micronutrient formula
5. Children would be able to swallow 15 pills a day
6. Children who continued to take the micronutrients would continue to show a benefit at the six month follow-up compared to the children who discontinued micronutrient use

Chapter 3: Method

3.1 Participants

Participants were recruited in Canterbury, New Zealand from September 2011 to January 2013 through on-going research files at the University of Canterbury, new referrals from general practitioners, private psychiatrists/psychologists, referrals from the Canterbury District Health Board, as well as through advertisements in the local paper and online community help pages. Out of 25 referrals, 14 children, aged 8-12 years old at their initial visit, participated in this study. The mean age of participants was 10.18 years and two (14%) were female. All participants met criteria for ADHD defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text-Revision (DSM-IV-TR) (American Psychiatric Association, 2000). After complete description of the experimental nature of the trial, as well as a review of conventional treatments available, all participants, along with their parent/caregiver, provided their written consent/assent before commencing the trial. The study was approved by both the National Upper South A Health and Disability Ethics Committee and the Human Ethics Committee at the University of Canterbury. The trial was registered with the Australia and New Zealand Clinical Trial Registry (ACTRN12612000645853).

3.1.1 Diagnostic Protocol for ADHD

All participants received an assessment for ADHD by a PhD level Clinical Psychologist. This process was completed at the University of Canterbury, Psychology Department, through the use of clinical interviews, based on the DSM-IV-TR and the *Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version* (K-SADS-PL), with the participant and their parent/caregiver. The *Conners' Parent Rating Scale-Revised: Long Form* (CPRS-R:L) (Conners et al., 1998), was also used to screen for the

presence of ADHD symptoms, as well as providing an appraisal of the severity of such problems. Nine (64%) of the participants had previously received a diagnosis of ADHD by other mental health professionals.

3.1.2 Inclusion Criteria

As part of the criteria, participants were between the ages of 8-12 and were required to have been off medication for at least 4 weeks prior to the start of the study. Participants were discouraged from coming off a conventional method of treatment that was working in order to participate in the study. Participants were required to be able to eat at least a snack three times a day, so the capsules were not ingested on an empty stomach. Participants needed to meet criteria for ADHD based on the K-SADS-PL diagnostic interview, alongside T scores above 70 on one or more of the three DSM-IV subscales of the Parent Conners' Rating Scales.

3.1.3 Exclusion Criteria

Exclusion criteria included: children unwilling or unable to have their blood taken, children with a neurological disorder involving brain or other central functioning or any serious medical condition that required intervention during the duration of the study. Children with abnormal blood results, and children commencing participation in any new forms of therapy or alternative medicines at the same time of the trial, were also excluded. One child was excluded due to abnormal blood work (low white blood cell count, low lymphocyte count, high activated partial thromboplastin time for coagulation tests, and low iron), one child was excluded due to being unable to have blood taken, three were excluded due to currently being on medication, one chose to buy the supplement independently, and four families who enquired about the study, did not respond to emails or phone contact to arrange a meeting to discuss the study.

3.2 Measures

3.2.1 Demographic Variables

Demographic variables were collected from each participant's family. These variables included: ethnic group, marital status, occupation, partner's occupation, and yearly household income. Using the New Zealand Socioeconomic Index of Occupational Status (NZSEI; Milne, Byun, & Lee, 2013), an estimate of socioeconomic status (SES) was obtained, scores ranged from 10 to 90, based on the individual's occupation, with a higher number indicating a higher SES.

3.2.2 Screening:

The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) is a semi-structured diagnostic interview, for school aged children (6-18 years), designed to assess current and past episodes of psychopathology according to *DSM-IV* criteria. The K-SADS-PL is administered by a trained clinician to the parent/caregiver and the child. The K-SADS-PL includes five diagnostic supplements (affective disorders, psychotic disorders, anxiety disorders, behavioural disorders and substance abuse and other disorders) that are administered depending on the Screen Interview results. The Screen Interview reviews primary symptoms of diagnoses that are assessed using the K-SADS-PL. The K-SADS-PL has been found to have high inter-rater reliability (98%) and excellent test-retest reliability (Kaufman, et al., 1997).

3.2.3 Clinician-Rated (completed at every visit)

Clinical Global Impressions Scale (CGI) (Guy, 1976). The CGI is a standardised assessment tool that consists of three subscales: 1) severity of illness; 2) global improvement and 3) an overall clinical impression. It was modified for use with ADHD patients. Severity

of illness assesses the clinician's impression of the participant's state of illness during that assessment period. These scores range from 1, being normal, not ill, to 7, being very severely ill. Global improvement assesses the participant's improvement from the beginning of the trial, their baseline measure. This scale ranges from 1, being very much improved, to 7, being very much worse. The overall clinical impression takes into consideration total clinical experience with the participant and the score reflects the intensity of the disorder in the participant at that assessment time. The score ranges from 1, being markedly improved, to 7, being markedly worse.

Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). The CGAS is based on an adaption of the Global Assessment Scale (GAS) for adults (Endicott, Spitzer, Fleiss, & Cohen, 1976; Rush, et al., 2008). It is a unidimensional, or global measure of social and psychiatric functioning for children 4-16 years old. The CGAS is used by the clinician to assess the overall severity of disturbance in children. The CGAS is a single numerical scale from 1 (most impaired) to 100 (healthiest) that is separated into 10-point sections indicating the child's level of functioning. From the basis of the descriptors a score is given regarding the child's social and symptomatic functioning. For example, a child who still has some difficulty in a single area but is generally functioning pretty well, would receive a score between 61-70. Those individuals scoring at the lower end of the scale, 1-10, indicate a need for constant supervision, whereas those who score above 70 are considered to be within the normal range. The CGAS has been found to have a test-retest reliability around 0.85 and high joint reliability of 0.83-0.91 in research settings (Rush, et al., 2008).

Young Mania Rating Scale (YMRS; (Young, Biggs, Ziegler, & Meyer, 1978): The YMRS is a clinician administered measure designed to assess the severity of manic symptoms as well as measuring the effect of treatment on mania severity. The YMRS is a checklist that includes 11 items ranked on a scale of 0-4 or 0-8. The four items that are scored

0-8, twice the range of the other seven, are given this range to compensate for the poor cooperation that is seen in severely ill participants. The YMRS includes items such as elevated mood, increased motor activity energy, sleep, irritability, speech (rate and amount), language-thought disorder, and disruptive-aggressive behaviour, which are all points of interest when dealing with the ADHD population. A total score ranging from 0 to 60 is obtained. Scores of 13 on the YMRS indicate minimal severity, 20 for mild severity, 26 for moderate severity and 38 for severe illness. As these scores are based on a small sample size it is important to interpret them cautiously (Young, et al., 1978). This scale has also been tested for use in children 5-17 years old (Youngstrom et al., 2002). Correlations for each individual item and the total score range from 0.41 to 0.85 and reliability for total scores of 0.93 was found (Young, et al., 1978). The validity of the YMRS has been tested through comparison with other scales: it has a correlation of 0.89 with the Petterson Mania Scale, 0.88 with the global mania rating scale, and 0.77 with the Bech-Rafaelsen Mania Scale (Rush, et al., 2008).

Children's Depression Rating Scale (CDRS; (Poznanski, Cook, & Carroll, 1979) is a 16-item measure, used for children aged 6-12 years old, measuring the severity of depression. Assessment information is based on interviews with the child and parent/caregiver. The CDRS items are measured on 3, 4 and 5 point scales. It offers an effective way to diagnose depression in children and monitor treatment response (Poznanski, Cook & Carroll, 1979; Shanahan, Zolkowski-Wynne, Coury, Collins, & O'Shea, 1987). Scores range from 0 to 61. A score of zero on an item indicates that information was unable to be obtained. A child who is behaving within a normal range of functioning across all items on the CDRS will receive a score of 15 (one point per item, with reversal of affect not included in total score). A score of 30+ indicates significant depression and scores between the 20 to 30 ranges indicate borderline depression.

3.2.4 Parent-Rated (CPRS-R:L & SDQ completed at switch points; ADHD-RS-IV & CMRS completed at weekly visits)

Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L) (Conners et al., 1998) contains 80 items and 10 subscales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Psychosomatic, Conners' Global Index, ADHD Index and DSM-IV Symptom Subscales. Parents/caregivers are asked to answer the items while considering their child's behaviour over the last month by using a 4-point Likert scale with 0= not very true at all to 3= very much true. All scores can be converted to T-scores based on gender and age of the child. T-scores above 65 indicate clinical elevations. High internal consistency coefficients for the CPRS-R:L subscales have been found. For the DSM-IV Hyperactive-Impulsive subscale a Cronbach α of 0.91 for boys and 0.87 for girls was found. Cronbach α values for the Oppositional subscale were 0.91 for boys and 0.90 for girls. Test-retest reliabilities over a six-week interval were 0.85 for the Hyperactivity subscale and 0.57 for the Oppositional subscale. The CPRS-R:L's validity has been calculated to have 92% sensitivity, 95% specificity, 94% positive predictive power and 93% negative predictive power (Rush, et al., 2008).

Strengths and Difficulties Questionnaire (SDQ) is a brief screening questionnaire for child mental health problems that is suitable for parents/caregivers and teachers to fill out (Goodman, 1997). The SDQ screens for positive and negative psychological attributes, measuring both problem behaviour and competencies at an early age (Stone et al., 2010). The 25 items are divided between 5 scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour. Total Difficulties Score ranging from 0-13 fall within the normal range, 14-16 borderline range and 17-40 abnormal range. The SDQ also provides an impact score which is derived from ratings based on how much their present difficulties are interfering with their lives. The score is

obtained using a 4-point likert scale from 'Not at all' to 'A great deal' in four different categories for the Parent version: home life, friendships, classroom learning and leisure activities. An Impact Score of 0 is normal, 1 is borderline and 2 or greater is abnormal. Research has shown that the SDQ has acceptable internal consistency for the total difficulties (0.80; range 0.53-0.84) and impact score (0.81; range 0.69-0.87). The SDQ total difficulties showed good test-retest reliability (0.76; range 0.72-0.86); however, the impact score has been shown to be less reliable over time (0.57). In terms of concurrent validity, the SDQ total difficulties score were shown to be highly correlated (0.76) and impact score moderately (0.46) correlated with the Child Behavior Checklist (CBCL) (Stone, Otten, Engels, Vermulst, & Janssens, 2010).

ADHD Rating Scale-IV (ADHD-RS-IV) is a norm referenced checklist that measures the symptoms of ADHD according to DSM-IV criteria (DuPaul, Power, Anastopoulos, & Reid, 1998). The ADHD-RS-IV is an 18-item questionnaire that provides clinicians with a means of gathering information from parents/caregivers and teachers regarding the frequency of certain behaviours. The scale consists of two subscales: inattention and hyperactivity-impulsivity. Scores falling at and above the 93rd percentile (total score of 20 and higher for 8-13 year olds) are optimal for clinical cutoff. Scores that fall at the 85th percentile (total score of 14 for 8-10 year olds and 16 for 11-13 year olds) and lower are more likely to represent a normal population. The ADHD-RS-IV has been found to have high internal consistency (0.92 for total; 0.86 for the inattention subtype; 0.88 for the hyperactivity-impulsivity subtype) and test-retest reliability (0.85 for total; 0.78 for inattention; 0.86 for hyperactivity-impulsivity). Moderate inter-rater agreement was found between parents and teachers (0.41 total; 0.45 inattention; 0.40 hyperactivity-impulsivity), suggesting that characteristics of ADHD may be different across the home and school environment (DuPaul, Power, Anastopoulos, & Reid, 1998; Collett, Ohan, & Myers, 2003).

Child Mania Rating Scale, Parent Version (CMRS-P) is a 21-item screening tool for pediatric mania that is based on DSM-IV criteria that is designed to be completed by a parent/caregiver. It incorporates age-specific items applicable to ages 5 to 17 years. The CMRS-P is worded in a way that makes it easy for parents/caregivers to understand, even if they have limited reading ability (Pavuluri, et al., 2006). Items are answered on a four-point Likert scale ranging from O-Never/Rare, 1-Sometimes, 2-Often and 3-Very Often. Scores range from 0-63, with a cutoff score of 20 for possible pediatric mania. Internal consistency and retest reliability were 0.96. Correlation of the CMRS-P with the Washington University Schedule for Affective Disorders and Schizophrenia Mania Rating Scale, and the Young Mania Rating Scale was high (0.78-0.83) (Pavuluri, et al., 2006).

3.2.5 Child-Rated (completed at every visit)

Side Effects Questionnaire is a screening tool to assess for any possible side effects that may have been experienced between visits. The questionnaire covered the main reported side effects such as: nausea/vomiting, stomach aches, skin rash, headaches and dry mouth. Blank spaces were left for the child and/or parent/caregiver to write down if they were experiencing something other than these more commonly reported side effects. Scores were recorded across a five-point likert scale ranging from zero problems to major problems.

The Measure Yourself Medical Outcome Profile (MYMOP) (Paterson, 2004) was adapted to cover hyperactivity, attention, impulsivity, mood (low and high) and sleep. The child rated themselves on each item, on a 5-point likert scale, from zero problems to major problems. At the initial meeting, the child and parent/caregiver were asked if they wished to monitor any other specific behaviours (e.g. arguing with siblings; homework compliance; getting to school on time, etc.) and they were written down and monitored as well.

3.2.6 Teacher-Rated (completed at baseline and switch points)

Conners' Teacher Rating Scale-Revised: Long Form (CTRS-R:L) (Conners et al., 1998) contains 59 items and includes the same subscales as the CPRS-R:L, except the Psychosomatic subscale, which is only on the CPRS-R:L. Teachers were asked to consider the child's behaviour over the last month across the various items assessing child behaviour, using a 4-point Likert scale with 0= not very true at all to 3= very much true. All scores can be converted to T-scores based on gender and age of the child. T-scores above 65 indicate clinical elevations. The CTRS-R:L has high internal consistency coefficients with a Cronbach α of 0.94 for boys and 0.90 for girls on the Hyperactive-Impulsive subscale and 0.92 for boys and 0.91 for girls on the Oppositional subscale. Test-retest reliabilities for teachers completing the CTRS-R:L over a six-week period were 0.72 for the Hyperactivity subscale and 0.86 for the Oppositional subscale for the subscales has been found. The CTRS-R:L's validity has been calculated to have 97% sensitivity, 82% specificity, 84% positive predictive power and 97% negative predictive power (Rush, et al., 2008).

Strengths and Difficulties Questionnaire (SDQ) is a brief screening questionnaire for child mental health problems that is suitable for parents and teachers to fill out (Goodman, 1997). The teacher version serves the same function as the parent version, dividing the 25 items into the same 5 scales. Total Difficulties Score ranging from 0-13 fall within the normal range, 14-16 borderline range and 17-40 abnormal range. To generate an impact score from the teacher version, only two areas, peer relationships and classroom learning are included. Research has shown that the teacher version of the SDQ has acceptable internal consistency for the total difficulties (0.82; range 0.62-0.85) and impact score (0.85). The SDQ total difficulties showed good test-retest reliability (0.84; range 0.55-0.90); however, the impact score showed to be less reliable over time (0.68). In terms of concurrent validity, the SDQ total difficulties score were shown to be highly correlated (0.76) and impact score moderately

(0.53) correlated with the Child Behavior Checklist (CBCL) (Stone, Otten, Engels, Vermulst, & Janssens, 2010).

3.2.7 Neuropsychological Task (completed at baseline and switch points)

Conner's Continuous Performance Test (CPT-II) (Conners, 2000). The CPT-II is used as a measure of complex cognitive functioning, including attention, visual-motor speed, visual-motor integration, hyperactivity and impulsivity. The age range for the CPT-II is from 6 years of age and up. The task uses a short practice exercise just prior to the administration of the full test. This helps ensure that participants fully understand the task before continuing. The full test takes 14 minutes to complete and requires children to respond to the computer screen by pressing a space bar for every letter presented except for the letter 'X'. The inter-stimulus intervals are 1, 2 and 4 seconds, with a display time of 250 milliseconds. The computer generates an output that includes number of omissions (believed to be related to inattention and reflects the number of targets the individual did not respond to), number of commissions (believed to be a measure of impulsivity and reflects the number of times the individual responded to the non-target stimulus), reaction time, variability of reaction time, signal detection parameters (*d'*- a measure of attentiveness, that is how well the individual discriminates between targets and non-targets, and β – a measure of risk taking, that is how often the individual tends to respond, a higher score is indicative of less risk taking). To begin the interpretation of the CPT-II, T-scores and percentages are available. T-scores represent the score of the individual relative to a normative group who are within the same age group and the same gender as the participant. Percentages represent the percentage of a comparison group who scored lower than the individual's score. T-scores and percentiles relating to two separate groups, the general population (non-clinical) and an ADHD clinical sample (clinical) are available. A confidence index provides information regarding whether the participant closely matches the clinical population or the non-clinical population is also provided. These

scores are all based on respondent's gender and age. Epstein et al., (2004) found the CPT demonstrated the ability to distinguish clinical from non-clinical samples of children with ADHD.

3.3 Design and Procedure

The current study was an open-label withdrawal design. Recruitment and data collection took place between July 2011 and May 2014. Over the course of the study 14 participants visited the University fortnightly for a total of six months, as well as a follow-up visit six months later. Participant's parents/caregivers completed baseline measures of ADHD, mood, and overall functioning, and a demographic questionnaire. Measurements of ADHD, mood, and side effect monitoring were completed at each fortnightly visit. The core assessment measures, from both parent/caregiver and teacher, were collected, and CPT completed, at switch points: Baseline, On1 (after first 8 weeks on the micronutrient), Off1 (end of first withdrawal phase of 4 weeks), On2 (after the second 8 weeks on the micronutrient), Off2 (after the final 4 weeks off the micronutrient) and at the six month follow-up. The number of pills required for a response was assessed by beginning participants at a smaller than recommended dose (8 pills taken as 4 twice daily) and if there was no indication of response by week four, the participant was offered an increase of up to 15 pills a day (5 pills taken 3 times a day). See Figure 1 for an illustration of the study design.

Once informed consent was completed, all participants were seen individually in a quiet laboratory within the Psychology Department at the University of Canterbury. Regardless of whether the child had been previously diagnosed, participants were first assessed for ADHD using the K-SADS-PL (Kaufman, et al., 1997) by a senior clinical psychologist, which took between one and a half and two hours total, to determine their suitability for the trial. Information sheets and consent forms are included in Appendix B-D.

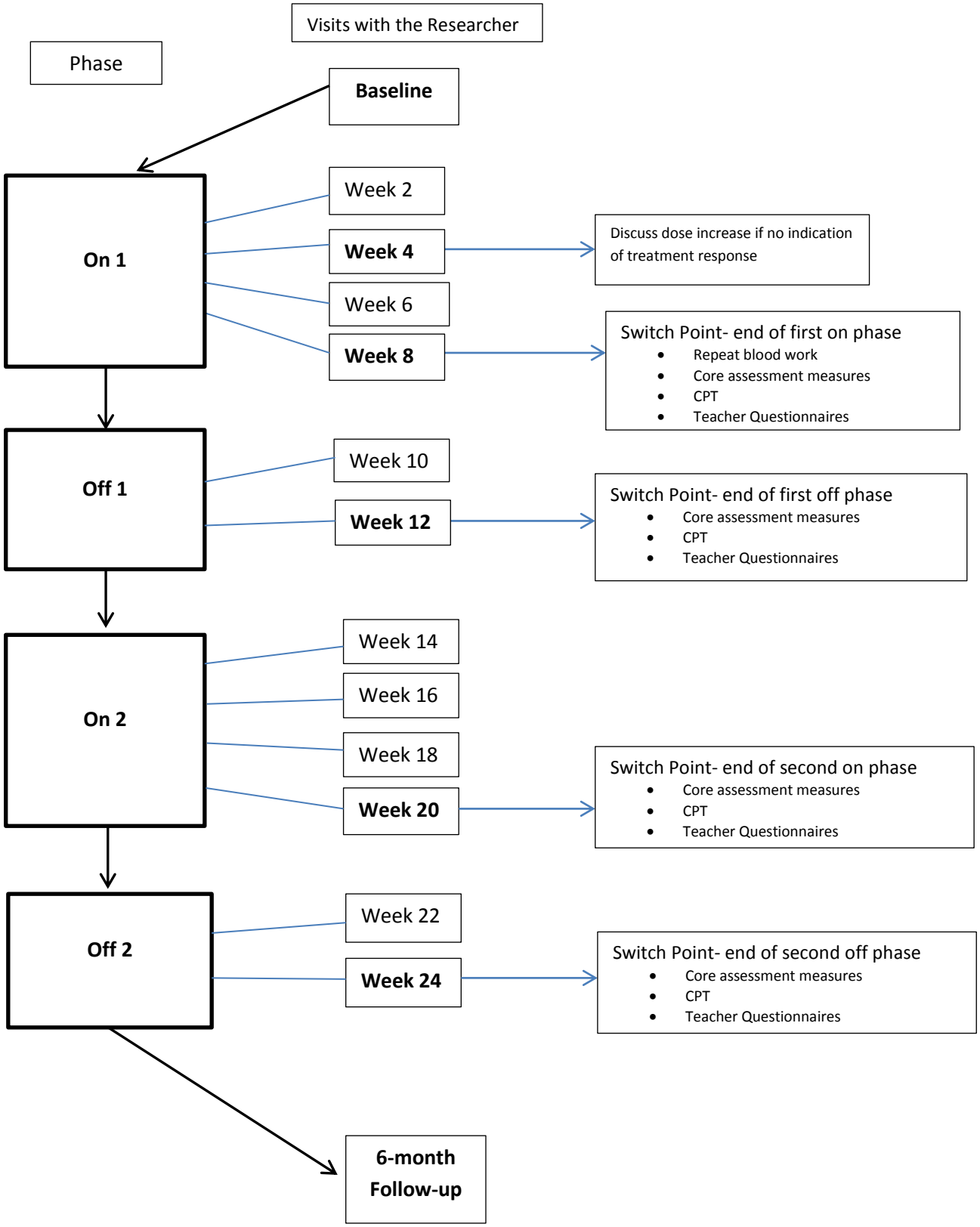


Figure 1. Flow diagram illustrating the design of the study

3.3.1 Pill Swallowing Video

Once consent was obtained, as the study required children to swallow a substantial number of pills, each participant watched a 9 minute segment, 'The New Method of Swallowing', of a training video 'Better than a spoonful of sugar' (http://research4kids.ucalgary.ca/pillswallowing). This video was developed to help people with pill swallowing difficulties discover new ways to swallow pills, based on head posture and placement (Kaplan, et al., 2010). After the video was watched, the participant was given a sheet with the different head positions, a bottle of water and some small candies to practice with. They practiced swallowing the candies in each direction and recorded on the sheet, by circling a smiley face, how comfortable or uncomfortable that head position was for swallowing pills. Each participant was offered a copy of the video to watch at home and additional copies of the data sheet so they could keep track of their preferred head position. Some children did not require practice, others required the full two weeks of practice in order to become fully comfortable with the procedure. For those who were unable to swallow the pills, even after the two week period when the pill swallowing exercise was completed, a powder form that could be incorporated into a smoothie or milkshake just prior to them drinking it was offered. Two participants opted for the powder version after difficulty swallowing pills, however, one switched to pills halfway through the study. Both participants were offered a choice between the chocolate mint and berry flavours and chose their preferred flavour.

3.3.2 Safety Data

Once the diagnosis of ADHD was confirmed, participants underwent baseline haematological and biochemistry screening before beginning the trial. The screening included testing of: thyroid function, serum lipids, blood clotting, iron, copper, zinc, prolactin and

fasting glucose. All lab results were monitored by a physician. Blood screening was also completed post 8 weeks (at the end of the initial micronutrient phase). The blood work was conducted to determine whether there were any abnormalities that may preclude participation in the trial (e.g. Wilson's disease) and also allowed for monitoring of safety of the micronutrients for each participant. As part of the baseline screening, previous assessments were reviewed as necessary (medical records, psychological assessments) and questionnaires were completed by the teachers with parental consent. Together with the blood work and psychiatric interview, the participants' caregivers completed several questionnaires (CPRS-R:L; SDQ; CMRS-P, and ADHD-RS-IV), as well as teacher completed questionnaires (CTRS-R:L; SDQ), to gather a baseline level of symptoms. Interviewer rated measures were also administered at baseline, before they started the study (CGAS, CGI, CDRS, and YMRS). See Appendix E for the schedule of events. The baseline assessment was followed by an open-label trial using EMP+ for eight weeks.

3.3.3 Experimental design

The present study used an ABABA repeated measures design replicated across the 14 participants in order to evaluate the effectiveness and feasibility of treating ADHD behaviours with a micronutrient formula. Baseline (A) data was collected for each participant before they began the study. Participants then began taking the micronutrient formula for eight weeks during the first on phase (B), which was followed by the first four week off phase (A). Upon completion of this phase participants began taking the micronutrient formula for the final eight week on phase (B), which was followed by the final four week off phase (A).

Titration and dosing

The EMP+ capsules were donated by Truehope Nutritional Support Ltd. (Raymond, Alberta, Canada). The ingredients of EMP+ as well as the recommended upper limits for children aged 8-12 years old are included in Appendix F. The preferred method of administration was to have the child swallow the micronutrient formula in pill form.

A pill box was given to each participant and the initial eight week period began once the first capsule was taken. Participants were instructed to begin by taking four capsules per day divided into two doses (i.e. 2, 2). They were instructed that on the fourth day to increase to eight capsules per day, divided into two doses (i.e. 4, 4). Participants were advised to take the capsules with plenty of water and food to reduce the potential of gastrointestinal upset and headaches. Any adverse effects experienced were collected at each visit with the child and caregiver. After the week four assessment, and depending on response (if the response was moderate to large based on CGI, no change was made to dose, if there was no change or minimal change, a dose increase was recommended), caregivers were given the choice, along with input from the participant, to either give the participant the recommended therapeutic dose (15 capsules taken as five capsules three times a day) for the remainder of the trial or to stay at the lower dose of eight capsules a day. For some, the increase was slower and this was recorded at their fortnightly assessment. Dosage could also be reduced at any time due to adverse side effects, upon discussion with the principal investigator. For the remainder of the trial, during the on phases, participants took a maximum of 15 capsules per day, divided however they liked, but preferably in three doses of five capsules each, with at least two hours between doses.

During the trial, participants were monitored fortnightly. Capsules were dispensed at these assessment times and participants, as well as caregivers, were asked to monitor

compliance of taking the capsules. At each fortnightly visit, the participant's overall functioning was reviewed using a variety of measures (YMRS, CDRS, CGI, CGAS). Participants were instructed to return the bottles with remaining pills at each appointment, in order to monitor adherence. Participant compliance was monitored by recording any missed doses and the number of pills consumed at this dose. Side-effects and non-related medical problems were identified and monitored at each visit and blood pressure and weight were monitored monthly. Towards the completion of the initial eight week period on the capsules, participants were instructed to have their blood work repeated and then informed to stop taking the capsules. The battery of questionnaires completed at baseline was repeated to assess for change in severity of symptoms.

Participants then entered the first off phase of four week duration. Participants were monitored fortnightly throughout this phase and at the completion of the first off phase, the battery of questionnaires (CPRS-R:L; SDQ; CMRS-P and teacher rated CTRS-R:L; SDQ) was administered again. After the first four week off phase, participants then entered the second on phase. Participants were instructed to slowly titrate back to the optimal dose established in the first phase (ie between 8 and 15 capsules) and remain at that dose for the 8 weeks of the second on phase. During this second on phase, participants continued to be monitored at the University fortnightly and at the end of this phase the battery of questionnaires initially completed was repeated.

Participants then entered the last phase of the study, the second off phase with a maximum duration of four weeks. Participants continued to be monitored fortnightly during this time and at the end of this phase completed the battery of questionnaires once again. Due to a significant relapse in symptoms during the second off phase, in addition to requests from the caregiver, five participants began taking EMP+ before the four week off phase was completed (participant number 3: 1 week off, participant number 9: 2 weeks off, participant

number 10: 2 weeks off, participant number 12: 3 weeks off, and participant number 13: 2 weeks off). The battery of questionnaires completed to assess change were administered before the participant chose to begin taking the capsules again and this point was considered the end of their second off phase.

Participants were asked to not begin any therapies, medication or alternative medications during the course of the study. Participants were informed that if any medication needed to be taken during the course of the study that they let the investigator know in order to determine whether the medications (i.e. paracetamol for pain relief, Robitussin® for sore throat) interfered with the effectiveness of the micronutrients. All clinical interviews and fortnightly meetings were conducted within the Psychology Department at the University of Canterbury. A summary of the assessment was shared with the participant's caregiver, the participant's General Practitioner as well as the referring clinician/service. The participant's caregiver was given a 10-dollar petrol voucher to cover the cost of travelling to and from University. The EMP+ capsules/powder were provided at no cost to the participant.

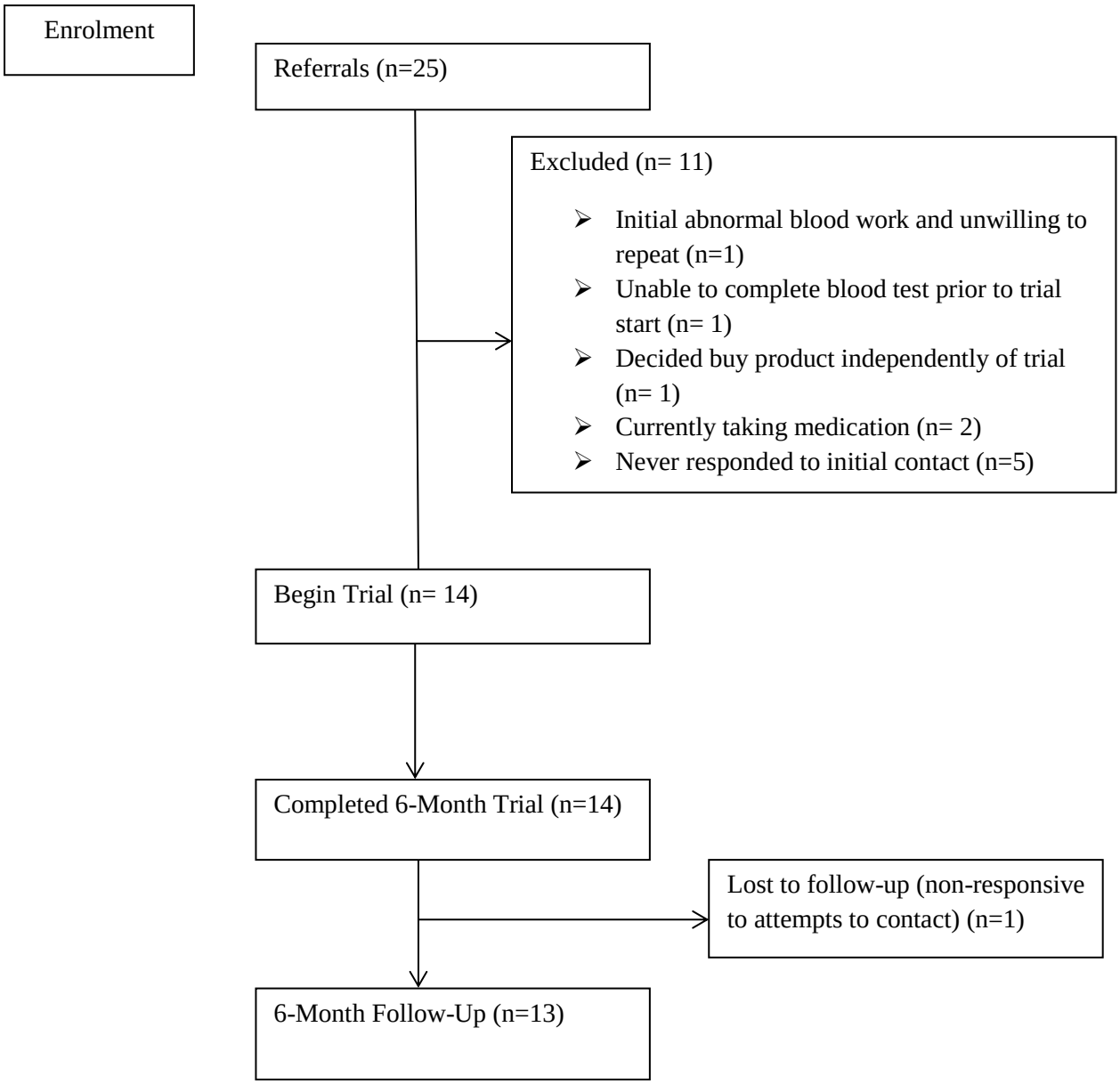


Figure 2. Consort flow diagram indicating participant inclusion/exclusion, completion, and dropout over the course of the study.

3.3.4 Follow-Up Data

After approximately six months, regardless of whether the participants had chosen to stay on the micronutrients or decided to discontinue, the participants were invited to take part in a six-month follow-up phase (see Appendix G). A consent form was completed and 13 out of the 14 participants attended a follow-up appointment. One participant was not contactable. The participants current functioning was assessed through an interview and the use of the following measures: CPRS, SDQ, CMRS, CDRS, YMRS, CGAS, CGI, and MYMOP. The participant and the caregiver were asked whether they continued to take the micronutrient, why they chose to stay on or come off the micronutrients, and about any side-effects they were experiencing from taking the capsules. If they had chosen to come off the micronutrients, and another treatment was chosen, this information was collected as well.

3.4 Data Analysis

The current research is an open-label withdrawal design. Time series graphs were used to demonstrate the trend, variability, immediacy of effect and consistency of data patterns across similar phases (i.e. on1 and on2), for each individual participant's ADHD behaviours, using the ADHD Rating Scale. Modified Brinley Plots were used to display individual changes across the different phases (Blampied, 2007, 2014; Jacobson, Follette, & Revenstorf, 1984; Sobell, Sobell, & Gavin, 1995), using the parent outcome measures (CPRS and CMRS) and the clinician rated outcome measures (YMRS, CDRS and CGAS). Paired sample *t*-tests, with *p*-values, were used to compare group means, and Cohen's *d* effect sizes (Cohen, 1992) were used to detect the size of the effect. Mean differences and 95% confidence intervals were used to show the change across times.

Chapter 4: Results

Demographic characteristics as well as current and past psychiatric diagnoses for each participant in the final sample are presented in Table 3. The male to female ratio reflects the preponderance of males diagnosed with ADHD compared to females in the general population. The percentage of participants who reported at least one other psychiatric disorder is consistent with the ADHD literature. Fifty-seven percent of participants were currently experiencing at least one co-occurring psychiatric disorder, with 10 (71%) of the participants experiencing at least one co-occurring psychiatric disorder in the past. Nine (64%) participants had trialled psychiatric medication prior to beginning the study.

Table 3

Demographic Characteristics, Current and Past Diagnoses of Final Sample and Previous Psychiatric Medications

Participant	Age at Start of Study	Gender	Ethnic Origin	Estimated Household Income	Past Medications	Past Diagnosis	Current Diagnosis
1	9	M	NZ European/Pakeha	More than $100,000	None	None	ADHD Inattentive Type, ODD, Tics (vocal)
2	11	M	Italian European	$40,000 to $60,000	None	ADHD Combined Type, ODD, SAD, Enuresis, Tics (motor)	ADHD Combined Type, ODD, SAD, Enuresis
3	12	M	NZ European/Pakeha	More than $100,000	Focalin, Methylphenidate, Atomoxetine	ADHD Combined Type, MDD, Enuresis	ADHD Combined Type, PTSD (earthquake related),Social Anxiety,
4	9	M	NZ European/Pakeha	$60,000 to $80,000	Methylphenidate	ADHD Inattentive Type, Enuresis	ADHD Inattentive Type, Enuresis
5	8	M	NZ European/Pakeha	$60,000 to $80,000	None	ADHD Combined Type, ODD, Enuresis	ADHD Combined Type, Enuresis
6	9	M	NZ European/Pakeha	$40,000 to $60,000	Methylphenidate, Fluoxetine	ADHD Combined Type, Enuresis, PDD	ADHD Combined Type, Enuresis, PDD
7	8	M	NZ European/Pakeha	More than $100,000	None	ADHD Inattentive Type	ADHD Inattentive Type
8	11	F	European	$60,000 to $80,000	Methylphenidate	ADHD Inattentive Type	ADHD Inattentive Type
9	8	M	NZ Maori	$20,000 to $40,000	Methylphenidate, Dexamphetamine	ADHD Combined Type	ADHD Combined Type
10	12	M	NZ European/Pakeha	$40,000 to $60,000	Methylphenidate	ADHD Combined Type	ADHD Combined Type
11	10	M	NZ European/Pakeha	More than $100,000	None	ADHD Inattentive Type, ODD, Dysthymia	ADHD Inattentive Type, ODD, Dysthymia
12	8	M	European	$60,000 to $80,000	None	ADHD Combined Type	ADHD Combined Type
13	7	M	NZ European/Pakeha	$40,000 to $60,000	None	ADHD Combined Type, ODD, PTSD (earthquake related)	ADHD Combined Type, ODD
14	10	F	NZ European/Pakeha	More than $100,000	None	ADHD Inattentive Type	ADHD Inattentive Type

Note. ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, SAD = Separation Anxiety Disorder, MDD = Major Depressive Disorder, PDD = Pervasive Developmental Disorder, PTSD = Post Traumatic Stress Disorder

4.1 Statistical Analyses

The following section provides a methodological description of the rationale and methods used to analyse the data in the current study. The primary outcome measures defined a priori were the ADHD rating scales (CPRS-R:L, ADHD-RS-IV, CTRS-R:L), the CGI, and the parent and teacher rated SDQ. Secondary outcome measures were the CGAS, CDRS, YMRS, CMRS, and the CPT-II. The data from this study were analysed both using conventional null-hypothesis statistical tests and more ideographically, using modified Brinley Plots (Blampied, 2007; 2014; Jacobson, Follette, & Revenstorf, 1984; Sobell, Sobell, & Gavin, 1995; Stunkard & Penick, 1979). Results will be presented phase by phase, as specified by the reversal design, namely baseline, on micronutrients (On 1), withdrawal of micronutrients (Off 1), reintroduction of micronutrients (On 2) and final withdrawal of micronutrients (Off 2). First, time series graphs will demonstrate individual patterns of treatment response and treatment withdrawal on ADHD behaviours. Modified Brinley plots will then be used to show individual changes across experimental phases (Blampied, 2007, 2014; Jacobson et al., 1984; Sobell et al., 1995). Tables will display individual changes in outcome measures across phases (Table 5), group mean comparisons between baseline and consequent phases (Tables 8 & 9), and neuropsychological comparisons (Table 10). Finally, further analyses demonstrating clinical impression (Figure 8), severity of illness (Figure 9) and percentage of overall change (Table 12) will be presented.

4.2 Time Series Data

The primary focus of the current research was to assess change in ADHD behaviours, as measured by the ADHD Rating Scale-IV (ADHD-RS-IV) and the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L). The ADHD-RS-IV was completed fortnightly and the CPRS-R:L was completed at baseline and switch points. They both contain identical

questions on the ADHD scales; the ADHD-RS-IV is a condensed version of the CPRS-R:L, resulting in the same ADHD total score. Results from both the ADHD-RS-IV and the CPRS-R:L will be used to visually portray the ADHD behaviours across the study. A visual analysis of this data is presented in single-case ABAB format, attending to the level of ADHD problem behaviours, trends over time and variability within each case. The cases are presented in the following order: from the shortest time spent on the first on phase, to the longest time spent on the first on phase; and then grouped as closely with other participants who had similar time lengths at the consecutive phases. Table 4 displays the number of weeks a participant spent in each phase of the study.

Table 4
Number of Weeks Spent During Each Phase

Participant #	Baseline	On 1	Off 1	On 2	Off 2
1	8/31/11	10	4	12	4
2	9/1/11	10	16	10	4
3	10/27/11	12	3	12	1
4	2/28/12	10	4	10	4
5	3/14/12	10	4	10	4
6	4/11/12	8	6	8	4
7	4/12/12	10	4	8	4
8	4/17/12	8	6	8	4
9	6/19/12	10	4	6	2
10	8/7/12	8	4	6	2
11	7/25/12	10	4	8	4
12	9/21/12	8	4	8	3
13	9/13/12	8	2	10	2
14	24/01/13	8	6	8	4

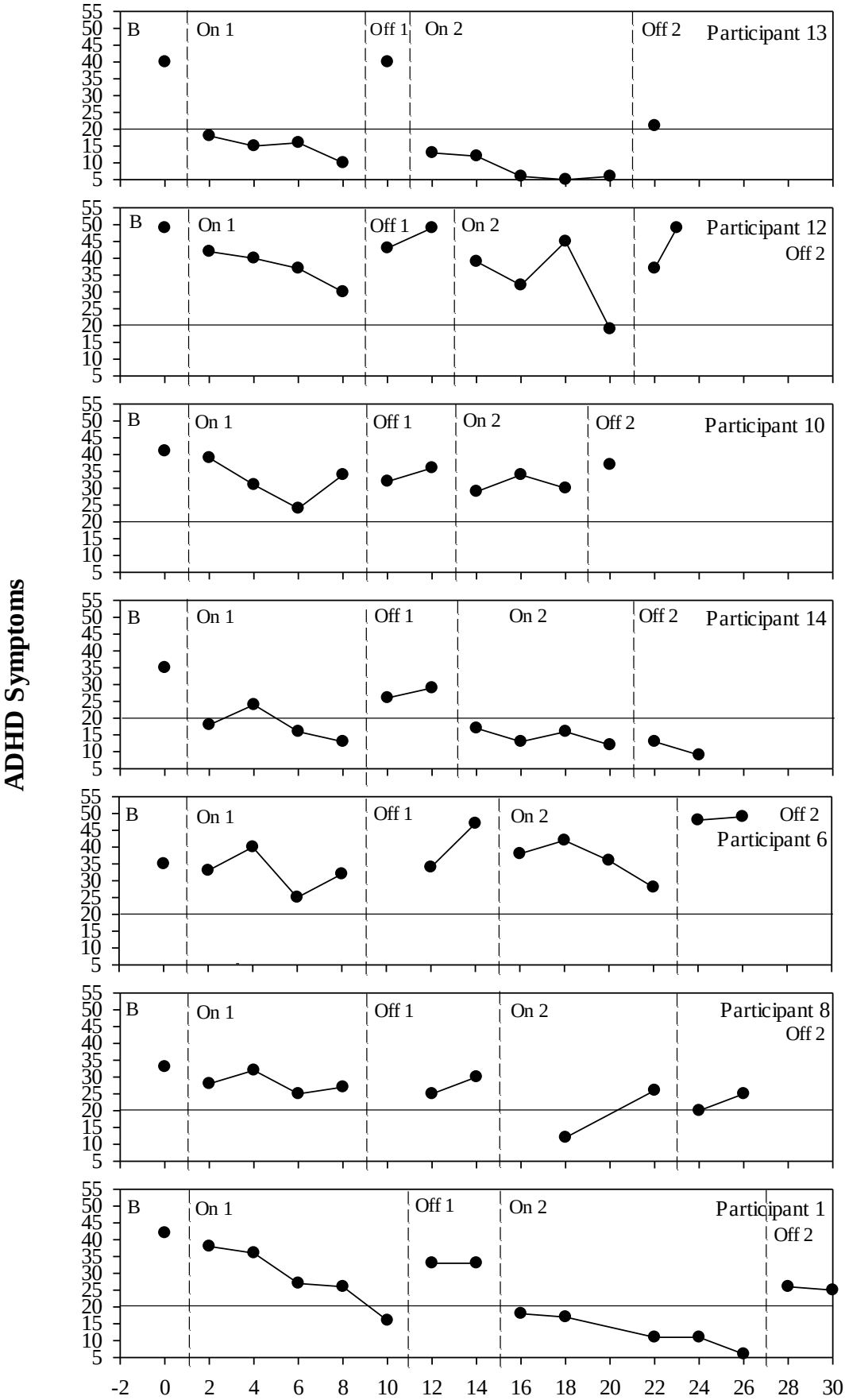
Baseline (B). Figure 3 illustrates that all participants had elevated ADHD scores, placing them into clinical range at baseline.

Treatment phase (On 1). Figure 3 shows a gradual decrease in ADHD symptoms during the first on phase, with all of the participants falling below their baseline score by the end of the first treatment phase.

Treatment withdrawal/Reversal phase (Off 1). Figure 3 shows a return of ADHD symptoms. For some, this return of symptoms was gradual and for others the reoccurrence of ADHD symptoms was evident within the first two weeks off.

Reintroduction of treatment (On 2). Figure 3 illustrates that ADHD symptoms again reduced after the reintroduction of the micronutrients, replicating responses demonstrated in the first treatment phase. For some participants the reintroduction of treatment resulted in immediate reduction of symptoms (i.e. 1, 11, 13 & 14), for others, the effect was more gradual (i.e. 4, 5, & 12).

Treatment withdrawal/Reversal phase (Off 2). Figure 3 shows again the return of ADHD symptoms when treatment was withdrawn. A similar pattern was found on the second off phase with a gradual return of ADHD symptoms for some and an immediate return of symptoms for others. Participants 3, 9, 10 and 13 chose to reintroduce the micronutrient formula early due to the return of ADHD symptoms.


ADHD Symptoms
Weeks
B
On 1
Off 1
On 2
Off 2
Participant 13
Participant 12
Participant 10
Participant 14
Participant 6
Participant 8
Participant 1

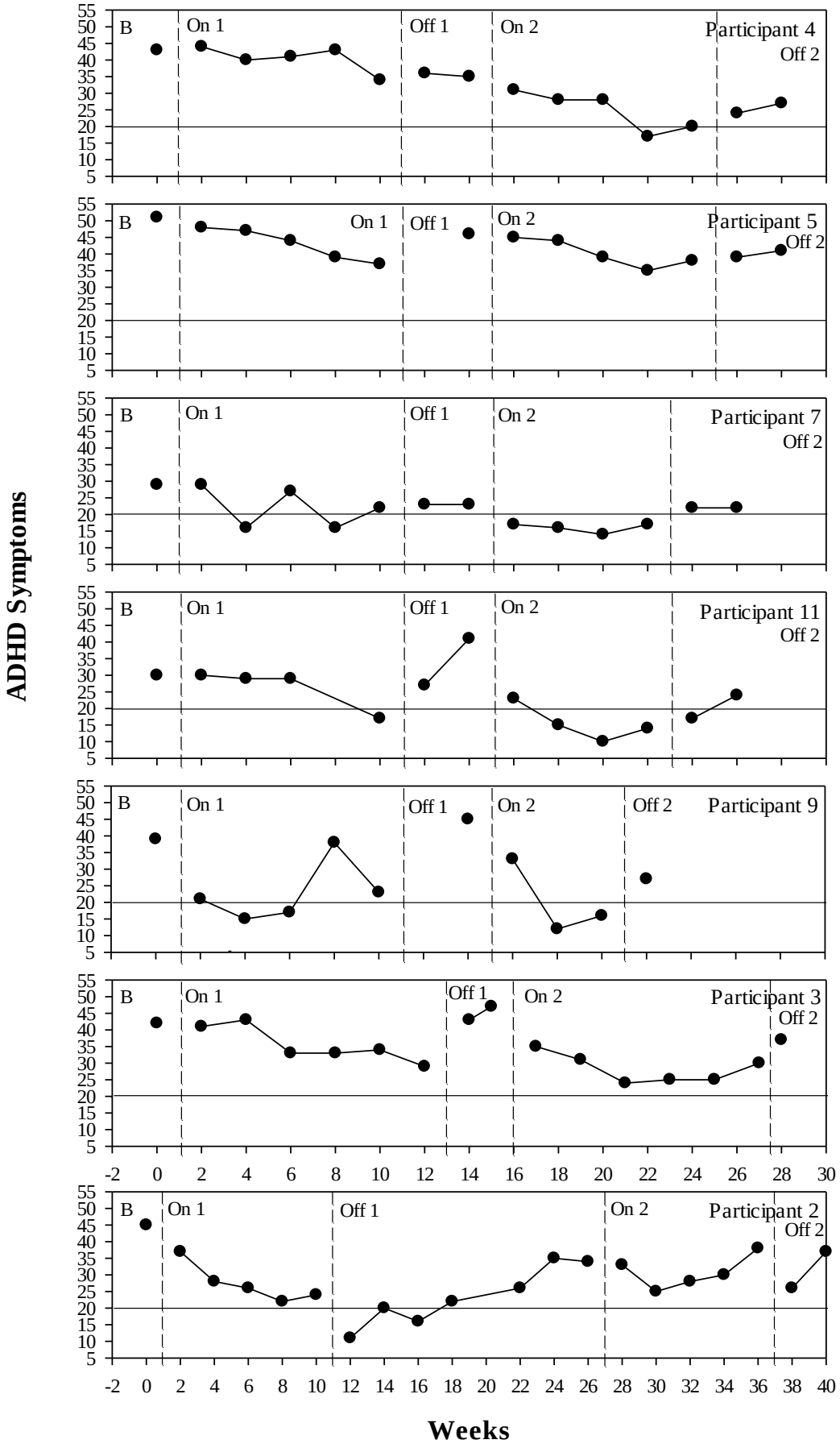


Figure 3. Changes in ADHD symptoms as measured by ADHD-RS and CPRS-R:L
Note. Dashed lines indicate different phases of the study, B= Baseline, On 1= first phase on micronutrients, Off 1= first phase off micronutrients, On 2= second phase on micronutrients, Off 2= final phase off micronutrients; scores above solid line at 20 indicate the clinical cutoff for symptoms

4.3 Modified Brinley Plot Analyses

The response to the micronutrient treatment was evident in changes in a wide range of outcome measures, and modified Brinley plots were, therefore, used as a way to efficiently display and summarise the findings of this study. Modified Brinley plots can be used to display individual change over time in a way that simultaneously displays data from each participant. Brinley plots were originally used to present group mean data from cognitive psychology experiments (Brinley, 1965). Subsequently it has been shown (Blampied, 2014; Jacobson, et al., 1984; Sobell, et al., 1995; Stunkard & Penick, 1979) that modified Brinley plots are useful in identifying systematic effects of an intervention when modified to display each individual's data (Capstick & Blampied, 2004; Blampied, 2014). The way modified Brinley plots display data is as a scatter-plot that using orthogonal X-Y coordinates with the same origin and scale. Time 1 (pre-treatment) scores for each participant are normally plotted on the X-axis and Time 2 (post-treatment) scores on the Y-axis. If there are no systematic differences between the two conditions the data points will lie on or around the 45^0diagonal line of no change, X = Y; however, if there are systematic differences between the conditions then the data points will deviate from the line (either above or below). When a higher score indicates greater impairment, an individual's points that fall above the line indicate greater impairment and those that fall below the line indicate less impairment. When a higher score indicates greater functioning, then points that fall above the line indicate better functioning and points that fall below the line indicate greater impairment. An indication of direction of desired change is displayed on the graph as an arrow and lines that indicate clinical cut-offs are also displayed on the graph (Blampied, 2014; Jacobson, et al., 1984), as shown in Figure 4. To assist interpretation, the zones on the graph created by the intersections of the cut-off lines and the diagonal can be assigned meaning. As further assistance with interpretation, the mean values for the within-phase data and confidence intervals for the means may be

displayed as crosses on the graph, with the point of intersection where the lines cross represents the mean on the X and Y axis respectively. The length of each intersecting line is drawn to indicate +/- the 95% CI of the relevant mean. The location of the means and the lengths of the 95% CI lines can be usefully interpreted. Since the 95% CI "estimates μ [the population mean] with 95% confidence' (Kline, 2013, p 41), or as Cumming (2012, p 79) puts it "the values in the interval are plausible as true values for μ", if a limb of the line indicating the margin of error does not cross the diagonal, we can have considerable confidence that the associated mean is different from what it would have been if there had been no change from time 1 to time 2. Similarly, if a limb of the CI line does not cross the cut-off line we can have considerable confidence that the mean is different from the value represented by the cut-off.

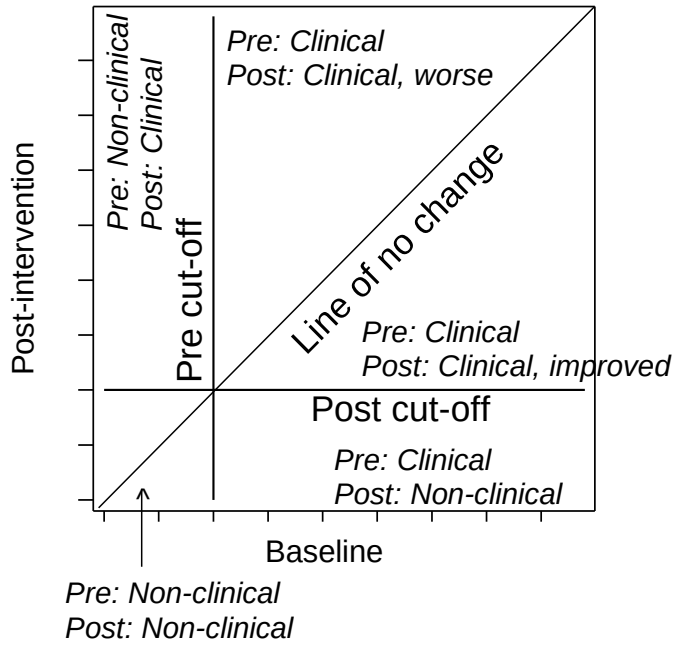


Figure 4. Use of clinical cut-off lines to assist with the interpretation of modified Brinley plots. In this example, lower scores are indicative of reduced symptoms and therapeutic improvement, as indicated by the line with the arrowhead (adapted from Rucklidge & Blampied, 2011).

In the section below a series of modified Brinley plots show individual change over time. Phases of the study run left to right. For each individual, a measurement made at Baseline is plotted on the X axis against a measurement on the same variable, for that same individual, at the subsequent time (i.e., On 1, Off 1, On 2, Off 2), which is plotted on the Y axis. Subsets of measures are shown as rows, with changes over time in all components of a measure visible in the closely grouped array of plots. The subscales of the CPRS-R:L are dependent variables that are shown as separate rows in the figure, and for the remaining outcome measures plotted, where there is one dependent variable per construct, a single row is shown.

Figure 5 below displays changes in the parent-rated outcome measures (i.e., CPRS-R:L and CMRS). Where data on the CPRS-R:L was missing, scores from the ADHD-RS-IV were used. This was employed for five different participants; one participant at the end of the first on phase, two participants at the end of the first withdrawal phase, and two participants at the end of the second withdrawal phase. These modified Brinley plots show a cut-off T-score of 65, reflecting clinical elevations in ADHD behaviours on the CPRS-R:L, while scores above the cut-off of 20 on the CMRS indicate possible paediatric mania. The top three by four array of plots in Figure 5 illustrates the effect the micronutrient intervention had on the primary measure of ADHD, namely the CPRS-R:L, differentiated by subscales. The top row shows individual changes on the CPRS-R:L, Inattention subscale, from Baseline to Phase On 1. All participants fall above the clinical cut-off of 65 at Baseline. Nine of the 14 participants (64%) dropped below the clinical cut-off after the first exposure to micronutrients (Phase On 1). The next plot displays Baseline versus Off 1 and shows most participants returning back to baseline levels, with most individuals' data points falling on or close to the line of no change and with 12 of the 14 participants (86%) returning above the cut-off. The third plot in the row displays Baseline versus Phase On 2, the final phase of

micronutrient consumption, and closely replicates the pattern of results shown during the first On phase. Nine (64%) of the participants dropped below the clinical cut-off. The final plot displaying Baseline versus Phase Off 2 shows participants reverting back towards baseline levels. The mean and confidence intervals for each phase follow a similar pattern, generally falling below the clinical cut-off during the on phases and above the cut-off during the off phases.

The second row of plots in Figure 5 shows individual data for the CPRS-R:L Hyperactive-Impulsive subscale. These data show a similar pattern to the inattentive subscale; however, with more variability in the scores. Data shown in the third row (CPRS-R:L Combined subscale) also follow the same pattern with few participants falling below the cut-off during the off phases (2 in Off 1 phase; 5 in Off 2 phase).

Figure 5 also illustrates the effect micronutrients had on the parent-rated CMRS. The four plots in the lower row of Figure 5 show a similar pattern to that shown in the upper rows, where data points fall closer to the line of no change when comparing baseline to the off phases than when on the micronutrients.

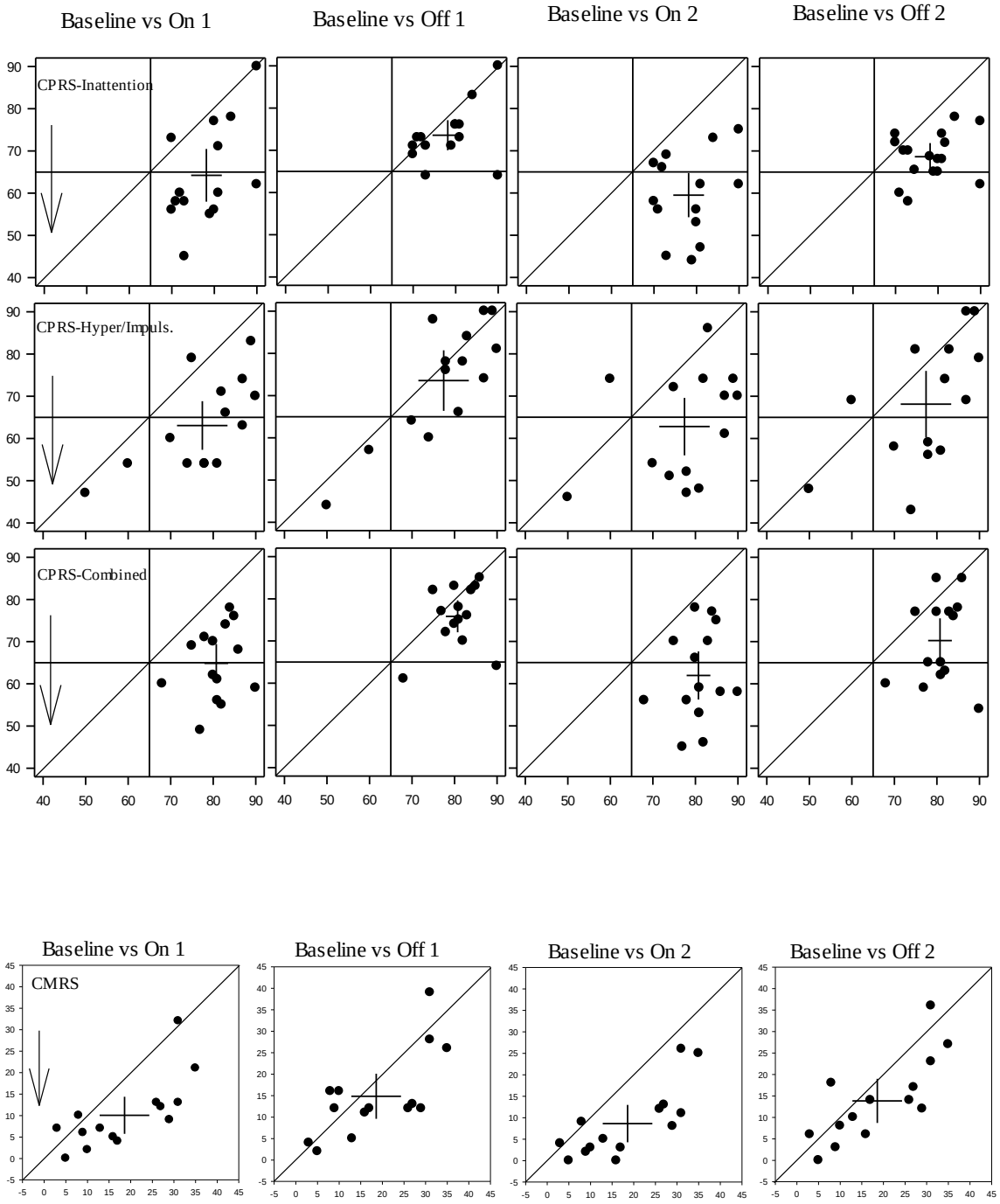


Figure 5. Modified Brinley plots displaying change on parent-rated ADHD outcome measure, CPRS-R:L, and the CMRS

Note. Arrows indicate direction of desired change. Graphs plotted X axis as baseline versus On 1, baseline versus Off 1, baseline versus On 2 and baseline versus Off 2.

Figure 6 displays changes in the clinician-rated outcome measures (YMRS and CDRS) across the micronutrient intervention. YMRS cut-off scores are as follows: 13 minimal severity, 20 mild severity, 26 moderate severity and 38 severe illness. At the beginning of the study, six participants (43%) fell within the minimal severity range and one participant fell within the moderate severity range. The initial plot, Baseline versus On 1, shows a decrease in scores on the YMRS during the On 1 phase. A reversal effect is demonstrated on the next plot, during the first off phase (Off 1), with data points falling closer to the line of no change. This trend continues over plots three, the second on phase demonstrating a decrease in YMRS scores, and plot four, illustrating a return to baseline scores during the second off phase. The means and confidence intervals for these time points fall in the direction of desired outcome, falling below the line of no change during the on phases and on the line of no change during the off phases.

Figure 6 illustrates the effect the micronutrients had on low mood as measured by the CDRS. Cut-off scores for the CDRS are: 30 and above indicate significant depression, 20-30 borderline depression and a minimum score of 16. At baseline, two participants (14%), met criteria for significant depression and 11 (79%) met criteria for borderline depression. Over the four plots for CDRS a trend similar to the other outcome measures is found. Plots one and three demonstrate an increase in mood when participants were on the micronutrients compared to when they were off the micronutrients. A return to baseline scores when the micronutrients were withdrawn is shown in plots two and four. Confidence intervals reflect this pattern as well, falling below the line of no change and within the minimum score during on phases and on the line of no change or above for off phases.

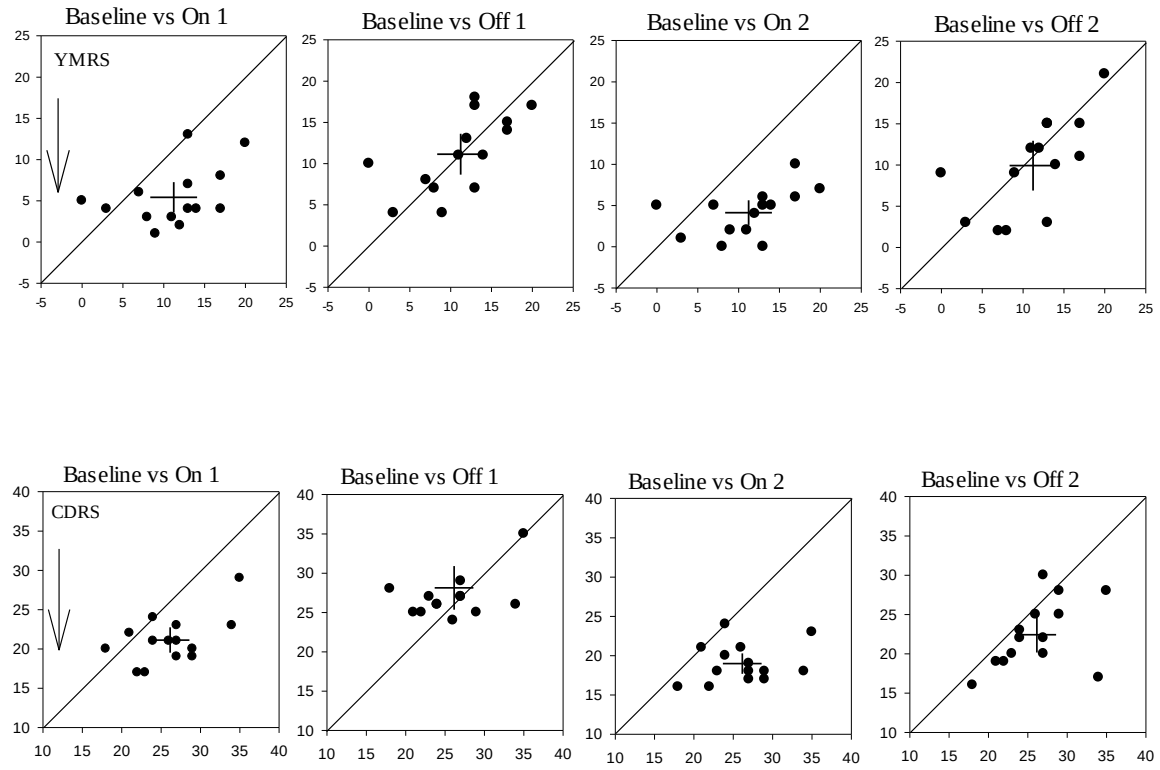


Figure 6. Modified Brinley plots displaying change in clinician-rated YMRS and CDRS scores
Note. Downward arrow indicates direction of desired change

Figure 7 shows the effect the micronutrients had on the participants' overall functioning as measured by the CGAS, a global measure of overall functioning assigned by the clinician in a single number from 1 (most impaired) to 100 (healthiest). Scores at the lower end of the scale, 1-10, indicate a need for constant supervision, whereas those who score above 70 are considered to be within the normal range. Across the four plots you can see the on/off pattern that is consistent with the other outcome measures. The two participants with the greatest difficulties who fell towards the lower end of functioning (31-40), and who displayed major impairment in several areas of life and were generally unable to function without great assistance in at least one area, moved nearly two 10 point sections on the CGAS while on the micronutrients, as illustrated on plots one and three. Plots two and four show this gain returning to baseline or below baseline functioning when they were no longer

on the micronutrients. Nearly all participants made gains after the initial on phase, three falling within the normal range as shown on plot one, and plot three illustrates that all participants made gains in the second on phase, with four participants falling within the normal range after the micronutrient treatment was reintroduced. Plot four shows that during the second off phase, participants are generally still doing better than reported at baseline.

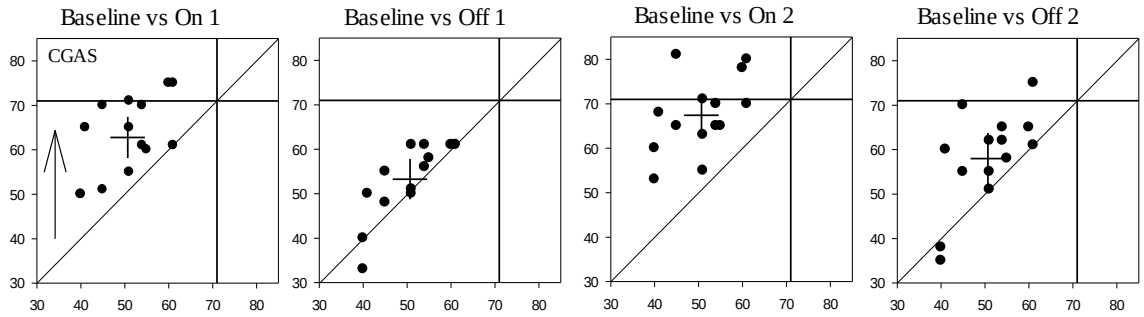


Figure 7. Modified Brinley plots displaying change in overall functioning as rated by the clinician on the CGAS
Note. The upward arrow indicates the higher the score the greater the overall functioning

Table 5 below presents the scores for each participant on outcome measures across each phase of the study. Scores have been highlighted to indicate the severity of the symptoms (CPRS-R:L & CDRS), as well as signifying a score within the range of 'normal functioning', as measured by the CGAS.

Table 5

Individual Changes in Outcome Measures

	Baseline	On 1	Off 1	On2	Off 2
CPRS-R:L Total (Parent)					
1	**82**	**55**	**70**	**46**	**63**
2	**80**	**62**	**74**	**78**	**77**
3	**75**	**69**	**82**	**70**	**77**
4	**78**	**71**	**72**	**56**	**65**
5	**85**	**76**	**83**	**75**	**78**
6	**80**	**70**	**83**	**66**	**85**
7	**68**	**60**	**61**	**56**	**60**
8	**84**	**78**	**82**	**77**	**76**
9	**81**	**61**	**75**	**59**	**65**
10	**83**	**74**	**76**	**70**	**77**
11	**81**	**56**	**78**	**53**	**62**
12	**86**	**68**	**85**	**58**	**85**
13	**77**	**49**	**77**	**45**	**59**
14	**90**	**59**	**64**	**58**	**54**
CMRS Total (Parent)					
1	**16**	**5**	**11**	**0**	**6**
2	**27**	**12**	**13**	**13**	**17**
3	**8**	**10**	**16**	**9**	**18**
4	**26**	**13**	**12**	**12**	**14**
5	**35**	**21**	**26**	**25**	**27**
6	**31**	**32**	**39**	**26**	**36**
7	**3**	**7**	**4**	**4**	**6**
8	**13**	**7**	**5**	**5**	**10**
9	**17**	**4**	**12**	**3**	**14**
10	**29**	**9**	**12**	**8**	**12**
11	**9**	**6**	**12**	**2**	**3**
12	**31**	**13**	**28**	**11**	**23**
13	**10**	**2**	**16**	**3**	**8**
14	**5**	**0**	**2**	**0**	**0**
CGAS Total (Clinician)					
1	**45**	**70**	**55**	**81**	**70**
2	**41**	**65**	**50**	**68**	**60**
3	**40**	**50**	**33**	**60**	**35**
4	**45**	**51**	**48**	**65**	**55**
5	**51**	**65**	**51**	**55**	**55**
6	**40**	**50**	**40**	**53**	**38**
7	**55**	**60**	**58**	**65**	**58**
8	**61**	**61**	**61**	**70**	**61**
9	**51**	**55**	**50**	**63**	**51**
10	**54**	**70**	**61**	**70**	**65**
11	**54**	**61**	**56**	**65**	**62**
12	**51**	**71**	**61**	**71**	**62**
13	**60**	**75**	**61**	**78**	**65**
14	**61**	**75**	**61**	**80**	**75**
CDRS Total (Clinician)					
1	**33**	**22**	**25**	**17**	**16**
2	**26**	**20**	**26**	**16**	**19**
3	**28**	**18**	**43**	**16**	**27**
4	**29**	**20**	**25**	**17**	**25**

5	24	21	26	24	22
6	26	21	24	21	25
7	24	24	26	20	23
8	21	22	25	21	19
9	27	23	27	19	30
10	22	17	25	16	19
11	35	29	35	23	28
12	27	19	29	18	22
13	23	17	27	18	20
14	18	20	28	16	16
YMRS Total (Clinican)					
1	8	3	7	0	2
2	11	3	11	2	12
3	13	7	18	5	15
4	9	1	4	2	9
5	17	4	15	10	11
6	20	12	17	7	21
7	3	4	4	1	3
8	0	5	10	5	9
9	13	13	17	6	15
10	14	4	11	5	10
11	13	4	7	0	3
12	17	8	14	6	15
13	12	2	13	4	12
14	7	6	8	5	2

Note. CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Form, CMRS-P = Child Mania Rating Scale-Parent Version, CGAS = Children's Global Assessment Scale, CDRS = Children's Depression Rating Scale . YMRS = Young Mania Rating Scale. High scores on the CGAS represent better functioning, whereas higher scores on other measures represent greater impairment. Red scores on the CDRS represent significant depression, Orange scores represent borderline depression and Black indicates scores were below the cutoff ranges. Green scores on the CGAS represent scores within the normal range of functioning. Red scores on the CPRS-R:L are score above the clinical cut off of 65.

4.4 Group Analyses

4.4.1 Cohen's *d* Effect Sizes, 95% Confidence Intervals and Paired Sample *t*-tests

Cohen's d effect sizes, 95% confidence intervals and paired sample *t*-tests were completed to determine whether there were significant differences in clinician-rated measures, parent-rated measures, self-report measures, teacher-rated measures, and on the neuropsychological task when taking the micronutrient formula compared to when off the micronutrient formula. The results of these tests are discussed in the following sections.

4.4.1.1 Parent and Clinician-rated Measures

Table 6 shows the data for each phase as within phase means, standard deviations, mean difference, effect sizes (Cohen's *d*), 95% confidence intervals (95% CI), *t*-test and *p* values, separately for each dependent variable. The alpha was adjusted using the Bonferroni correction to reduce the risk of Type 1 error due to multiple paired sample *t*-tests conducted simultaneously on a single data set (baseline scores). As four *t*-tests were conducted for each dependent variable $p = .05$ was divided by four, therefore $p = .01$ is the criterion used to signify significance. An adjusted effect size was also calculated to determine an estimated true effect for the micronutrient intervention phases. A Cohen's *d* effect size was calculated for each of the intervention phases and the effect size found during the consequent withdrawal phase was then subtracted to estimate the likely effect of the micronutrients after eliminating nonspecific factors associated with treatment trials.

The results show a clear on/off effect when comparing the baseline phase to the consequent phases: when participants are taking the micronutrients there is a drop in ADHD behaviours, an improvement in mood, and an increase in overall functioning. When participants stop taking the micronutrients ADHD behaviours return towards baseline level, there is deterioration in mood and an overall decrease in general functioning, although this is less clear for the last off phase with participants showing some maintained improvements in behaviours.

Large effect sizes were observed, and statistically significant improvements found, when comparing the baseline mean to the intervention mean (On 1 & On 2) on all CPRS-R:L ADHD subscales, the CMRS, CDRS, CGAS and YMRS. Effect sizes were still in the medium to large range after adjustments were completed. These results confirm clinically meaningful change from baseline to intervention phases. The mean scores of ADHD

symptoms, as measured by the CPRS-R:L, dropped below the clinical cut-off score (65) during the on phases and exceeded the cut-off score during the off phases. However, large effect sizes, and statistically significant differences were also observed when comparing baseline scores to the second off phase (Off 2) scores, for both the inattention subscale and combined subscale of the CPRS-R:L. Nonetheless, these second off phase scores, although showing a significant decrease in ADHD symptoms compared to baseline, reverted back above the clinical cut-off for ADHD.

In measures of mood (parent and clinician rated) and the overall functioning of the participant (clinician rated), this pattern is repeated; all yielding medium to large adjusted effect sizes and significant change is found when comparing baseline scores to intervention phase scores (see Table 6 below).

Table 6

Means, Standard Deviations, Mean difference, Effect Sizes, 95% Confidence Intervals, Paired sample t-tests, and Adjusted Effect Sizes for Baseline and Consequent Phase comparisons for Outcome Measures

CPRS-R:L DSM-IV: Inattentive (ADHD symptoms-parent-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	
Baseline	78.14	6.87							
On 1	64.21	11.92	13.93	8.08 to 19.78	1.43	0.62 to 2.10	5.15	<.001***	0.76
Off 1	73.57	6.80	4.57	0.45 to 8.69	0.67	0.05 to 1.21	2.40	.03	
On 2	59.50	9.99	18.64	12.39 to 24.90	2.17	0.87 to 2.55	6.44	<.001***	0.71
Off 2	68.64	6.13	9.50	4.73 to 14.27	1.46	0.45 to 1.82	4.30	<.001***	
CPRS-R:L DSM-IV: Hyperactivity/Impulsivity (ADHD symptoms-parent-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	
Baseline	77.43	11.33							
On 1	63.07	10.98	14.36	8.93 to 19.78	1.29	0.73 to 2.30	5.72	<.001***	0.98
Off 1	73.57	13.69	3.86	-0.51 to 8.22	0.31	-0.06 to 1.06	1.91	.08	
On 2	62.79	12.98	14.64	6.81 to 22.48	1.20	0.40 to1.73	4.04	<.001***	0.50
Off 2	68.14	15.03	9.29	2.19 to 16.38	0.70	0.15 to 1.34	2.83	.01**	
CPRS-R:L DSM-IV: Total Combined (ADHD symptoms-parent-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	
Baseline	81.00	5.92							
On 1	64.86	8.68	16.14	10.57 to 21.71	2.17	0.84 to 2.48	6.26	<.001***	1.39
Off 1	75.86	7.24	5.14	0.19 to 10.09	0.78	0.02 to 1.16	2.24	.04	
On 2	61.93	10.86	19.07	12.38 to 25.76	2.18	0.82 to 2.45	6.16	<.001***	0.88
Off 2	70.21	10.14	10.79	4.19 to 17.38	1.30	0.30 to 1.57	3.54	<.001***	
CMRS (Mood-parent-rated)									
	Mean	SD	Compared to Baseline						
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	Adjusted ES[e]
Baseline	18.57	10.95							
On 1	10.07	8.26	8.50	4.12 to 12.88	0.88	0.43 to 1.78	4.19	<.001***	0.53
Off 1	14.86	10.05	3.71	-1.02 to 8.45	0.35	-0.11 to 1.00	1.69	.11	
On 2	8.64	8.31	9.93	5.95 to 13.91	1.02	0.67 to 2.18	5.38	<.001***	0.57
Off 2	13.86	9.84	4.71	0.58 to 8.85	0.45	0.07 to 1.23	2.46	.03	
CDRS (Mood-clinician-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	
Baseline	26.14	4.70							
On 1	21.14	3.09	5.00	2.71 to 7.29	1.26	0.54 to 1.96	4.72	<.001***	0.86
Off 1	28.14	5.29	-2.00	-5.23 to 1.23	0.40	-0.19 to 0.89	-1.34	.20	
On 2	19.00	2.48	7.14	4.36 to 9.92	1.90	0.70 to 2.24	5.55	<.001***	1.08
Off 2	22.43	4.29	3.71	1.05 to 6.38	0.82	0.19 to 1.40	3.01	.01**	
CGAS (Overall Functioning-clinician-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	

Baseline	50.64	7.48							
On 1	62.79	8.86	-12.14	-16.49 to -7.80	1.48	0.79 to 2.41	-6.04	<.001***	1.15
Off 1	53.29	8.65	-2.64	-5.44 to 0.16	0.33	-0.03 to 1.10	-2.04	.06	
On 2	67.43	8.48	-16.79	-21.46 to -12.11	2.10	1.12 to 3.01	-7.76	<.001***	1.32
Off 2	58.00	10.99	-7.36	-12.19 to -2.53	0.78	0.08 to 1.25	-2.53	.01**	
YMRS (Mood-clinician-rated)									
	Mean	SD	Compared to Baseline						Adjusted ES[e]
			MD[a]	MD 95% CI[b]	ES[c]	ES 95% CI[d]	*t*-test	*p*-value	
Baseline	11.21	5.47							
On 1	5.43	3.52	5.79	2.82 to 8.75	1.26	0.44 to 1.78	4.22	<.001***	1.25
Off 1	11.14	4.72	0.07	-2.39 to 2.54	0.01	-0.51 to 0.54	0.06	.95	
On 2	4.14	2.85	7.07	4.33 to 9.81	1.62	0.70 to 2.25	5.57	<.001***	1.40
Off 2	9.93	5.77	1.29	-1.42 to 3.99	0.22	-0.26 to 0.80	1.03	.32	

Note. CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Form, CMRS = Child Mania Rating Scale, CDRS = Children's Depression Rating Scale, CGAS = Children's Global Assessment Scale, YMRS = Young Mania Rating Scale; **denotes statistically significant difference at $p<.01$ level; ***denotes statistically significant difference at $p<.001$ level

a. Mean Difference compared to baseline
b. MD 95% CI = 95% confidence interval of the mean difference
c. ES = Cohen's *d* effect size measured as the mean difference baseline-post/pooled SD
d. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size
e. Adjusted ES = Cohen's *d* effect size of withdrawal phase (Off 1 & Off 2) subtracted from Cohen's *d* of intervention phase (On 1 & On 2) to estimate the likely effect of the micronutrient intervention i.e., On 1 – Off 1 = Adjusted ES

Table 7 below presents the Cohen's *d* effect sizes, 95% confidence intervals and paired sample t-tests and for the parent-rated SDQ. Due to missing data, baseline scores were compared the end of the second on phase scores for both the SDQ and CPRS-R:L subscales. Large effects were observed, confirming clinically meaningful change, and significant improvements found for total difficulties $d = 1.09$ (95% CI [0.53, 1.95], $t(13) = 4.69$, $p < .001$), and overall impact on the participants' distress and social impairment $d = 1.83$ (95% CI [0.63, 2.11], $t(13) = 5.17$, $p < .001$). Large effects were also observed for conduct problems $d = 1.05$ (95% CI [0.38, 1.70], $t(13) = 3.94$, $p < .001$), and hyperactivity subscales $d = 1.29$ (95% CI [0.66, 2.18], $t(13) = 5.36$, $p < .001$), after the second on phase compared to baseline. Small effects were found when comparing baseline prosocial behaviour and peer

difficulties to the second intervention phase (On 2). However, paired sample t-tests for the emotional symptoms and peer problems subscales revealed no significant change from baseline to the second on phase.

Table 7

Means, Standard Error of the Means, Mean Difference, Effect Sizes, 95% Confidence Intervals, and Paired Sample t-tests Comparing Parent-Rated Baseline SDQ Total Difficulties, 5 subscales (Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems and Prosocial Behaviour), and Impact Scores to the Second On Phase Scores

	Baseline		On 2		Comparing baseline to On 2 phase					
SDQ-parent	Mean	SEM[a]	Mean	SEM[a]	MD[b]	MD 95% CI[c]	ES[d]	ES 95% CI[e]	*t*-test	*p*-value
Total Difficulties	19.57	1.44	13.64	1.49	5.93	3.20 to 8.66	1.09	0.53 to 1.95	4.69	<.001**
Emotional Symptoms	2.21	0.43	1.86	0.56	0.36	-0.77 to 1.48	0.19	-0.35 to 0.71	0.69	.50
Conduct Problems	4.43	0.71	2.07	0.47	2.36	1.06 to 3.65	1.05	0.38 to 1.70	3.94	<.001**
Hyperactivity	8.71	0.38	6.36	0.57	2.36	1.41 to 3.31	1.29	0.66 to 2.18	5.36	<.001**
Peer Problems	4.21	0.54	3.36	0.57	0.86	-0.42 to 2.14	0.41	-0.16 to 0.92	1.45	.17
Prosocial Behaviour	6.07	0.72	6.64	0.78	-0.57	-1.11 to -0.03	0.20	0.03 to 1.17	-2.28	.04*
Impact Score	6.14	0.57	2.21	0.58	3.93	2.29 to 5.57	1.83	0.63 to 2.11	5.17	<.001**

Note. SDQ = Strength and Difficulties Questionnaire, which consists of five subscales, Emotional Symptoms Scale, Conduct Problems Scale, Hyperactivity Scale, Peer Problems Scale and Prosocial Scale. The Total Difficulties score is generated by summing the scores from all of the scales except the prosocial scale. **denotes statistically significant difference at $p<.01$ level; *denotes statistically significant difference at $p<.05$ level

a. SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$
b. MD = mean difference of On 2 compared to Baseline
c. MD 95% CI = 95% confidence interval of the mean difference
d. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference
e. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size

Large effect sizes, confirming clinically meaningful change from baseline to the On 2 phase, were found for three of the six subscales of the CPRS-R:L: Oppositional behaviour d = 0.87 (95% CI [0.43, 1.78], $t(13) = 4.19$, $p = .001$), Social Problems d = 0.95 (95% CI [0.36, 1.66], $t(13) = 3.82$, $p = .002$), and Emotional Lability d = 1.30 (95% CI [0.52, 1.93], $t(13) = 4.63$, $p < .001$). Small to medium effects were detected in areas of perfectionism, shyness, and psychosomatic behaviours (see Table 8 below).

Table 8

Means, Standard Error of the Means, Mean Difference, Effect Sizes, 95% Confidence Intervals, and Paired Sample t-tests Comparing Parent-Rated Baseline CPRS-R:L Subscale t-Scores to On 2 Phase Subscale t-scores

	Baseline		On 2		Comparing baseline to On 2 phase					
CPRS-R:L	Mean	SEM[a]	Mean	SEM[a]	MD[b]	MD 95% CI[c]	ES[d]	ES 95% CI[e]	*t*-test	*p*-value
Oppositional	66.07	3.53	55.07	3.22	11.00	5.33 to 16.67	0.87	0.43 to 1.78	4.19	.001***
Anxious-Shy	53.29	2.46	49.07	3.47	4.21	-1.15 to 9.58	0.38	-0.10 to 1.00	1.70	.11
Perfectionism	55.07	3.97	49.21	2.76	5.86	-0.70 to 12.41	0.46	-0.05 to 1.07	1.93	.08
Social Problems	75.29	4.12	62.29	3.14	13.00	5.65 to 20.35	0.95	0.36 to 1.66	3.82	.002**
Psychosomatic	61.93	4.10	52.57	2.64	9.36	-0.96 to 19.68	0.73	-0.05 to 1.08	1.96	.07
Emotional Lability	63.79	3.17	49.64	2.60	14.14	7.54 to 20.74	1.30	0.52 to 1.93	4.63	<.001***

Note. CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version. **denotes statistically significant difference at $p<.01$ level; ***denotes statistically significant difference at $p<.001$ level

a. SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$
b. MD = mean difference of On 2 compared to Baseline
c. MD 95% CI = 95% confidence interval of the mean difference
d. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference
e. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size

4.4.1.2 Teacher-rated Measures

Cohen's *d* effect sizes, confidence intervals and paired sample *t*-tests for the teacher-rated CTRS-R:L and SDQ were completed, comparing baseline data with on phase data. Eleven of the 14 participants had teacher data for an on phase; three participants had no teacher data for either on phase. This was due to the study period falling over school breaks. When comparing baseline to an on phase, data was taken from the second on phase, where this was missing, data from the first on phase was used instead. Small effects were found for the Hyperactivity/Impulsivity $d = 0.27$ (95% CI [-0.28, 0.94], $t(10) = 1.12$, $p = .29$), Combined $d = 0.22$ (95% CI [-0.33, 0.87], $t(10) = 0.91$, $p = .38$), Anxious-Shy $d = 0.25$ (95% CI [-0.34, 0.87], $t(10) = 0.90$, $p = .39$), Perfectionism $d = 0.46$ (95% CI [-0.20, 1.04], $t(10) = 1.42$, $p = .19$), and Social Problems subscales $d = 0.26$ (95% CI[-0.26, 0.96], $t(10) = 1.18$, $p = .27$). Paired sample *t*-tests of the 11 participants revealed there were no significant changes based on teacher reports when comparing baseline to post-intervention (see Table 9).

Table 9

Means, Standard Error of the Means, Mean Difference, Effect Sizes, 95% Confidence Intervals, and Paired Sample t-tests Comparing Teacher-Rated Baseline CTRS-R:L Subscale Scores to Post Intervention Subscale Scores of 11 Participants

	Baseline		On phase		Comparing baseline to on phase					
CTRS-R:L	Mean	SEM[a]	Mean	SEM[a]	MD[b]	MD 95% CI[c]	ES[d]	ES 95% CI[e]	*t*-test	*p*-value
DSM-IV: Inattentive	66.09	3.51	64.00	3.34	2.09	-4.60 to 8.78	0.18	-0.39 to 0.80	0.70	.50
DSM-IV: Hyperactive-Impulsive	67.45	4.73	63.18	4.72	4.27	-4.25 to 12.79	0.27	-0.28 to 0.94	1.12	.29
Combined: DSM-IV Total	68.18	4.31	65.09	4.19	3.09	-4.46 to 10.65	0.22	-0.33 to 0.87	0.91	.38
Oppositional	61.27	4.61	59.55	4.34	1.73	-3.35 to 6.80	0.12	-0.38 to 0.82	0.76	.47
Anxious-Shy	56.55	4.16	53.73	2.59	2.82	-4.19 to 9.83	0.25	-0.34 to 0.87	0.90	.39
Perfectionism	57.55	4.00	51.91	3.43	5.64	-3.21 to 14.48	0.46	-0.20 to 1.04	1.42	.19
Social Problems	68.09	5.31	63.64	4.87	4.45	-3.95 to 12.86	0.26	-0.26 to 0.96	1.18	.27
Emotional Lability	60.91	5.18	59.27	4.40	1.64	-4.06 to 7.33	0.10	-0.41 to 0.79	0.64	.54

Note. CTRS-R:L= Conners' Teacher Rating Scale- Revised: Long Version.

a. SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$
b. MD = mean difference of On 2 compared to Baseline
c. MD 95% CI = 95% confidence interval of the mean difference
d. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference
e. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size

Table 10 shows a small effect $d = 0.30$ (95% CI [-0.20, 1.04], $t(10) = 1.42$, $p = .19$), on the Conduct Problems subscale reported by the teacher. There was no effect found for teacher-rated total difficulties (emotional, conduct, hyperactivity, and peer problems) measured by the SDQ; baseline scores (M = 15.91, SE = 2.27) were not significantly

different to the total difficulties measured after the micronutrient intervention (M = 14.45, SE = 2.36), d = 0.19 (95% CI [-0.34, 0.87], $t(10) = 0.90$, $p = .39$). However, the Impact Score generated by the SDQ, that reports a measure of the individuals overall distress and social impairment, revealed a medium effect d = 0.67 (95% CI [-0.04, 1.26], $t(10) = 2.06$, $p = .07$). The teacher-rated baseline impact score (M = 3.00, SE = 0.49) was higher than the reported impact score at the end of the micronutrient phase (M = 1.91, SE = 0.50). An impact score of 2 or more is classified as abnormal, a score of 1 is borderline and 0 is normal. This suggests that the teachers may have witnessed the micronutrients having an effect on the participants' overall distress and social impairment.

Table 10

Means, Standard Error of the Means, Mean Difference, Effect Sizes, 95% Confidence Intervals, and Paired Sample t-tests Comparing Teacher-Rated Baseline SDQ Total Difficulties, 5 Subscales (Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems and Prosocial Behaviour), and Impact Scores to the On Phase Scores of 11 Participants

	Baseline		On phase		Comparing baseline to on phase					
SDQ-teacher	Mean	SEM[a]	Mean	SEM[a]	MD[b]	MD 95% CI[c]	ES[d]	ES 95% CI[e]	*t*-test	*p*-value
Total Difficulties	15.91	2.27	14.45	2.36	1.45	-2.13 to 5.04	0.19	-0.34 to 0.87	0.90	.39
Emotional Symptoms	1.00	0.49	0.82	0.40	0.18	-0.66 to 1.02	0.12	-0.45 to 0.74	0.48	.64
Conduct Problems	3.64	0.98	2.73	0.83	0.91	-0.51 to 2.33	0.30	-0.20 to 1.04	1.42	.19
Hyperactivity	7.55	0.78	7.36	0.86	0.18	-1.34 to 1.71	0.07	-0.51 to 0.67	0.27	.80
Peer Problems	3.73	0.69	3.55	0.86	0.18	-0.94 to 1.30	0.07	-0.49 to 0.70	0.36	.72
Prosocial Behaviour	4.55	0.62	4.55	0.82	0.00	-0.90 to 0.90	0.00	0.00 to 0.00	0.00	1.00
Impact Score	3.00	0.49	1.91	0.49	1.09	-0.09 to 2.27	0.67	-0.04 to 1.26	2.06	.07

Note. SDQ = Strength and Difficulties Questionnaire, which consists of five subscales, Emotional Symptoms Scale, Conduct Problems Scale, Hyperactivity Scale, Peer Problems Scale and Prosocial Scale. The Total Difficulties score is generated by summing the scores from all of the scales except the prosocial scale.

a. SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$
b. MD = mean difference of On 2 compared to Baseline
c. MD 95% CI = 95% confidence interval of the mean difference
d. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference
e. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size

4.4.1.3 Child-rated Measures

Cohen's *d* effect sizes, 95% confidence intervals and paired sample *t*-tests were also calculated for the child-rated MYMOP, comparing baseline with the end of the second on phase. The results show medium to large effects of the micronutrient intervention and significant improvements on each measure, indicating clinically meaningful change from baseline to the end of the second on phase (see Table 11).

Table 11
Means, Standard Error of the Means, Mean Difference, Effect Sizes, 95% Confidence Intervals, and Paired Sample t-tests Comparing the Child-Rated MYMOP at Baseline Compared to their Scores at the End of the Second On Phase

	Baseline		On 2		Comparing baseline to On 2 phase					
MYMOP-Self-Report	Mean	SEM[a]	Mean	SEM[a]	MD[b]	MD 95% CI[c]	ES[d]	ES 95% CI[e]	*t*-test	*p*-value
Hyperactivity	1.75	0.32	0.71	0.29	1.04	0.14 to 1.93	0.92	0.08 to 1.24	2.5	.03*
Impulsivity	2.18	0.37	1.07	0.27	1.11	0.34 to 1.88	0.92	0.21 to 1.43	3.11	.01**
Inattention	2.42	0.20	1.61	0.32	0.82	0.01 to 1.63	0.81	0.005 to 1.14	2.18	.05*
Sleep	2.00	0.39	1.14	0.33	0.86	0.15 to 1.57	0.63	0.10 to 1.27	2.60	.02*
Low Mood	1.5	0.39	0.39	0.22	1.11	0.27 to 1.94	0.94	0.16 to 1.36	2.87	.01**

Note. MYMOP = Measure Yourself Medical Outcome Profile, is a self-report measure adapted to monitor the participants hyperactivity, impulsivity, inattention, sleep and mood. A score of 0 indicates zero problems and a score of 4 indicates major difficulty. **denotes statistically significant difference at $p<.01$ level; *denotes statistically significant difference at $p<.05$ level

a. SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$
b. MD = mean difference of On 2 compared to Baseline
c. MD 95% CI = 95% confidence interval of the mean difference
d. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference
e. ES 95% CI = 95% confidence interval of the Cohen's *d* effect size

4.4.1.4 Conners' Continuous Performance Test (CPT-II)

Only 12 of the 14 participants had completed both an on phase and an off phase for the CPT-II, so the analyses included only these 12 participants. Results from paired sample *t*-tests, comparing the end of the second on phase to the end of the second off phase, revealed no significant difference in responding patterns whether the participant was taking the micronutrient formula or off the micronutrient formula (see Table 12 below).

Table 12
Changes in ADHD as Measured by the CPT-II: a Neuropsychological Task, Comparing On 2 Phase to Off 2 Phase of 12 Participants

	On 2 Mean (SD)	Off 2 Mean (SD)	*t*-test	*p*-value
CPT-II (T-scores)				
Omissions	61.06 (18.98)	54.22 (8.49)	0.12	ns
Commissions	51.30 (11.05)	55.67 (10.66)	0.15	ns
Reaction Time	53.61 (14.72)	52.97 (10.80)	0.77	ns
Variability	57.15 (9.26)	55.25 (8.41)	0.48	ns
Confidence Index	72.86 (17.28)	69.12 (13.39)	0.46	ns

Note. ns= not significant; CPT-II = Conner's Continuous Performance Test

4.5 Further Analyses

Additional analyses were undertaken to investigate the participants' general functioning when on the micronutrient formula compared to baseline functioning and off phases. The overall clinical impression, measured by the CGI, was that most participants were much improved after the second on phase, with a small percentage of non-responders showing no change. No participants' symptoms worsened due to taking the micronutrients. Figure 8 below shows the distribution of percentage of improvement after the second eight weeks on the micronutrients.

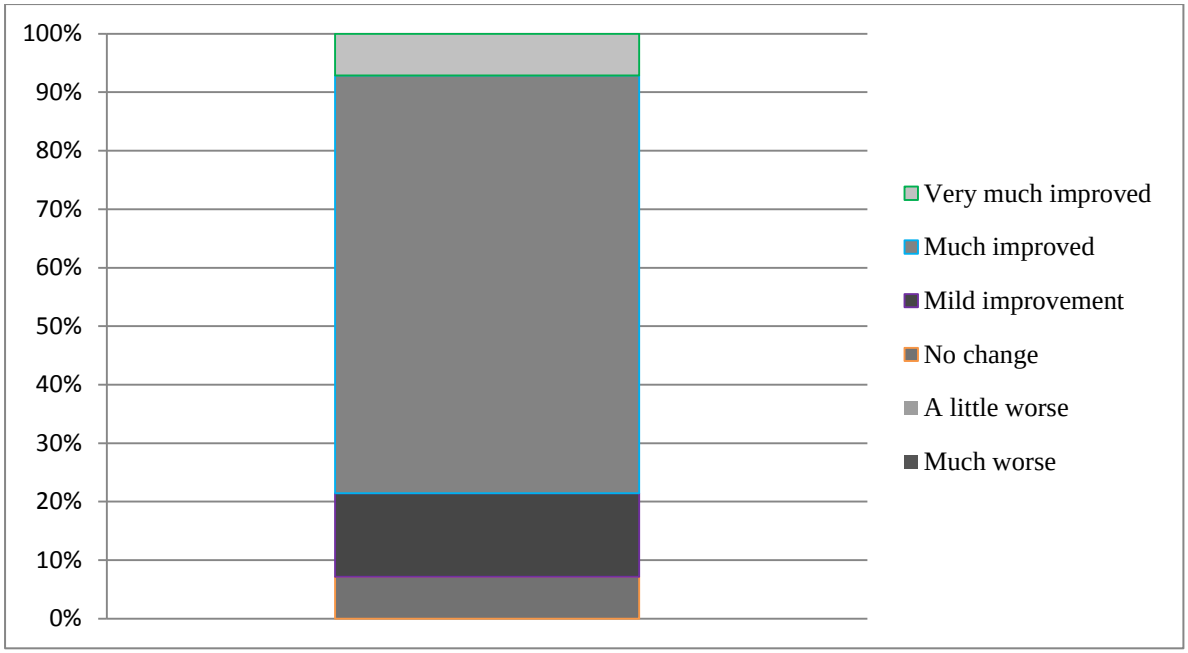


Figure 8. CGI-Overall Clinical Impression at end of second on phase (On 2).
Note. CGI= Clinical Global Impressions Scale.

Figure 9 below represents the severity of ADHD, as rated by the clinician, after the second eight weeks on the micronutrient compared to the severity of ADHD at baseline. There was a decrease in overall severity of ADHD, with participants no longer within the markedly ill category (50% originally) and nearly 30% falling within the normal or mildly ill category by the end of the second on phase. A large effect, indicating clinically meaningful change $d = 2.34$ (95% CI [1.02, 2.82], $t(13) = 7.23$, $p < .001$), was detected when comparing baseline severity to post-intervention severity.

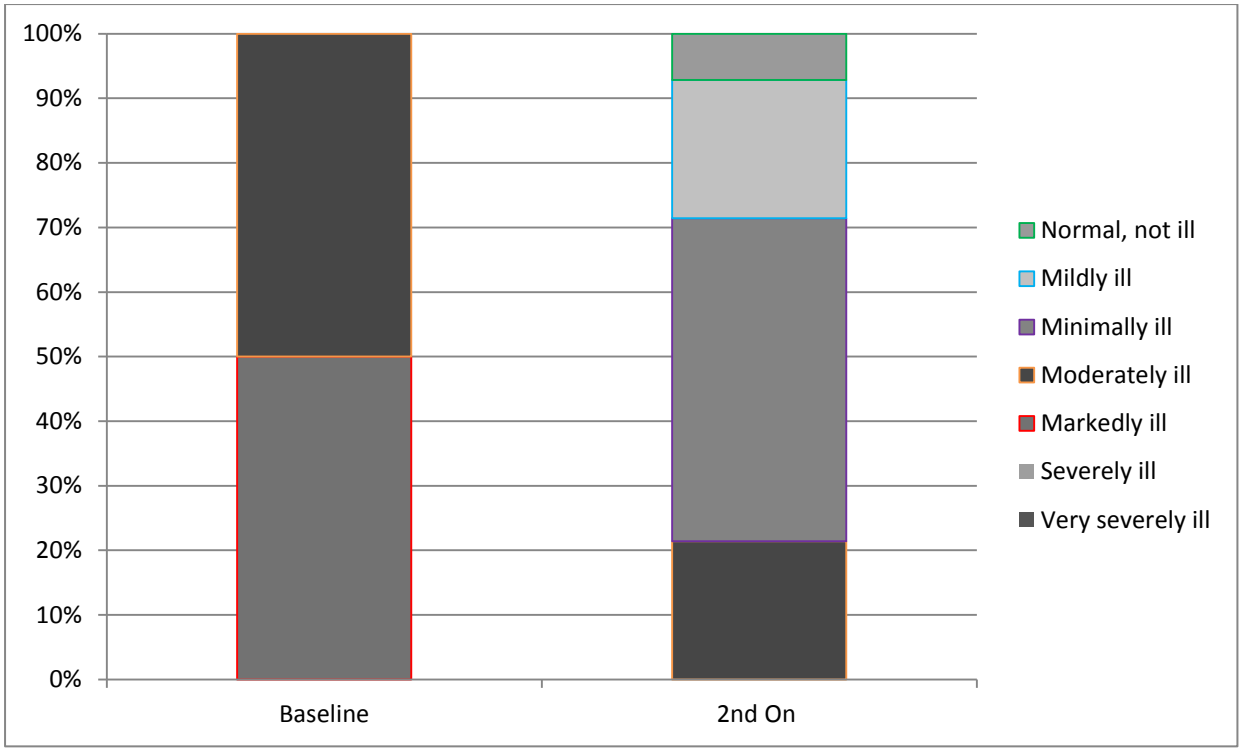


Figure 9. CGI-ADHD Severity of Illness at baseline and end of second on phase (On 2).
Note. CGI= Clinical Global Impressions Scale.

Table 13 presents the raw scores and percentage of change in total ADHD symptoms (combined inattention and hyperactive/impulsive) from baseline compared to the end of the second phase on the micronutrient, as rated by the parents on the CPRS-R:L. Half of the participants had a 50% or greater decrease in total ADHD symptoms by the end of the second on phase, and 71% of the participants had at least a 30% decrease in total ADHD symptoms, which is the typical cutoff used in the ADHD literature to classify a person as a responder. Fifty percent of the participants were no longer above the clinical cut-off score (T score of 65 and higher) for ADHD on the three DSM-IV corresponding diagnostic criteria subscales (Inattentive type, Hyperactive-Impulsive type, and Combined type), and 30% of participants fell below a T score of 60 at the end of the second on phase.

Table 13
Percentage of Change on the Parent-Rated CPRS-R:L DSM-IV: Total Raw Score (Combined Inattentive and Hyperactive-Impulsive type ADHD)

Participant	Baseline Total Raw Score	End of On 2 phase Total Raw Score	Percentage of Change
1	46	6	87
2	43	38	12
3	35	30	14
4	41	17	58
5	49	38	22
6	44	28	36
7	30	17	43
8	31	26	24
9	44	21	52
10	43	30	30
11	45	14	69
12	50	19	62
13	40	6	85
14	37	12	68

Note. CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version

4.6 Safety and Adherence

Participants experienced adverse events that were rated as no worse than mild to moderate in intensity and that were typically remedied by addressing the consumption of appropriate amounts of food and water along with the micronutrients. Two of the fourteen participants experienced adverse events that were definitely related to the intervention. One participant consistently struggled with nausea/vomiting when taking the morning dose so split the dose between two time points (breakfast and morning tea) to remedy this, and the other participant only experienced the nausea/vomiting on one occasion. One participant switched to Daily Essential Nutrients (DEN), the successor of EMP+, due to the nausea experienced on EMP+ and reported a decrease in nausea when taking DEN. DEN contains the same minerals and vitamins as EMP+, although they have increased vitamin D and several B vitamins and included vitamin K; a different proprietary blend has been used to

improve energy metabolism and improve nerve function, citrus bioflavonoids have been removed, and organic lithium has been added.

Eleven (79%) of the participants reported stomach aches as an adverse event, most commonly described at the beginning of the on phases, and this generally occurred as a single event. Participants were not always able to articulate the cause of feeling unwell and sometimes reported adverse events occurring before consumption of the micronutrients. As adverse events were not recorded during off phases we were unable to interpret the frequency of 'adverse events' while off the micronutrient formula. Headaches, dry mouth and skin irritation were also reported at some point in the trial by some participants. One participant experienced an increase in agitation that appeared to respond to slowly decreasing the micronutrient and a slower increase when the micronutrients were reintroduced following the off phase. The same participant experienced what appeared to be an absence seizure at the end of the first on phase. After consultation with the participant's General Medical Practitioner and family, it was decided the 'episode' was unlikely due to the micronutrients. They were closely monitored throughout the rest of the study, without further incident. A table reporting all of the adverse events throughout the course of the study is presented below (Table 14). No other adverse events were reported.

Table 14
Treatment Associated Adverse Events Reported by Participants During the Trial

Adverse event	Definitely related		Possibly related	
	n	%	n	%
Stomach ache			11	79
Nausea/Vomiting	2	14	8	57
Agitation			1	7
Headache			8	57
Dry mouth			8	57
Skin Rash			6	43
Achy Joints			1	7

Compliance was measured by the rate at which the participant was able to adhere to the treatment protocol. Compliance was defined as ingesting a minimum of 80% of the designated doses throughout the trial. Participants were considered non-compliant if they consumed less than 80% of their determined dose. Two participants had difficulty swallowing the pills so opted for the powder form. Both reported difficulty in having three blended drinks a day and alternated between the two flavours available. One participant switched to capsule form half way through, becoming a proficient pill swallower, and the other continued with the powder form throughout the study. They were both reportedly compliant in taking the formula. All 14 participants were considered compliant in terms of adherence to the dose designated suitable for that individual participant. Of the 14 participants, 7 (50%) took the recommended dose of 15 pills, or equivalent powder, per day,

two participants took 11-13 pills per day, and five participants took an average of 8-10 pills per day.

Consistent with previous research (Rucklidge et al., 2014; Simpson et al., 2011), the current research did not identify any significant adverse events or safety concerns. Blood work collected at baseline and post-treatment are presented in Table 15 below. The data is based on 13 of the 14 participants, as one participant refused to have blood drawn at the second visit. A medium effect was detected in a few safety markers and one nutrient marker, namely in aspartate aminotransferase $d = 0.76$ (95% CI [0.30, 1.64], $t(12) = -3.56$, $p < 0.004$), alanine aminotransferase $d = 0.65$ (95% CI [0.06, 1.27], $t(12) = -2.45$, $p = 0.03$), thyroid stimulating hormone $d = 0.53$ (95% CI [0.05, 1.27], $t(12) = -2.42$, $p = 0.03$), and nutrient levels of zinc $d = 0.75$ (95% CI [0.20, 1.48], $t(12) = -3.07$, $p = 0.01$), after taking the micronutrient formula, compared to baseline; however, the increases still placed the means well within the normal ranges.

Table 15

Baseline and Post-treatment Data Blood Results of 13 participants

	Baseline, Mean (SD)	Post, Mean (SD)	Change, Mean	ES[a]	*t*-test	*p*-value
Safety markers						
Prolactin, mlU/I	149.77 (86.30)	182.77 (111.91)	33.0	0.33	-1.37	0.20
Creatinine, µmol/I	63.54 (7.89)	63.69 (5.76)	0.15	0.02	-0.10	0.92
Fasting Glucose, mmol/I	4.95 (0.39)	4.87 (0.90)	-0.08	0.12	0.27	0.79
APT time, s	30.00 (2.66)	30.42 (4.19)	0.61	0.12	-0.60	0.56
Platelets, x 10(9)/L	297.23 (82.83)	280.38 (63.96)	-16.85	0.23	1.64	0.13
WBC, x 10(9)/L	5.92 (1.49)	6.13 (1.19)	0.21	0.16	-0.41	0.69
Lymphocytes, x 10(9)/L	2.43 (0.54)	2.39 (0.36)	-0.04	0.09	0.33	0.74
Neutrophils, x 10(9)/L	2.65 (0.99)	2.84 (0.84)	0.19	0.21	-0.56	0.59
GGT, U/L	14.46 (4.10)	13.77 (2.80)	-0.69	0.20	0.65	0.53
AST, U/L	24.69 (4.64)	27.92 (3.88)	3.23	0.76	-3.56	**<0.004****
ALT, U/L	16.77 (3.42)	19.92 (5.95)	3.15	0.65	-2.45	**0.03***
Triglyceride, mmol/L	0.82 (0.39)	0.87 (0.53)	0.05	0.11	-0.24	0.82
Cholesterol, mmol/L	4.44 (0.60)	4.34 (0.65)	-0.10	0.16	0.88	0.39
HDL cholesterol	1.38 (0.29)	1.40 (0.29)	0.02	0.07	-0.22	0.83
TSH, mIU/L	1.40 (0.46)	1.64 (0.44)	0.24	0.53	-2.42	**0.03***
Nutrient levels						
Magnesium, mmol/L	0.92 (0.07)	0.89 (0.05)	-0.02	0.49	1.39	0.19
Ferritin, µg/L	47.00 (23.26)	42.62 (21.58)	-4.39	0.20	1.08	0.30
Iron, µmol/L	15.77 (4.69)	16.77 (5.04)	1.00	0.21	-0.60	0.56
Zinc, µmol/L	12.12 (1.29)	13.18 (1.53)	1.06	0.75	-3.07	**0.01****
Copper, µmol/L	15.47 (4.07)	14.68 (1.82)	-0.79	0.25	0.91	0.38

Note. APT = Activated partial thromboplastin, WBC = White blood cells, GGT = Gamma-glutamyl transpeptidase, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, HDL = High-density lipoprotein, TSH = Thyroid-stimulating hormone; **denotes statistically significant difference at $p<.01$ level; *denotes statistically significant difference at $p<.05$ level SEM = standard error of the mean, SEM = $\frac{\sigma}{\sqrt{n}}$

a. ES = Cohen's *d* measured as the mean difference pre-post/mean SD of the difference

Table 16 presents reference ranges and the number of participants that fell outside the normal reference ranges for the blood work collected.

Table 16

Reference Ranges of Safety Markers and Nutrient Levels and the Participant Numbers of Those Who Fell Outside These Ranges at Baseline and Post Intervention (i.e., The Same Person had Platelet Elevations at Baseline and End of Micronutrient Intervention).

		Outside Normal Reference Ranges			
		Baseline		**Post**	
	Reference Ranges	Deficient	Elevated	Deficient	Elevated
Safety markers					
Prolactin, mlU/I	Male 50-350 Female 50-550	0	1 (11)	0	2 (3,7)
Creatinine, µmol/I	40-80	0	1 (1)	0	0
Fasting Glucose, mmol/I	3.9-5.8	0	0	0	0
APT time, s	25-35	0	1 (10)	0	2 (3,10)
Platelets, x 10(9)/L	150-425	0	1 (3)	0	1 (3)
WBC, x 10(9)/L	5.0-14.5	0	0	0	0
Lymphocytes, x 10(9)/L	1.4-4.5	0	0	0	0
Neutrophils, x 10(9)/L	1.5-7.0	1 (5)	0	0	0
GGT, U/L	< 30.00	0	0	0	0
AST, U/L	15-40	0	0	0	0
ALT, U/L	10-35	0	0	0	0
Triglyceride, mmol/L	> 1.70	0	0	0	0
Cholesterol, mmol/L	> 5.20	0	0	0	0
HDL cholesterol	> 1.00	0	0	0	0
TSH, mIU/L	0.32-5.00	0	0	0	0
Nutrient levels					
Magnesium, mmol/L	1.6-2.3	0	0	0	0
Ferritin, µg/L	15-200	1 (9)	0	1 (9)	0
Iron, µmol/L	6-25	0	0	0	0
Zinc, µmol/L	10-17	0	0	0	0
Copper, µmol/L	13.2-21.4	4 (3,6,7,9)	2 (2,12)	2 (7,9)	0

Note. APT = Activated partial thromboplastin, WBC = White blood cells, GGT = Gamma-glutamyl transpeptidase, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, HDL = High-density lipoprotein, TSH = Thyroid-stimulating hormone; The total number of participants outside the normal range are represented by one number, the numbers in parenthesis identifies the participant i.e,. 4 (3,6,7,9) = four participants were elevated or deficient, and these four participants are participant number 3, 6, 7 and 9

4.7 Follow-up Data

Thirteen of the original 14 participants accepted the invitation to take part in the 6-month follow-up phase. The fourteenth participant did not respond to attempts at contact. Participants were considered to be 'on' the micronutrient if they were taking the dose that was considered optimal for that individual, as it ranged from 8-15 depending on the participant. Five of the 13 participants who attended the six-month follow-up were currently taking the micronutrient formula, EMP+, or DEN (Daily Essential Nutrients, a newer, but very similar, version of EMP+). Three participants reported taking the micronutrients consistently since the study ended, and had noticed continued improvements and expressed no wish to discontinue the treatment. Two participants had stopped taking EMP+ after the study finished but had begun taking them again a few months before the follow-up visit after a return of symptoms. Seven participants stayed off the micronutrient at the end of the study and one began taking 40mg of Ritalin alongside two micronutrient capsules a day. As the one participant taking medications was also taking a micronutrient dose significantly lower than the recommended dose of 15 a day, and below the optimal dose for him (i.e., 12) as determined through the completion of the study, he is considered to be part of the group that came off the micronutrient formula following the study's completion.

Of the participants who discontinued taking EMP+, one participant stopped taking the capsules after the study ended as they were "annoying to take" and the participant struggled to eat breakfast in the morning, which made taking the capsules even more difficult. Another participant's family were trialling the "fail safe diet", which is designed to eliminate food additives, salicylates, and flavour enhancers. Although the family thought the micronutrients had helped, the participant disliked the taste, and mentioned some stomach discomfort. The family was currently looking for some counselling to help with some unwanted behaviours. Another participant was undertaking an assessment process with

Whakatata House, a Child and Family Specialty Service, with the possibility of trying stimulant medication. Three participants described phasing out the micronutrients over the six-months after the trial, with two expressing interest in trialling DEN. One participant's parent described a benefit in well-being and overall mood while their child was taking the micronutrients, but experienced continuous difficulty with concentrating in class. Three months after completing the study the participant started taking 40mg of Ritalin, alongside 2 EMP+ capsules a day, "to fit in with the expectations at school", although the mother preferred the micronutrients. This participant was considered to be in the group of participants who came off the micronutrient treatment due to currently taking stimulant medication and the low dose in which the micronutrient was being consumed. The final participant who discontinued the micronutrients showed significant improvement while taking EMP+, noted by both family and friends; however, the participant decided against taking the micronutrients once the study ended and his family was not able to persuade him to continue. These findings suggest that long-term compliance may be more difficult for some individuals.

4.7.1 Modified Brinley Plot Analyses for Follow-up Data

In the figures below, a series of modified Brinley plots display individual change at the six-month follow-up compared to different phases of the study. For each individual a measurement made at Baseline, On 2 and Off 2 is plotted on the X axis against a measurement on the same variable, for that same individual, at the six-month follow-up, which is plotted on the Y axis. The subscales of the CPRS-R:L are dependent variables that are shown as separate rows in Figure 10, and for the YMRS, CDRS and CGAS outcome measures a single row is shown (see Figures 11 and 12).

The first column on Figure 10 shows that the majority of participants' are functioning above their baseline score at the six-month follow-up, whether they continued to take the micronutrients (solid dots) or came off the micronutrients (hollow dots). This is illustrated by nine of the individual plots on the inattention subscale falling below the line of no change and 11 of the participants falling below the line of no change for both the hyperactive-impulsive subscale and combined subscales. The second column compares individual scores after the second intervention phase (On 2) to their six-month follow-up scores. Two participants from each group appear to be functioning just as well at follow-up as their second intervention phase, falling on the line of no change, or slightly better, for all three subscales. However, the majority of participants appear to be experiencing greater difficulties, regardless of whether they are still taking the micronutrients or not, at the follow-up compared to the second on phase. The final column, which compares the end of the study (Off 2) to the six-month follow up, reveals a greater decrease in ADHD symptoms for those that stayed on the micronutrients, with a majority of individuals, as well as the mean (as represented by the solid cross), falling below the line of no change. For the participants who chose to discontinue taking the micronutrients, the means (as represented by the dotted cross) and individual plots are closer to the line of no change.

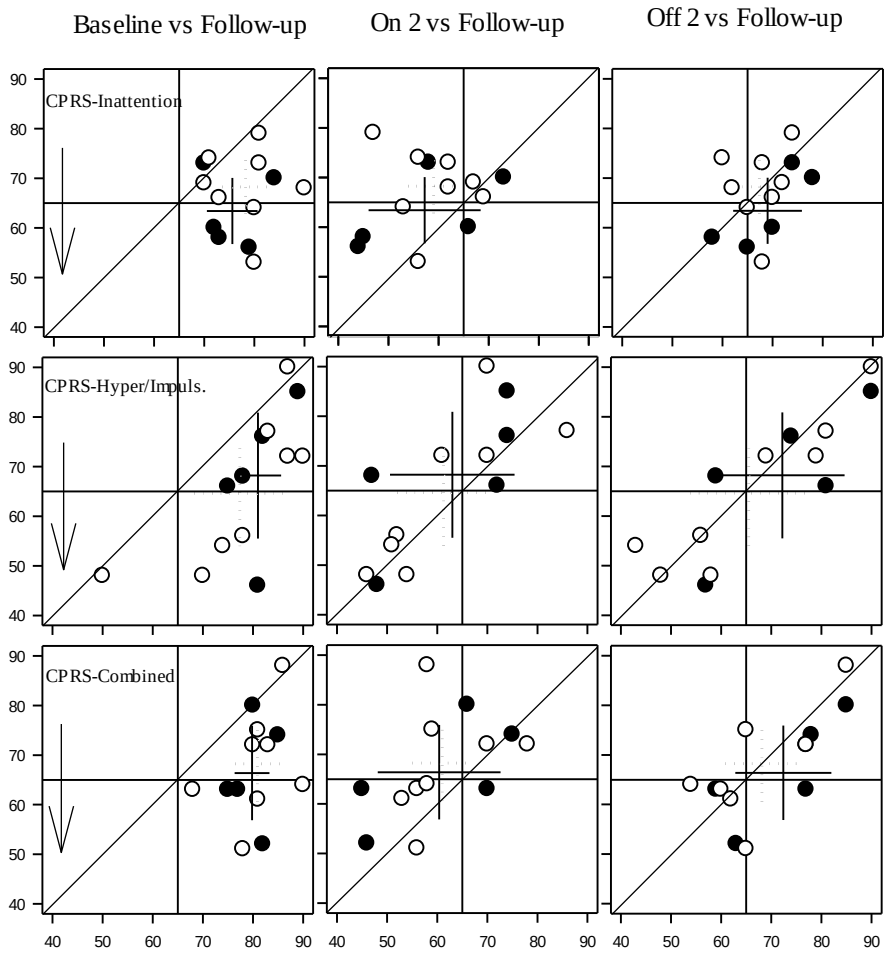


Figure 10. Modified Brinley plots displaying change on parent-rated outcome measure, CPRS-R:L, at the six-month follow-up compared to baseline, second on (On 2) and second off (Off 2) phases

Note. ○ = represents those who came off the micronutrient, ● = represents those who stayed on

= represents means and confidence intervals for those who came off the micronutrients

= represents means and confidence intervals for those who stayed on

Figure 11 illustrates changes in the clinician-rated outcome measures (YMRS and CDRS) at the six-month follow-up compared to different phases of the study. Similar to the reported ADHD behaviours above, there is an improvement shown at the follow-up compared to baseline; regardless of whether they stayed on the micronutrients or came off them. The majority of participants have improved mood at the follow-up compared to their baseline mood (initial plot on both measures). The second plot, comparing the second

intervention phase to the follow-up phase, illustrates that most of the participants who stayed on the micronutrients are experiencing an increase in mood at the six-month follow-up that is similar to the end of the intervention phase on both the YMRS and CDRS. For the individuals who chose to come off the micronutrients, the majority of individual plots fall above the line of no change signifying a decrease in mood compared at the six-month follow-up compared to the end of the second intervention. The final plot compares mood the end of the study (Off 2) to mood at the six-month follow-up. Both groups show slight improvement in mood on the YMRS at the follow-up compared to the end of study, three of the five that stayed on the micronutrients and four of the eight that came off the micronutrients. No significant change on the CDRS was found at follow-up compared to the end of the study, with the majority of individual plots falling along the line of no change, regardless of the group.

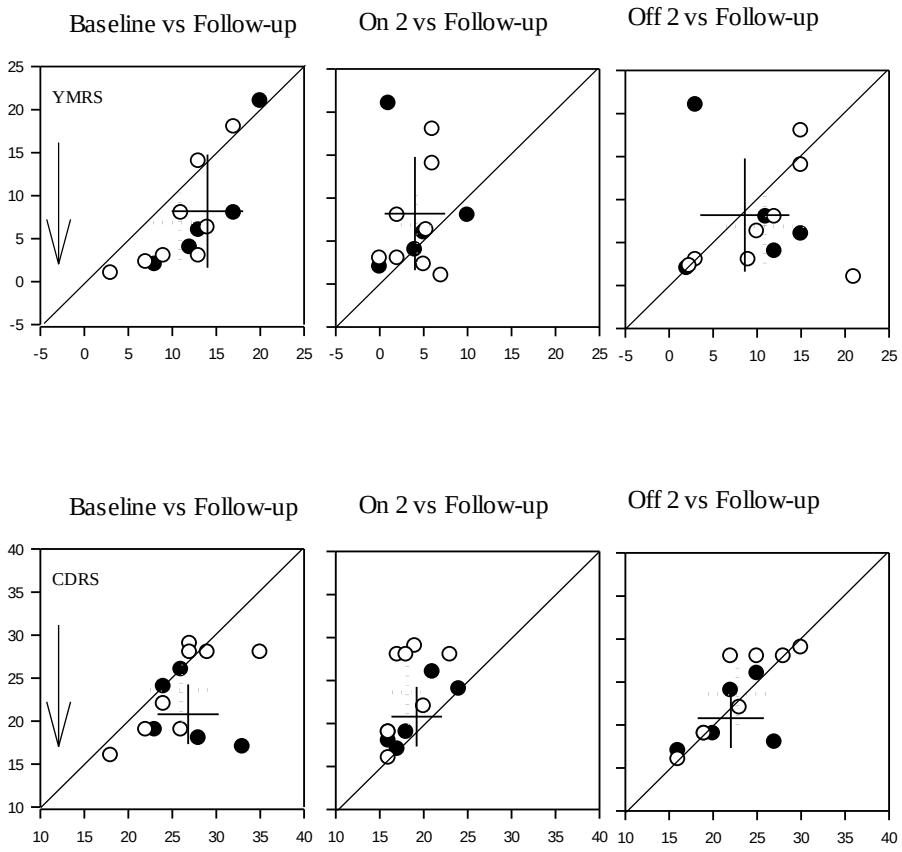


Figure 11. Modified Brinley plots displaying change in clinician-rated YMRS and CDRS, at the six-month follow-up compared to baseline, second on (On 2) and second off (Off 2) phases

Note. ○ = represents those who came off the micronutrient, ● = represents those who stayed on

= represents means and confidence intervals for those who came off the micronutrients

= represents means and confidence intervals of those who stayed on

Figure 12 shows the individual participants' overall functioning at the six-month follow-up compared to other phases of the study. Again, individuals show an improvement in functioning at the six-month follow-up visit, compared to baseline functioning, regardless of whether they continued or discontinued taking the micronutrients (first plot). However, those who stayed on the micronutrients show greater improvements in overall functioning, compared to those who came off the micronutrients. The second plot reveals that those who came off the micronutrients have a decrease in overall functioning compared to their scores after the second intervention phase. Individuals who continued taking the micronutrients at the six-month follow-up were generally performing the same as their functioning at the end of the second intervention phase. All participants who continued taking the micronutrients are doing better at the six-month follow-up compared to the end of the study (Off 2), whereas those who came off the micronutrients display no change in functioning at six-months compared to the second withdrawal phase (Off 2), as revealed in the final plot.

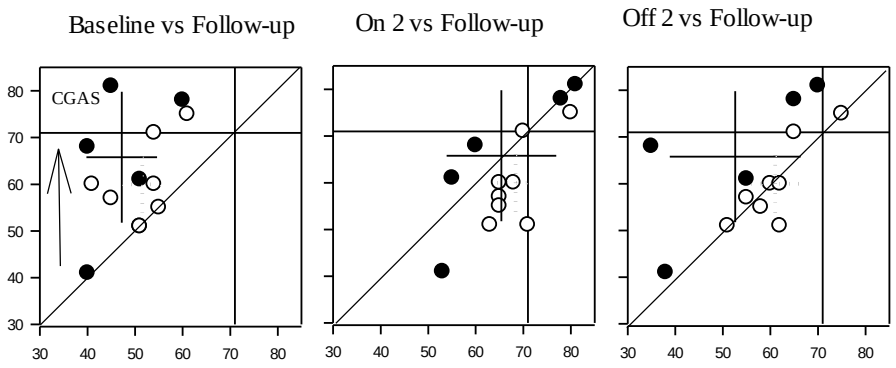


Figure 12. Modified Brinley plots displaying change in clinician-rated overall function on the CGAS, at the six-month follow-up compared to baseline, second on (On 2) and second off (Off 2) phases

Note. ○ = represents those who came off the micronutrient, ● = represents those who stayed on

= represents means and confidence intervals for those who came off the micronutrients

= represents means and confidence intervals of those who stayed on

4.7.2 Group Analyses for Follow-up Data

Cohen's *d* effect sizes, 95% confidence intervals and paired sample *t*-tests, when investigating within group differences across time, and independent *t*-tests, for comparisons across groups, were used to analyse the six-month follow-up data. Cohen's *d* effect sizes between the two groups were adjusted using a calculation of pooled SD with weights for the differing sample sizes. Figure 13 illustrates the inattention scores reported by parents on the CPRS-R:L. Scores at the 6-month follow-up show the participants who chose to stay on the micronutrient formula dropped below the clinical cut-off of 65 for problems with attention (M = 63.40, SE = 3.40). Those who chose to come off the micronutrient formula following the study, although the scores did not return to baseline severity, stayed above the cut-off for inattention (M = 68.25, SE = 2.76). A medium effect was found for those that stayed on the micronutrient, compared to those who discontinued micronutrient use $d = 0.63$ (95%CI [-0.53 to 1.76], $t(11) = -1.10$, $p = .30$), however, the two groups were not statistically different at the 6-month follow-up. A large effect was found when comparing scores at the end of the study, Off 2, to 6-month follow-up scores for the group that stayed on the micronutrients $d = 0.73$ (95% CI [-0.32, 2.33], $t(4) = 2.65$, $p = .057$). No effect on inattention was found at the 6-month follow-up, compared to the end of the study (Off 2), for the group that came off the micronutrients $d = 0.13$ (95% CI [-0.60, 0.79], $t(7) = -0.29$, $p = .78$).

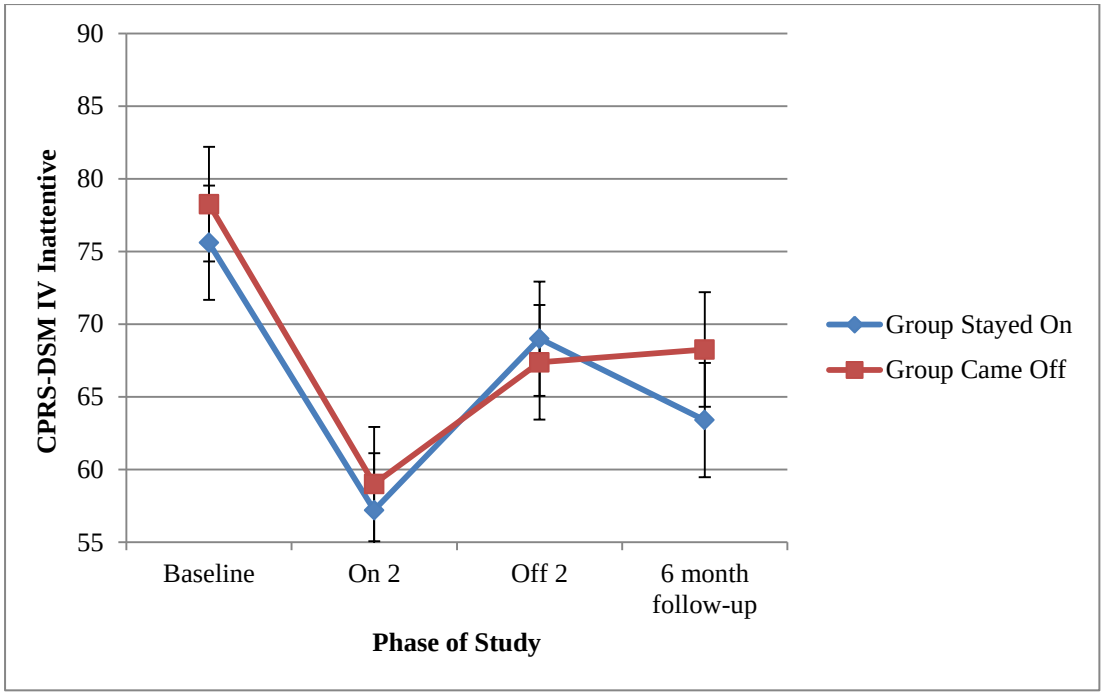


Figure 13. CPRS-DSM IV inattention scores (*T*-scores)- across time for those who stayed on micronutrients versus those who came off. Means and SE bars are shown for the different groups at each phase.

Note. Scores above 65 indicate clinical elevations in ADHD symptoms; CPRS = Conners' Parent Rating Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

Group mean hyperactive-impulsive scores for different phases of the study are displayed in Figure 14 below. Scores on the CPRS-R:L hyperactive-impulsive subscale showed a greater decrease in hyperactivity and impulsive behaviours, at the six-month follow-up compared to the end of the study (Off 2), for those who continued to take the micronutrient formula (M = 4.00, SE = 4.34) compared to those who came off the micronutrients (M = 0.88, SE = 2.27). A small effect was observed when comparing the two groups at the end of the six-month follow-up; however, an independent t-test revealed the difference was not significant d = 0.24 (95% CI [-0.89, 1.36], $t(11)$ = 0.42, p = .69).

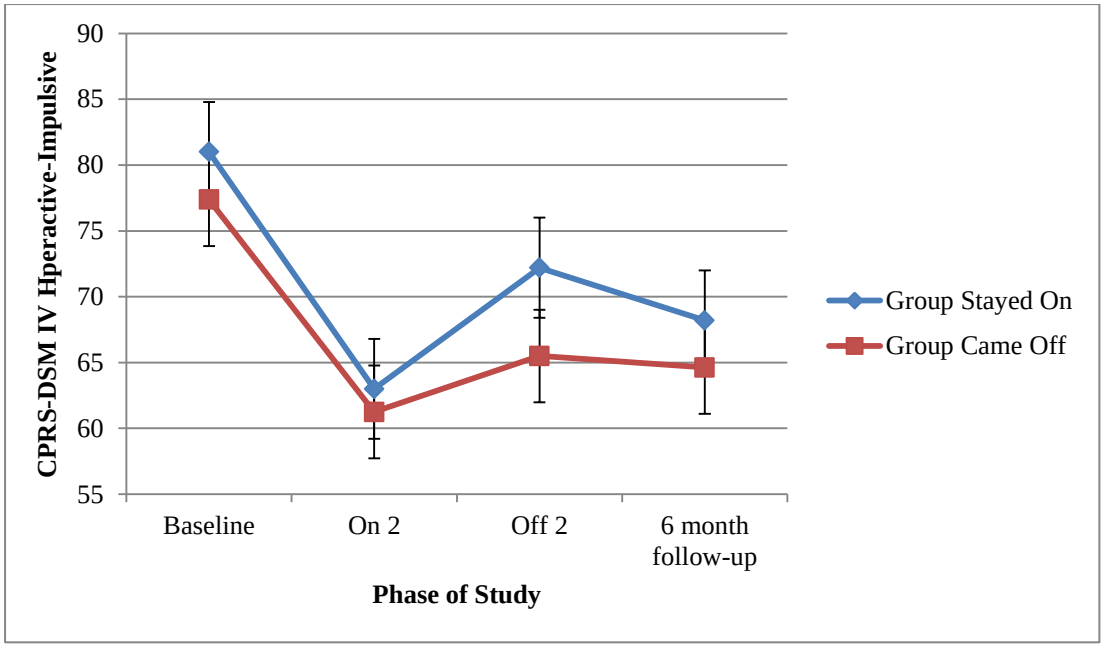


Figure 14. CPRS-DSM IV hyperactivity/impulsivity scores (*T*-scores)- across time for those who stayed on micronutrients versus those who came off. Means and SE bars are shown for the different groups at each phase.

Note. Scores above 65 indicate clinical elevations in ADHD symptoms; CPRS = Conners' Parent Rating Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

Figure 15 shows mean scores for the different groups on the CPRS-R:L combined subscale. Those who continued micronutrient use display a steady decrease in overall symptoms of ADHD at the 6-month follow-up, mean difference of 6.0, SE = 3.11; where the score for those who discontinued micronutrients stayed relatively stable, with only a slight increase in symptoms from the end of the study to the 6-month follow-up, mean difference of -0.13, SE = 2.88. No effect was detected when comparing the two groups at the 6-month follow-up d = 0.17 (95% CI [-0.95, 1.29], $t(11)$ = -0.30, p = .77), as evident in Figure 12.

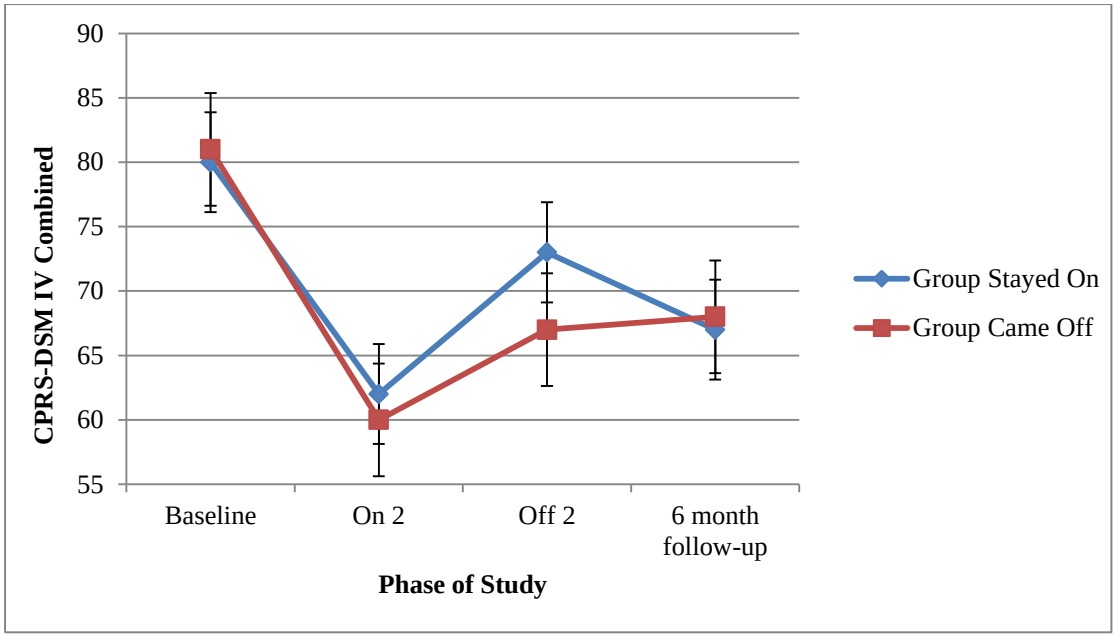


Figure 15. CPRS-DSM IV Combined total scores (*T*-scores)- across time for those who stayed on micronutrients versus those who came off. Means and SE bars are shown for the different groups at each phase.

Note. Scores above 65 indicate clinical elevations in ADHD symptoms; CPRS = Conners' Parent Rating Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

Those who continued micronutrient use displayed improvements in mood at the 6-month follow-up, whereas those who discontinued micronutrients showed a decrease in mood when compared to their scores at end of the study (Off 2). A medium effect for mood was observed on the CDRS at the six-month follow-up $d = 0.59$ (95% CI [-0.57, 1.72], $t(11) = -1.03$, $p = .32$); however, an independent *t*-test found this difference non-significant. Although the 6-month data did not detect statistically significant difference across the groups, the graph illustrates that those who stay on the micronutrient may experience fewer difficulties with mood over time and those who come off the micronutrient may experience greater difficulties with mood as time goes on (see Figure 16).

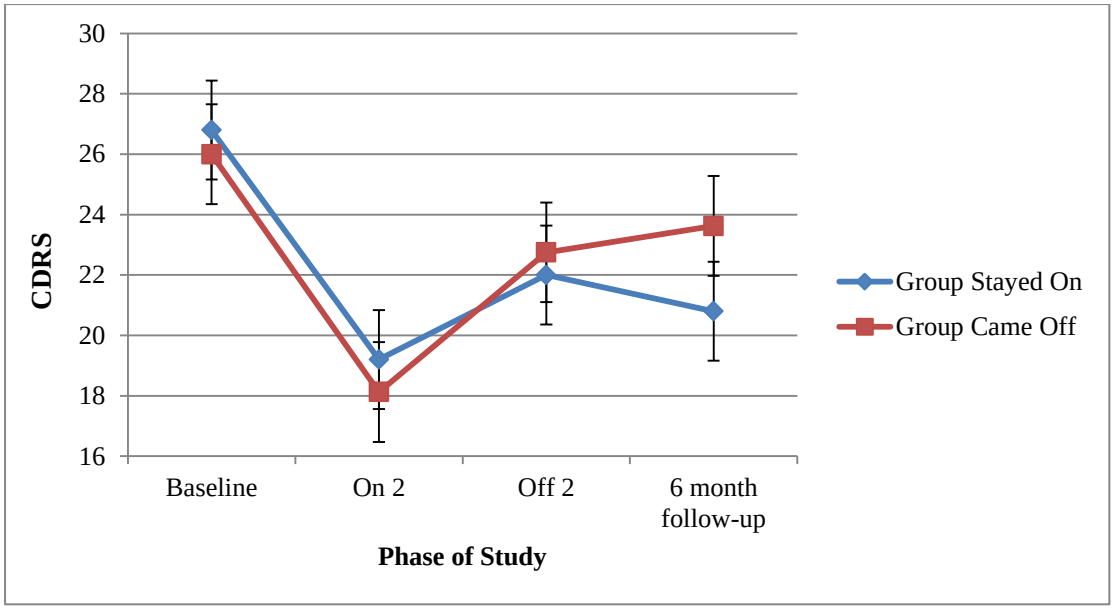


Figure 16. CDRS- depression scores across time for those who stayed on the micronutrients versus those who came off. Means and SE bars are shown for the different groups at each phase. *Note*. The higher the score the greater the mood difficulties; CDRS= Children's Depression Rating Scale.

At 6-months follow-up the CGAS was used, by the clinician, to measure the participants overall functioning. For those that stayed on the micronutrient, the mean overall functioning was 66.0, compared to a score of 60.0 for those that discontinued micronutrient use. When comparing the groups at follow-up, a small effect was found, although this difference was not statistically significant d = 0.49 (95% CI [-0.66, 1.61], $t(11)$ = 0.85, p = .41). A large effect was found when comparing the end of the study (Off 2) functioning to follow-up functioning for the group that stayed on the micronutrients d = 0.83 (95% CI [-0.07, 2.24], $t(4)$ = -2.51, p = .066). It is also important to note that at the end of the study (Off 2), the group that came off were doing better (M = 61.0, SE = 2.54) than the group that ended up staying on the micronutrient (M = 52.6, SE = 7.01). A medium effect was found when comparing the two groups at the end of the Off 2 phase, however, an independent t-test found the difference was not statistically significant d = 0.76 (95% CI [-0.52, 1.78], $t(11)$ = -1.13, p

=.31). The group that stayed on the micronutrients showed an increase in functioning by 13 points compared to a decrease in functioning of 1 point for the group that discontinued using micronutrients (Figure 17 below).

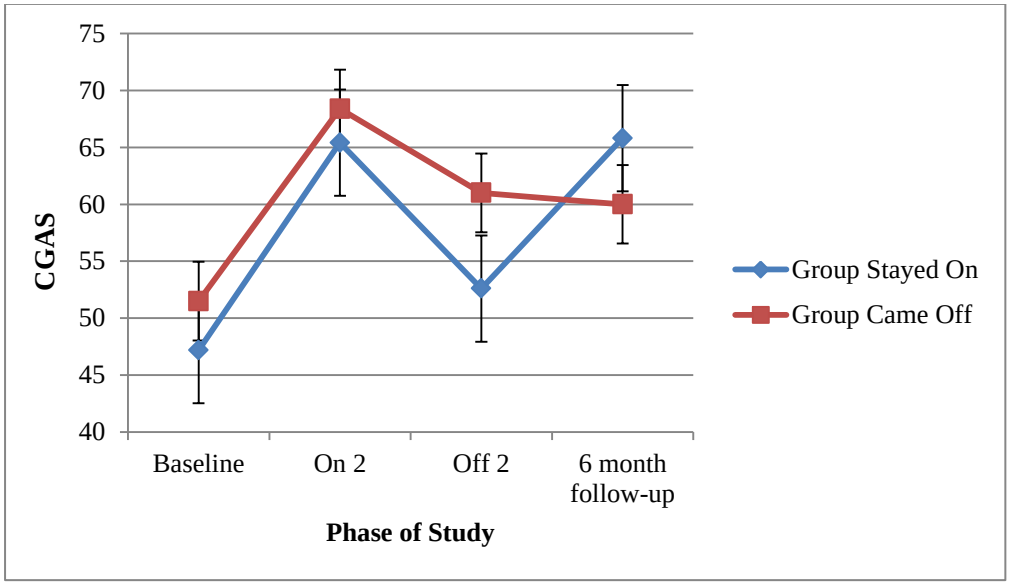


Figure 17. CGAS- overall functioning across time for those who stayed on the micronutrients versus those who came off. Means and SE bars are shown for the different groups at each phase.
Note. The higher the score the better the functioning, a score above 70 indicates 'normal functioning'; CGAS= Children's Global Assessment Scale.

At the 6-month follow-up, the CGI was used to gather an overall clinical impression of each participant's functioning. All participants began with a score of four at baseline; as indicated by the line of 'No Change' on Figure 18 below. After the second on phase, On 2, all participants were rated as 'Much Improved'. When comparing the two groups at the second off phase, a large effect was found d = 1.13 (95% CI [-0.11, 2.31], $t(11)$ = 1.97, p = .075). The group that stayed on the micronutrients showed a reversal to baseline functioning when the micronutrients were withdrawn (Off 2). The group that came off the micronutrients showed a slight reversal when the micronutrients were withdrawn, however, at the second off

phase they still show some improvement as compared to baseline functioning. At the 6-month follow-up, those who chose to stay on the micronutrients had greater improvement in functioning (M = 2.40, SE = 0.58), compared to those who came off the micronutrients (M = 3.38, SE = 0.38), a score closer to four signifies less change. A large effect was observed for clinicians impression of participant functioning, however, this difference was not statistically significant d = 0.85 (95% CI [-0.34, 2.00], $t(11) = -1.49$, $p = .17$).

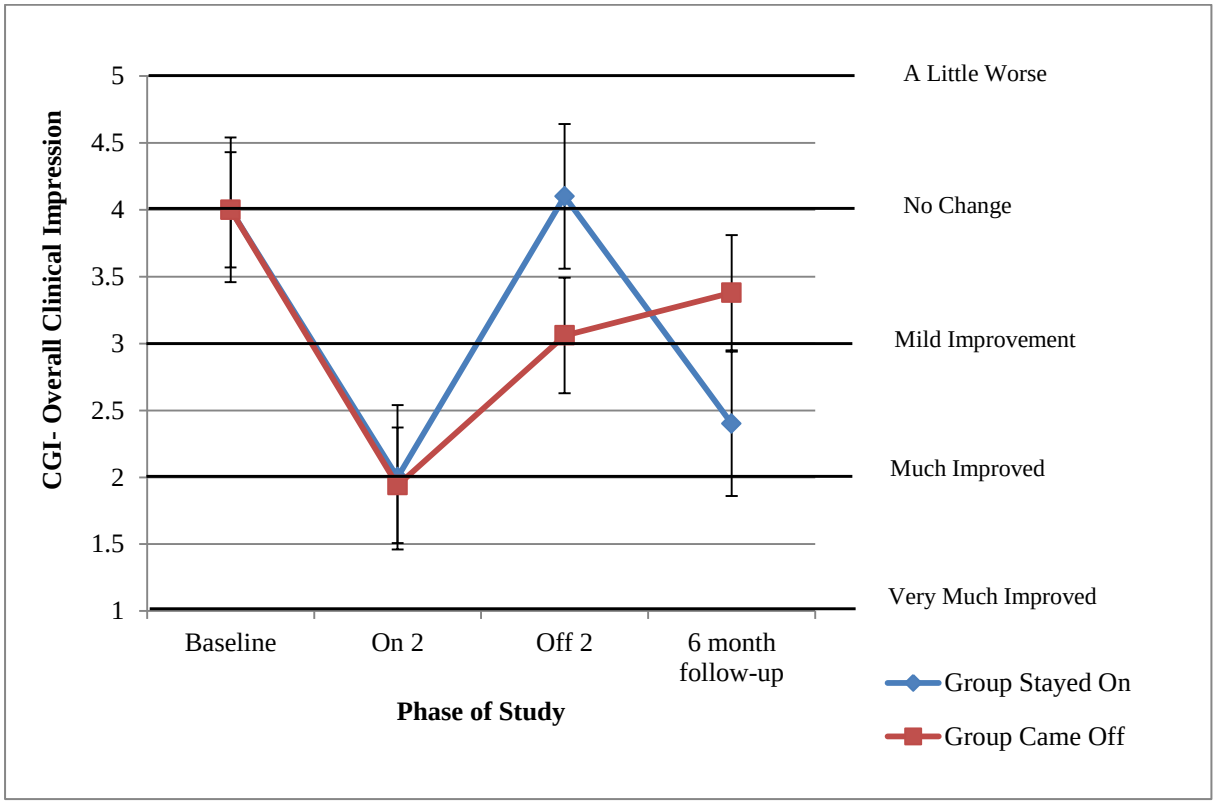


Figure 18. CGI- Mean Overall Clinical Impression of each group at the different phases of the study. Means and SE bars are shown for the different groups at each phase.

Note. The lower the score the better the functioning, a score of 1 indicates 'Very Much Improved', a score of 2 = 'Much Improved', 3 = 'Mild Improvement', 4 = 'No Change', 5 = 'A Little Worse', 6 = 'Much Worse'; CGI= Clinical Global Impressions Scale.

The CGI was also used to indicate the severity of ADHD, as rated by the clinician, at the end of each phase of the study (see Figure 19). A large and significant effect was found for those who stayed on the micronutrients d = 1.09 (95% CI [0.44, 3.76], $t(4) = 4.74$, p = .01); participants who continued taking the micronutrients had a significant decrease in ADHD severity at the 6-month follow-up, compared to their end of study score (Off 2). No effect or significant difference in ADHD severity was found for participants who chose to discontinue micronutrient use, when comparing the end of study mean score to the 6-month follow-up mean score (Off 2) d = 0.09 (95% CI [-0.59, 0.80], $t(7) = 0.31$, p = .76). At the 6-month follow-up, for those who stayed on the micronutrients, there was a decrease in ADHD severity similar to the second on phase scores (M = 2.8, SE = 0.60); where those who came off the micronutrients stayed relatively stable to their end of study (Off 2) scores (mean difference = 0.06). The six-month follow-up data revealed a large effect for ADHD severity d = 1.11 (95% CI [-0.12, 2.30], $t(11) = -1.95$, p = .077).

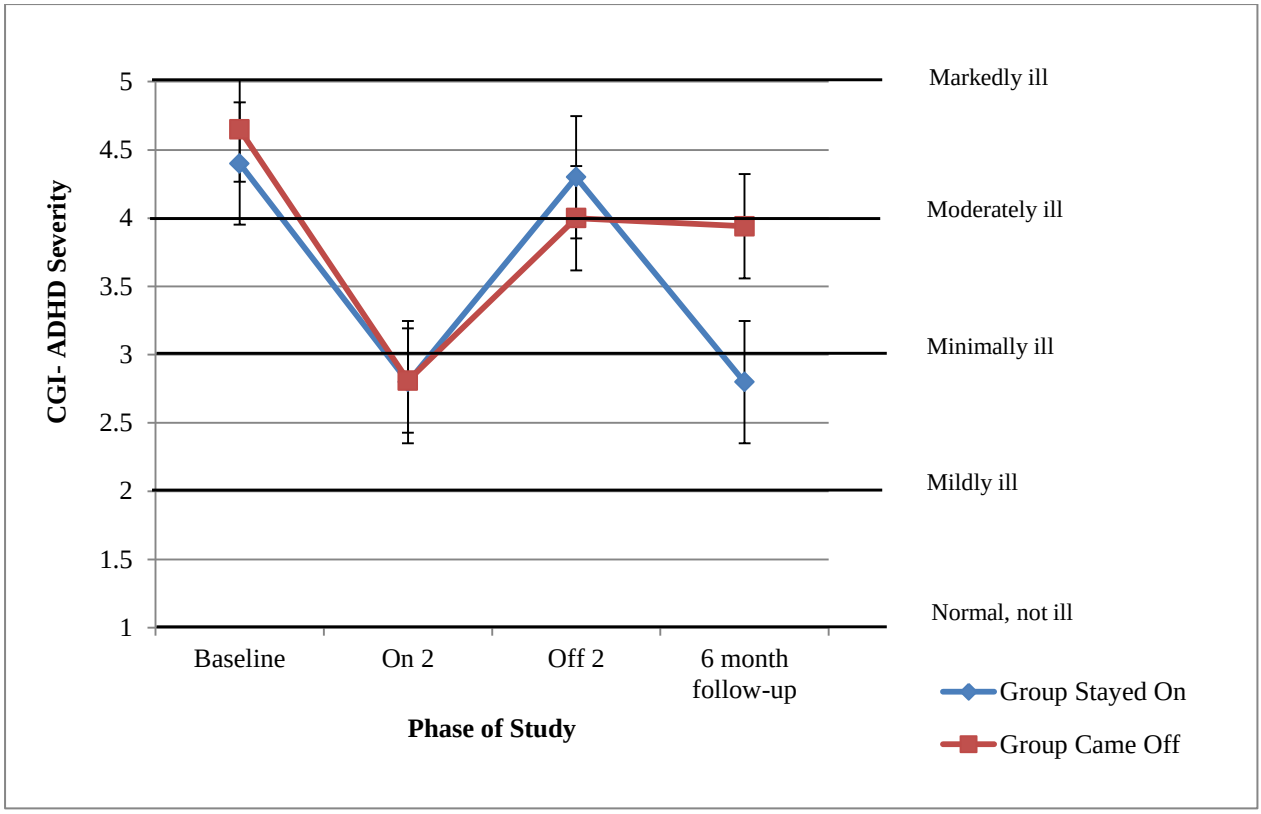


Figure 19. CGI- Mean ADHD Severity across phases of the study for each group. Means and SE bars are shown for the different groups at each phase.

Note. The lower the score the better the functioning, a score of 1 indicates 'Normal, not ill', a score of 2 = 'Mildly ill', 3 = 'Minimally ill', 4 = 'Moderately ill', 5 = 'Markedly ill'; CGI= Clinical Global Impressions Scale.

Chapter 5: Discussion

This chapter will first highlight the current research objectives and then explore the key findings. The potential mechanisms of action and theoretical frameworks will be reintroduced and discussed regarding the current study's findings. The current research's strengths and limitations will be discussed in detail, as well as the feasibility, general implications and recommendations for future research.

5.1 Thesis Objectives

The current research set out to achieve the following objectives that were outlined as hypotheses in the introductory chapter (Section 2.5).

1. To determine if the consumption of the micronutrient formula would be associated with a decrease in ADHD behaviours and improvements in overall general functioning associated when taking the micronutrient.
2. Whether ADHD behaviours would return to baseline or near baseline symptom severity when the micronutrients were withdrawn, as well as deterioration in overall functioning when not taking the micronutrients.
3. Whether improvements in overall general functioning, and a decrease in ADHD behaviours, would occur when the micronutrient formula was reintroduced, replicating any improvements found during the initial on phase.
4. To document any adverse events experienced by the participants when taking the micronutrient formula.
5. To determine whether children would be able to swallow 15 pills a day.
6. To determine whether children who continued to take the micronutrients would continue to show a benefit at the six month follow-up compared to the children who discontinued micronutrient use.

Objectives one, two and three were achieved throughout the course of the study, given that the reversal design revealed a clear on/off effect replicated across participants. Objectives four and five were achieved through close monitoring throughout the study. For those who ingested fewer than 15 pills a day, this reduction in consumption was due to the effect of the number of pills that had been consumed and not due to lack of swallowing ability. Objective six was achieved for 13 of the 14 participants six months post end of study.

5.2 Summary of Key Findings

The current study contributes to the sparse literature investigating micronutrients as a treatment for children with ADHD. The micronutrient intervention brought about a clinically significant reduction in ADHD symptoms and an increase in overall functioning. The results from the current study are consistent with the most recent research using EMP+ for an adult ADHD population (Rucklidge et al., 2014a), and the limited research available in terms of micronutrient interventions for children with ADHD. During the intervention phases a significant decrease in ADHD behaviours was found, as well as an increase in mood and overall functioning as rated by the parent, child and clinician. These positive results were clearly presented in time series graphs and modified Brinley plots, quantified by positive Cohen's *d* effect sizes, 95% confidence intervals and tested by *t*-tests.

The current study was a single case reversal (ABABA) design that investigated the effectiveness of micronutrients on ADHD and other psychiatric symptoms (i.e. depression and mania). The study also included a 6-month follow-up assessment to determine the longer-term effectiveness of micronutrients in treating ADHD behaviours, and collect data on any long-term adverse events the participants may have experienced. The current sample reflects a group of children diagnosed with ADHD. Eight of the 14 participants also met criteria for at least one comorbid DSM-IV disorder, which is representative of the ADHD population, and

all were experiencing significant daily impairment prior to the first treatment phase. A majority of participants had trialled psychiatric medications in the past. They either did not respond to the medication, and therefore may represent a treatment-resistant population, or did not tolerate the side-effects associated with the psychiatric medication. Of clinical interest, adverse events experienced on the micronutrient formula, if present at all, were only minor and transitory, consisting mainly of gastrointestinal discomfort and headaches.

The hypotheses were generally supported. The primary hypothesis proposed that the micronutrient intervention would be associated with a decrease in ADHD behaviours and improvements in overall functioning after the initial micronutrient intervention. This hypothesis was supported in that participants experienced a significant decrease in ADHD symptoms after the micronutrient intervention that resulted in the mean score for all three ADHD subscales falling below the clinical cut off of 65 after the initial intervention phase. The modified Brinley plots display the clear on/off pattern of the intervention on ADHD behaviours as rated by the parents. The initial plot, of the four array of plots, demonstrated the decrease in ADHD symptoms as the individual plots fall away from the line of no change and the cross representing the group mean and standard deviation also deviates from the line of no change. This was particularly clear on the inattention and combined subscales of the CPRS-R:L, which is to be expected as none of the participants in the current study were diagnosed predominantly hyperactive-impulsive. The clinician-rated overall functioning (CGAS) found participants experienced an improvement in overall functioning associated with the micronutrient intervention, with three participants functioning at a level considered to be within the 'normal range' at the end of the initial micronutrient intervention phase.

Results from the current study are consistent with the previous literature indicating that the micronutrient intervention, EMP+, is associated with significant improvements in mood and general functioning (Popper, 2001; Simmons, 2002, Frazier et al., 2009; Frazier et

al., 2012; Gately & Kaplan, 2009; Rucklidge & Harrison, 2010; Rucklidge et al., 2010; 2011; 2014a). Parent- and clinician-rated mood measures revealed improvements in mood after the initial micronutrient treatment, as recorded by the CMRS, YMRS and CDRS. These improvements were clearly represented by the pattern displayed on initial modified Brinley plot of each outcome measure.

It is important to highlight that participants did seem to get better when comparing baseline scores to subsequent phases of the study, regardless of whether they were on or off the micronutrient formula. Small to large effect sizes were found when off phases were compared to baseline on parent- and clinician-rated measures (CPRS-R:L, CMRS, CDRS, CGAS & YMRS), suggesting that there was still an effect on symptoms during the reversal phases compared to baseline. Potential reasons for an effect to occur during a withdrawal phase are described in further detail when discussing the second hypothesis below. The estimated true effect of the initial micronutrient intervention—the effect size from the first treatment phase minus the effect size during the first withdrawal phase—were still within the medium to large ranges for all parent- and clinician-rated outcome measures. This suggests that the initial micronutrient intervention, above and beyond possible unintended trial effects, had medium to large effects on the participants' ADHD symptoms, mood, and overall functioning as measured on the CPRS-R:L, CMRS, CDRS, CGAS, and YMRS. This is comparable to the most recent meta-analyses examining the effects of stimulant medication on ADHD behaviours, which found medium to large effect sizes (Faraone, 2009; Faraone & Buitelaar, 2010).

Although scores on the ADHD and CGAS outcome measures did not return to baseline symptom severity during the withdrawal phases (Off 1 & Off 2), as the second hypothesis proposed, there was a trend back toward baseline severity observed that is clearly visible on the modified Brinley plot graphs. After the first withdrawal phase, both the

hyperactivity subscale of the CPRS-R:L and the CGAS revealed increases in ADHD behaviours and a deterioration in overall functioning that was approaching baseline severity. The second withdrawal phase again resulted in a reversal of ADHD symptom severity and overall level of functioning trending towards baseline, as shown by the individual participant scores on the modified Brinley plots falling back towards the line of no change; however, the deterioration was less extreme than shown during the first withdrawal phase.

A similar trend was found for parent and clinician-rated measures of mood. A decline in participants' mood that exceeded baseline severity and approached clinically significant depression (scores of 30 and higher), was found on the CDRS after the first withdrawal phase. Parent and clinician measures of mania (CMRS & YMRS) revealed a deterioration towards baseline severity after the initial withdrawal phase, and again (although less robust) after the second withdrawal phase. The modified Brinley plots display this reversal in mood symptoms, on both parent- and clinician-rated measures, as individual plots move toward the line of no change and the plotted means fall on the line of no change, during the withdrawal phases.

As mentioned above, contrary to expectations, participants' symptoms were generally less severe during withdrawal phases than at baseline, with a large effect identified between the second withdrawal scores and baseline scores. One possible reason for the effects found during withdrawal phases is that participants may be experiencing residual effects of the micronutrient formula; build-up of the micronutrient formula may take varying amounts of time to dissipate for each individual. Another reason could be the significantly shorter withdrawal phases of the current study (four weeks or less) compared to the eight week duration of the on phases. This shorter time period was due to requests from participants to resume taking the micronutrients early, due to the return of symptoms. This may have particularly affected their reported functioning over the first couple of weeks during the off

phases. Also, the fortnightly visits may have given the participant, and their parent/caregiver, a place to discuss what has been going on for them over the past fortnight. Although no therapy or any intervention was offered, discussing behaviours and filling out questionnaires may have brought a focus to behaviours that may have otherwise gone unnoticed and therefore facilitated change. This could be due to factors such as the 'Hawthorne effect', which is associated with an increase in positive responding from the participant due to the increased attention received and knowledge of being observed (De Amici, Klersy, Ramajoli, Brustia, & Politi, 2000). Another factor that may have resulted in improved functioning during off phases compared to baseline is that, during the on phases, participants eating habits may have altered due to the requirement to consume plenty of food and water with the micronutrients. The potential increased intake of food and water at three meal times may have increased the participants' overall functioning, even during the off phases. It is also possible that ADHD symptom severity had been overestimated at baseline measurement with reported functioning at withdrawal phases a more accurate description of overall symptom severity.

The third hypothesis—that improvements would occur in ADHD symptoms, mood and overall general functioning after the micronutrients were reintroduced, replicating improvements found during the initial intervention phase—was also supported. There were further clinically significant decreases (dropping below the clinical cut-off) across the three ADHD subscales at the end of the second intervention phase, as measured by the CPRS-R:L. This intervention response is clearly presented through the modified Brinley plots revealing further reduction in ADHD symptoms at the end of the second intervention phase. Ten (71%) participants were observed to have at least a 30% decrease in combined ADHD symptoms at the end of the second on phase when compared to baseline functioning. Typically, a clinical response to an intervention has been defined as a 25% or 30% decline in ADHD symptoms

from baseline and/or a clinical global impression rating of one (very much improved) or two (much improved) at the intervention endpoint (Steele, Jensen, & Declan, 2006; Spencer et al., 2001).

Additional problematic behaviours were captured by subscales on the CPRS-R:L. Significant decreases were revealed in oppositional behaviours, social difficulties and emotional lability (rapid and excessive changes in mood) at the end of the second intervention phase compared to baseline scores. Consistent with results found on the CPRS-R:L, the parent-rated SDQ revealed a significant decrease in hyperactivity and conduct problems after the second micronutrient intervention, when compared to baseline. Large effects were found for the total difficulties reported, revealing clinically meaningful decreases in total difficulties and the impact score, when baseline was compared to the second on phase. The impact score on the parent-rated SDQ includes four areas of difficulty that impact the participants' everyday life, namely home life, friendships, classroom learning, and leisure activities. At baseline, the parent-reported difficulties that impacted the participants' daily lives typically fell between the 'quite a lot' and 'a great deal' categories. After the second micronutrient intervention parent ratings fell to between 'not at all' and 'only a little'.

The clinician-rated measures also supported the hypothesis that the reintroduction of the micronutrient intervention would be associated with a decrease in ADHD symptoms and an increase in overall functioning. Participants experienced an improvement in overall functioning associated with the micronutrient intervention, as measured by the clinician-rated CGAS, with four participants functioning at a level considered to be within the 'normal range' at the end of the second intervention phase. The CGI was utilised by the clinician to measure ADHD severity, and an overall impression of the participant, at each fortnightly visit. A large effect was found at the end of the second intervention phase, with one participant considered 'normal, not ill', ten participants in the 'minimally ill' to 'mildly ill'

categories and three participants considered ‘moderately ill’. The difference between baseline and the second on phase was statistically significant, with no participants exhibiting ADHD symptoms in the ‘markedly ill’ category, where seven participants were categorised within this category at baseline. The CGI also measured clinicians’ overall impression of the participant at the end of each visit. It was found, at the end of the second intervention phase, that one participant was ‘very much improved’, ten of the participants were ‘much improved’, two showed ‘mild improvement’ and one participant exhibited ‘no change’ compared to baseline.

The reintroduction of the micronutrients throughout the course of the second on phase resulted in further reductions in negative mood symptoms, as reported on parent- and clinician-rated measures. An overall improvement in participants’ mood was found on the CDRS, with the average score dropping below the borderline depression range (scores between 20 and 30). Parent- and clinician-rated measurements of mania (CMRS & YMRS) also showed replication of the improvements found in the initial micronutrient intervention phase, with statistically significant reductions in scores from baseline to the second on phase.

When comparing baseline teacher data to the micronutrient intervention phase, for the 11 participants that teacher data were available, small effect sizes were found for teacher-rated measures of hyperactivity/impulsivity, total ADHD symptoms, anxiety, perfectionism, social problems and conduct problems, as measured by the CTRS-R:L and SDQ, however, these changes were not statistically significant. A medium effect was found on the impact score as rated by the teacher. The impact score on the teacher-rated SDQ includes two areas of difficulty that impact the participants’ everyday life, namely peer relationships and classroom learning. Baseline scores revealed that teachers typically rated the difficulties as ‘quite a lot’ and after the micronutrient intervention their ratings fell between ‘not at all’ and ‘only a little’. Although this difference was not significant, the shift in categories reported

suggests there may have been a shift in participants' functioning that was not quantifiable by the questionnaires provided.

Both parent and teacher rating scales are preferred for clinical purposes (Pelham, Fabiano, & Massetti, 2005), however, it is unclear how well parent and teacher ratings correlate with each other. In a clinical population, teachers were found to have significantly less agreement with parent and self-reported ratings of externalising and internalising problems (Youngstrom, Loeber, & Stouthamer-Loeber, 2000). Another study found that although there was moderate to high levels of agreement on symptoms of ODD and CD between parent and teacher ratings, no agreement was found for ratings of ADHD symptoms (Antrop, Roeyers, Oosterlaan, & Van Oost, 2002). Variability in responding may be due to a number of factors such as perception of the individuals' difficulties, environmental factors and rater characteristics (Antrop et al., 2002; Sinn & Bryan, 2007). Due to the length of the current study, there were instances where switch points fell around holiday periods, which may have influenced their behaviour, and a few participants had changed schools or teachers just prior to beginning the trial. These factors may help explain the discrepancy discovered in the current study between parent and teacher ratings.

The current study also collected self-report measures from the participants, to gather the child's perspective of their difficulties, although participants did not always appear to have insight into the magnitude of their difficulties or the effect these had on their overall functioning. However, participants appeared to notice a change in their functioning between baseline and second micronutrient intervention. There was a significant decrease in self-reported hyperactivity, impulsivity and inattention as rated by the participants at the end of the second intervention phase (On 2), compared to their baseline scores on the MYMOP. Participants also reported less sleep disturbance and improved mood when comparing the second on phase to baseline. As participants were not always able to put into words what they

thought may have changed over the phases, this was an effective way to collect information about how they believed they were doing.

The neuropsychological task (CPT-II) used to measure complex cognitive function; including inattention, impulsivity and hyperactivity, found no overall treatment effects for the 12 participants who completed the task during an intervention phase and a withdrawal phase. There were no observed differences in performance on the CPT-II whether the participant completed the task during an intervention phase, or during a withdrawal phase. Although not significant, participants showed an increase of omissions (related to inattention—not responding to targets) and a decrease in commissions (related to impulsivity—responding to non-targets) while on the micronutrients compared to a decrease in omissions (increased attention) and an increase in commissions (increase in impulsivity) while off the micronutrients. Deterioration in performance on the CPT-II is not uncommon, as negative practice effects often occur (Conners, 1995). Participants found the CPT-II a tedious task in which they would often protest about completing at study switch points, rendering their results invalid. Their performance on the task may have been influenced by their opinion of the task and would therefore be less representative of their ability. While the current study had no placebo groups to compare the performance to, it may be that micronutrient intervention, although shown to have positive results on parent- and clinician-rated measures of ADHD, may be less effective in facilitating increased attention span on the CPT-II. An explanation for this may be the lack of appeal of the CPT-II design. One study designed a corresponding task in relation to the CPT-II which had, instead of letters, colourful Pokémon characters (a popular children's cartoon), of the same size presented for the same time. Instead of inhibiting response to the letter X, participants were instructed not to respond to Pikachu (Shaw, Grayson, & Lewis, 2006). In contrast to the control group, children with ADHD performed significantly worse on the CPT-II task, particularly impulsive responding,

compared to the equivalent Pokémon task. The improved performance on the Pokémon task compared to the CPT-II task was not found for the control group, suggesting the significant difference found was specific to children with ADHD and not the appeal and effects of computer games (Shaw et al., 2006). Participants in the current study may have responded more positively to a task that was more visually stimulating; however, further research is necessary to determine the applicability of the Pokémon task in place of CPT type tasks that help identify ADHD behaviours.

The micronutrient intervention was associated with mild to moderate adverse events reported by all 14 participants at some point in the study. The majority of the adverse events were mild (stomach aches), with one participant experiencing a moderate level of stomach ache and nausea after taking the morning dose, that persisted for the length of the study. The remaining participants reported adverse events that were transitory and able to be alleviated through adhering to directions regarding the consumption of enough food and water when consuming the micronutrient formula. There were no reports of sleep disturbance, decreased appetite, increased irritability or weight loss, issues that are typically reported in medication trials, identified as adverse events in the current study. No participant discontinued the study due to adverse events experienced.

Another hypothesis of the current study was that participants would be able to swallow 15 pills a day. Two participants had difficulty swallowing the pills and so chose to take the powdered form: one participant quickly found the additional effort in making blended drinks too cumbersome and switched back to the pill form without any difficulty. The other participant consumed the powder form throughout the study. The study allowed for flexibility in dose depending on response, as measured by ADHD symptoms and the participants overall functioning. Most participants (92%) were able to swallow the micronutrients at the initial trial dose of 8 capsules a day, and seven participants (50%)

completed the study at the recommended dose of 15 capsules a day. Seven of the participants maintained 15 pills a day after reaching that dose during the trial, seven of the participants took the micronutrients at a dose between the initial start dose (8 a day) and the recommended dose (15 a day). This was either due to a significant reduction in ADHD symptoms at the initial low dose (8 a day), difficulty taking the full morning dose, an increase in ADHD behaviours when taking 15 pills a day, or an increase in agitation when at the higher dose.

In terms of compliance, all 14 participants achieved at least an 80% compliance rate. This could be due to the particularly involved and committed parents/caregivers who were part of the research, ensuring their child adhered to the trials protocol. The parent/caregiver had to make quite a large commitment to allow their child to be part of the current study: fortnightly visits with the researcher, a number of questionnaires to fill in at each visit and being available during the business hours. The current study also distributed pill boxes to each participant, which may have served as a way to remind the participant whether or not they had taken each dose for that day. It is important to note that, although participants were instructed to bring in any remaining capsules from the previous fortnight, a few participants consistently forgot. The compliance rate was calculated by the participant and their parent/caregivers report of missed doses over the previous fortnight, and where capsules were returned this number was confirmed by the researcher through counting the number of capsules left in the bottle.

Contrary to the final hypothesis, this study did not find statistically significant differences between the participants who chose to stay on the micronutrient formula and those who discontinued micronutrient use at the six-month follow-up. Cohen's *d* effect sizes, however, indicated medium to large effects for measures of inattention, mood, overall functioning and ADHD severity when comparing the group still taking the micronutrient to

those who had discontinued micronutrient treatment. The absence of statistically significant group differences at the six-month follow-up may be due to the small sample size that was then naturalistically split into two even smaller groups of unequal size.

No effect or statistically significant difference was detected at the six-month follow-up between the groups on the hyperactivity and combined ADHD subscales. A possible reason for the lack of effect on measures of hyperactivity and combined total ADHD behaviours, and the small effect found for overall functioning, at the 6 month follow-up, is the mean group difference at the end of the study (second off phase). The group that chose to stay on the micronutrients had higher rates of hyperactivity/impulsivity and combined ADHD scores, and lower overall global functioning at the end of the study compared to the group that chose to come off the micronutrients. The group who chose not to continue taking the micronutrients after the study had better overall functioning at the end of the study than the group who continued to take the micronutrients and this improvement in functioning at the end of the study may have reduced the motivation to reintroduce the micronutrient formula after the study had finished, as the parents/caregivers may no longer have deemed the nutrient treatment necessary in light of their child's continued wellness while off the treatment.

The findings of the current study are consistent with the increasing body of research investigating the role of multi-ingredient micronutrient formulas in the treatment of ADHD (Harding et al., 2003; Kaplan et al., 2002; Katz et al., 2010; Rucklidge et al., 2009; 2010; 2011; 2014), including the most recently published double-blind randomised control trial investigating the effect of EMP+ for adults with ADHD (Rucklidge et al., 2014a). In addition to the positive effects of the micronutrients on ADHD behaviours, the current study replicated findings from a number of studies which demonstrated EMP+'s positive effects on mood (Gately & Kaplan, 2009; Kaplan et al., 2001; Kaplan et al., 2002; Kaplan et al., 2004; Kaplan et al., 2007; Popper, 2001; Rucklidge et al., 2010; Rucklidge et al., 2011; Rucklidge

et al., 2014). This is particularly important as ADHD frequently co-occurs with at least one other disorder, including mood disorders. While treatment with stimulant medications targets only ADHD symptoms, treatment utilising a broad-based micronutrient formula may result in a reduction in ADHD symptoms as well as a decrease in comorbid mood symptoms.

The current first line of treatment for children with ADHD is stimulant medication, reflecting the extensive research literature on the short-term effectiveness of stimulant medication on core ADHD symptoms. However, stimulant medications have been associated with unwanted adverse side effects, not limited to but including growth retardation, decrease appetite, weight loss, sleep disturbance, increased blood pressure and heart rate, and emotional outbursts and an increase in irritability (Greenhill, et al., 2002; Swanson et al., 2007; Wigal, et al., 2006). There are also a percentage of the ADHD population who do not respond to stimulant medication, or who respond negatively (Doggett, 2004; Sterman, 2000; Chabot, Merkin, Wood, Davenport, & Serfontein, 1996). Research has also indicated that although medication may be effective in relieving some symptoms of ADHD, these benefits are often only short-term and have shown little effect on educational outcomes (Sterman, 2000; Purdie et al., 2002). Furthermore, until more recently, there has been little research attention given to the effect that stimulants have on the developing brain (Anderson, 2005).

The current research suggests that this micronutrient intervention has a less severe adverse event profile than standard pharmacological treatments, and has shown to be effective at reducing ADHD symptoms and improving mood and overall general functioning. These findings warrant further research into the impact of micronutrient interventions for treating children with ADHD. In particular, it would be of great interest to determine if those individuals who do not respond or who respond negatively to stimulant medication benefit from treatment with micronutrients, as these individuals are in particularly urgent need of effective interventions.

5.2.1 Theoretical Frameworks and Mechanisms of Action

As discussed in Chapter Two of the Introduction, one explanation for the effect of broad-based micronutrient formulas may be that, in isolation, nutrients are not as effective; however, in combination they may result in promoting optimal functioning of the body, especially the brain. Mertz (1994) argued that, due to the complex role that micronutrients have physiologically, a single-nutrient treatment may actually cause more harm than good, as this approach may be oversimplified and it does not account for the hundreds of interactions among nutrients in the body. Pauling (1995) stated that an individual's requirement of multiple substances for optimal brain functioning may differ from what they receive in their diet, and that providing these individuals with optimal concentrations of micronutrients may be the preferable treatment for mental health disorders. The multi-ingredient approach to nutritional supplementation has been gaining support in areas of physical health, with increasing evidence for the application in the field of mental health (Rucklidge et al., 2014a; Rucklidge et al., 2014b; Kaplan et al., 2004; Harding et al., 2003; Rucklidge et al., 2011; Rucklidge & Harrison, 2010; Kaplan et al., 2002; Kaplan et al., 2001; Rucklidge, 2009; Rucklidge et al., 2010).

As examined in Chapter two, conceptual frameworks such as inborn errors of metabolism, mitochondrial function, and the triage allocation mechanism of nutrients, have been explored in order to ascertain how micronutrients may improve symptoms of mental health disorders. Firstly, inborn errors of metabolism have been implicated in key neurobiological pathways, for example, the synthesis and uptake of neurotransmitters (Kaplan et al., 2007; Kaplan et al., 2001). Kaplan and colleagues (2007) suggest that individuals with genetic mutations that result in brain dysfunction, may have a higher metabolic requirement of micronutrients in order to achieve normal metabolic functioning,

therefore, large doses of micronutrient supplementation should produce symptom improvement.

Secondly, mitochondrial function has been implicated as a possible factor in the pathogenesis of mental health disorders (Rezin et al., 2008; Rucklidge & Kaplan, 2013). As mitochondria are involved in essential processes such as energy metabolism of neurons and glial cells, a breakdown in these processes may result in a breakdown of other processes, such as synaptic communication (Rucklidge & Kaplan, 2013). There is a high prevalence of comorbid psychiatric illness in those with mitochondrial disorders, suggesting possible etiological implications (Fattal et al., 2007). Although in its infancy, there is a growing body of literature that suggests that micronutrients may be effective in treating the physical expressions of mitochondrial disorders; therefore, if mitochondrial function is an etiological factor in some mental health disorders, micronutrient interventions may prove to be an effective treatment.

It has also been proposed that long-term nutrient deficiencies eventually lead to mental health disorders over time (Kaplan et al., 2007). This is based on Ames's (2006) triage theory which suggests that, when the body is responding to stress, an increase in nutrients is required for the functions that are necessary for survival: priority is placed on short-term survival over long-term health. This diversion of nutritional resources, when the body experiences nutrient deficiency during times of stress, may lead to a mental health disorder.

These conceptual frameworks provide possible mechanisms behind the increasing evidence for the efficacy of multi-ingredient micronutrients in the treatment of psychiatric symptoms. These potential frameworks signify that some individuals with a higher genetic need for nutrients may require more nutrients than can be attained through diet, and at an amount that exceeds the recommended daily allowance. Furthermore, there may be some

people among this group with a higher genetic need who need more than others in this same group. This may explain the variability in optimal dose experienced by the participants in the current study, with 50% of participants requiring the full recommended dose of 15 capsules a day for maximum benefit and 50% of participants reporting optimal benefits at a lower dose (between eight and 13 capsules a day).

Furthermore, absorption of nutrients can be hindered by stress, as stress has been shown to reduce the numbers of helpful bacteria in the gut flora (Holzapfel et al., 1998; Kaplan et al., 2007; Knowles et al., 2008). A relationship between gluten sensitive individuals or Celiac disease and psychiatric symptoms has been identified (Jackson et al., 2012). Celiac disease and gluten sensitivity may result in malabsorption of nutrients, vitamins and minerals. Niederhofer and Pittschieler (2006) found that eliminating gluten from participants' diets for six months resulted in a decrease in ADHD-like symptoms. This highlights the importance of healthy gastrointestinal functioning, as it is required (among other things) for the absorption of nutrients that contribute to overall functioning.

Another consideration for the potential decrease in optimum nutrient intake is the increase in prevalence of Western dietary patterns (Howard et al., 2011) and the overall decline in food composition (Mayer, 1997). Some individuals may be more vulnerable to the higher intake of sodium, saturated fat, total fat, refined sugars and a lower intake of omega-3 fatty acids, fibre and folate found in the Western diet, and to the depleted nutrients found in foods and soil occurring over decades of use. Individual's vulnerabilities to mental health disorders may be particularly sensitive to this shift in and decline in nutrient content as they may have a higher nutrient requirement for optimal functioning (Kaplan et al., 2007). Although participants in the current study did not disclose any food sensitivities, and dietary patterns were not assessed, the changes in dietary patterns and the nutrient content of foods are worldwide phenomena, and are, therefore, important considerations. Dietary nutrients

have been shown to be relevant in mental health functioning for almost 90 years; however, broad-based micronutrient formulas have only relatively recently been investigated as a potential treatment for mental health disorders.

5.3 Research Strengths

There were a number of strengths in the current study that are noteworthy. Firstly, the study was designed to maximise the length of time spent taking the intervention to measure the effectiveness of the micronutrient formula on ADHD behaviours. The current study employed a single case ABABA (Reversal) design, a form of design which is particularly suitable to detecting the effect of pharmacological and related interventions (Hersen & Barlow, 1976) and a design which is able to identify a causal relationship between introducing the micronutrient formula and a reduction of ADHD symptoms and improvements in overall functioning. This was achieved through the introduction and withdrawal of the micronutrient formula over the course of the six-month study and the demonstration of concurrent changes in symptoms, replicated across participants. This study recruited children with ADHD from a diverse community-based population from a variety of referral sources. The inclusion and exclusion criteria enabled a broad sample of children with ADHD to be part of the current research. Children were only excluded from the study if they suffered from any serious medical condition, were currently taking psychiatric medication, or were unable to have the required blood work completed. Children with ADHD who had comorbid disorders were not excluded. Due the nature of the population sampled, this study is an 'effectiveness' study as participants more closely represent children seen in clinic settings (Flay, 1986; Flay et al., 2005).

Additionally, the use of modified Brinley plots to analyse the current data allowed for comprehensive understanding of the intervention outcome, without losing data through the

use of traditional group mean data analysis (Blampied, 2014; Jacobson et al., 1984; Sobell et al., 1995). This allows for a more individual-focussed approach to treatment outcome. Modified Brinley plots allowed systematic exploration of each phase (intervention phases and off phases) against baseline scores, and visually represented patterns of change across the different phases.

Another methodological strength to the current research was the inclusion of a six-month follow-up assessment to investigate any long-term benefits of taking the micronutrient formula. This enabled comparisons of participants who continued taking the micronutrient formula long-term to those who stopped at the end of the initial study period. This also allowed for the investigation of any long-term adverse events for those who chose to stay on the micronutrients.

Additionally, there were several strengths in the implementation of the current study. Firstly, participants were followed by the same researcher throughout the entirety of the study meaning that there was consistency in assessment and intervention. Further, where necessary, if a participant was unable to make their appointment, phone contact was made and questionnaires were posted to make sure data was collected during the appropriate week. The current study included, in addition to parent and teacher ratings, a self-report measure for children to complete at each appointment. This allowed the researcher to collect data on the child's interpretation of their current strengths, difficulties and overall functioning at each fortnightly visit.

Another strength of the current study was the lack of side effects or minimal side effects experienced by the participants throughout the length of the intervention. The absence of abnormal results from the collection of blood work, post micronutrient intervention, further supports previous research on the safety and tolerability of consuming the broad-

based micronutrient formula EMP+ (Rucklidge et al., 2014; Simpson et al., 2011). Additionally, the initial ABABA study incurred a zero percent dropout rate, and only one participant was lost to the six-month follow-up. This meant there was a minimal amount of missing data.

5.4 Research Limitations

The promising findings and strengths for the current study notwithstanding, limitations in research are inevitable, especially when investigating a clinical population. Some of the limitations experienced are examined below.

5.4.1 Design

A single case ABABA withdrawal design proved to be an efficient way to gather information about the effectiveness of the intervention for each individual participant, allowing the confirmation of whether any intervention effect experienced would reverse when the micronutrients were withdrawn and replicate the treatment effect when they were introduced. However, concluding the study on an off phase was not the ideal design. Participants who had responded quite positively while on the micronutrients may have forgotten their previous decrease in ADHD symptoms and their overall increase in functioning by the end of the last four week withdrawal phase. Ending on an off phase may have hindered any potential progress made in increasing the rate of compliance during the on phase. As the micronutrient intervention revealed a more gradual effect in the reduction of symptoms, compared to the quick-acting effects pharmacological treatments can have, this may have dissuaded participants and their families from continuing the micronutrient intervention post study completion due to ending on an off phase. This may have resulted from the additional commitment and effort placed on the parent/caregiver to ensure compliance and gradually titrate up to the optimal dose without the input and assistance

previously experienced with the researcher. Five participants and their families requested to finish the study early, as early as after one week off for one participant, in order to continue taking the micronutrients. Ending the trial on an intervention phase may have increased the number of participants who chose to stay on the micronutrient intervention. The positive effects experienced from the micronutrient would then be present, and for those who expressed difficulty in pill taking and remembering, the habits developed would more likely be entrenched and part of their daily routine.

As the current study reveals a dose response and gradual effect of the micronutrient intervention, the dosage amount and length of time on the micronutrients appear relevant to treatment outcome. The follow-up data, collected six-months post-study, proved difficult to interpret for those currently taking the micronutrient formula. This is due to participants who come off and go on treatments, try similar supplements, or are inconsistent in dose amount. For families who were inconsistent in treatment protocol, it was difficult to interpret how long the participant had been taking the micronutrient formula. However, information about all products consumed since the end of the trial was compiled for follow-up analysis. Note that these are issues affecting all follow-up research of pharmacological and nutritional research; they are not unique to this study (Rucklidge, et al., 2014).

Another possible limitation of the current study design was the inclusion of the CPT-II as a measure of neuropsychological functioning. Research examining the effectiveness of lab tests used to measure ADHD symptoms, including the CPT, have found very little evidence investigating the correlation between the CPT and ADHD symptoms (McGee, Clark, & Symons, 2000; Nichols & Waschbusch, 2004). As an alternative to the 14-minute long CPT task, a combination of neuropsychological tasks, designed to measure executive functions and processing speed, may be more beneficial at identifying micronutrient intervention effects for children with ADHD. Laboratory tasks such as the Stroop and

Wisconsin Card Sort Test (WCST), and more real-life tasks that are intrinsically motivating (i.e., videogames), may allow for results that are more representative of the participants' current functioning due to the variability across the tasks (Lawrence et al., 2004).

5.4.1.1 Generality

A key issue faced by all clinical or applied research is the issue of the generality of any findings from a single study, whether that study is of an individual or a group. As Sidman (1960) pointed out, simply conducting research with a large(ish) sample and demonstrating a statistically significant mean effect does not automatically confer generality on the findings. Generality of a treatment effect can only be established by systematic and clinical replication (Barlow, Knock, & Hersen, 2009), which in the instance of single-case research is built upon a foundation of successful direct replication (Barlow, et al., 2009) in the initial study. The positive effects of micronutrients on ADHD symptoms and behaviours was demonstrated in the present study by direct replication within individual participants via the reversal design, with these results consistently replicated across participants. The representativeness of the individuals across whom the replication of the micronutrient intervention occurred, supports the inductive generalisation that many, if not all, individuals with ADHD, may benefit from a broad-based micronutrient treatment. Confidence in this conclusion would be enhanced by further direct replications with individuals typical of those who have ADHD. Systematic replications are required to establish the generality of treatment with different micronutrient formulations and across treatment settings and therapists, and across the full range of manifestations of ADHD and related disorders (Barlow, et al., 2009). Finally, clinical replication will be required to establish the generality of micronutrient treatment in combination with other treatments, such as behavioural or cognitive-behavioural therapies, for the full range of ADHD presentations across the life-span. If at least two independent systematic replication series are successfully completed,

micronutrient treatment for ADHD can then be regarded as an empirically-supported efficacious treatment (Chambless & Hollon, 1998).

5.4.1.2 Open Label Design

A limitation to the current study is the open-label nature of the design, in which participants, caregivers, and clinicians knew when they were taking the micronutrients and knew when they were off the micronutrients. This means the responses given may have been influenced by expectancy effects. This cannot be determined without the use of a placebo control of some kind.

Although a placebo response contributing to the observed results cannot be ruled out, there are some convincing reasons why a possible placebo effect is unlikely to explain the therapeutic results found. For example, for most participants the therapeutic effect was gradual, with the most benefit shown several weeks after starting the micronutrients. Placebo/expectancy effects would likely have been observed relatively immediately. Further, those who continued to take the micronutrients maintained the benefits six months after they completed the study. Additionally, 64% of the participants had trialled at least one psychiatric medication prior to starting the study and had not experienced significant positive changes previously. Further, the researcher made it clear to each participant and their parent/caregiver that the treatment was experimental and that there was a chance it may not help. So while placebo effects cannot be ruled out, the reasons outlined above suggest it is unlikely a placebo effect is responsible for all or most of the positive effect of the micronutrient intervention. The promising results of the current study do highlight the need for future placebo-controlled studies investigating the effect of multi-ingredient micronutrient interventions for ADHD in a larger sample of children. Such studies can be done within the framework of single-case ABAB designs (e.g., France, Blampied, & Wilkinson, 1999).

Alongside a possible placebo effect, due to the open label nature of the current study, investigator bias should also be considered as a possible contributor to the positive results found in the current study. However, a multi-informant approach that included data collection from parent-, teacher-, self- and clinician-rated measures was utilised throughout the study to attenuate this possible bias.

Spontaneous remission of psychiatric symptoms should also be considered due to the length of the current study. Participants were involved in the current research for a total of 12 months; six months of fortnightly visits for the initial study phase, with a follow-up assessment six months later. Due to the age of the population studied (children between eight and 12 years old), participants may have matured over the course of the study and a decrease in symptoms may have been naturally associated with this development (i.e., decrease in hyperactivity as children reach adolescence) (Ingram, Hechtman, & Morgenstern, 1999). However, given the improvement in symptoms that was reported during intervention phases, and the reversal in symptoms that was evident during withdrawal phases, it is very unlikely spontaneous remission would explain the treatment effect observed. Indeed, it is one of the strengths of single-case reversal designs that they are robust against such developmental trends, especially when replications occur across individuals at different ages and/or developmental stages.

5.4.2 Contact with Researcher/ Therapeutic Input

Improvements in the current study may have been influenced by the therapeutic input involved in research trials. Participants in the current study experienced regular therapeutic input through contact with the researcher on a regular basis, consistent assessment of symptoms, assistance and suggestions when difficulties with compliance arose, and through empathic responses. The participant and/or parent/caregiver may have experienced a

reduction in symptomology purely through contact with the researcher, i.e., a therapist effect. However, most participants had previously experienced interactions with a health professional without significant improvement. Contact with the researcher was kept to a minimum with most appointments lasting less than 30 minutes (switch points were longer due to additional questionnaires and the neuropsychological task) and research lab visits no more frequent than fortnightly. The therapist effect is unlikely to explain the overall improvement in functioning seen throughout the intervention phases, as a reversal in overall functioning was found during the withdrawal phases, when participants came off the micronutrients but continued to visit with the researcher. For those who stayed on the micronutrients, changes were maintained over the six-month follow-up period, after contact with the researcher discontinued. Also, participants and their parents/caregivers did not receive any psychological strategies during their appointments: visits were purely assessment focused.

5.4.3 Sample Size

The small sample size is a limitation to the study. Although positive results were found in the current research, a larger confirmatory study is needed. The small sample size was especially evident at the six-month follow-up when they were split into two separate groups (five who continued micronutrient use and eight who discontinued micronutrient use).

5.4.4 Diet

Another factor that may have influenced the positive results found in the current study is the dietary intake of participants. The current research did not include a dietary assessment as it did not want to draw focus to diet and possibly influence a change in dietary pattern at the same time as the intervention. Participants were instructed to take the micronutrients with plenty of water and food at each dose (three times daily), which may have improved their

daily diet. In this context, although breakfast dietary patterns were not collected, several participants reported not eating regular breakfast prior to the study and any changes to this pattern necessitated by the micronutrient consumption requirements may have been beneficial, as may related changes in daily routines have influenced their behaviours, particularly mood and an increase in concentration for the better. As diet was not evaluated as part of the study, the extent that any changes in dietary patterns may have affected outcome cannot be assessed.

5.5 Feasibility

With any treatment approach, the feasibility and practicality of the intervention are important considerations. For the current study, compliance with the treatment regimen was an important issue to consider. Problems with maintaining compliance included struggles with pill swallowing, requiring two participants to move to using the powdered form. Taking the micronutrient formula in powder form resulted in different issues, as it required added preparation time and creativity to reduce boredom of the flavour choice, which resulted in one of the two participants using the powder form to switch to capsule form halfway through the study. Other challenges the participants reported were remembering to take all three doses each day, eating enough food and drinking enough water with each dose, and some complained of an unpleasant aftertaste. These challenges required additional effort from the participant's parent/caregiver, and input regarding alternative methods for pill consumption from the researcher. The parent/caregiver undertook a large commitment for their child to take part in the study as this required their attendance at appointments, assistance in their child's compliance, and filling out multiple questionnaires throughout the trial. Nevertheless, these issues are unlikely to have been greater in this study than in studies investigating either pharmacological or psychological treatments for ADHD.

The cost to continue to take the micronutrients when the study ended is another important issue to consider. Families were offered EMP+ at a discounted rate by the distributor after the completion of the trial, and for those who chose to continue taking the micronutrients, they appeared to make this purchase a priority when they realised the benefits EMP+ had on their child's behaviour. However, for some families the cost of the micronutrients (which remained fairly substantial even after the discount was applied) appeared to influence whether or not they continued the micronutrient treatment. One might hope that if sufficient empirical evidence accumulates as to the benefits of micronutrient treatment for this and other disorders that micronutrients would be made available via the health system as is currently the case for many other pharmacological treatments.

Challenges were sometimes experienced in making contact with parents/caregivers particularly with parents who were employed full time and so not available during normal business hours. Parents/caregivers would also often have their other children with them during appointment times, which could make conducting meetings more challenging. Email and text reminders were helpful in approaching these challenges, as well as a waiting area that included books and toys for the siblings to stay entertained during appointment times.

Finally, adverse events experienced from the micronutrient intervention also impact the feasibility of the current study. Eleven (79%) of the participants experienced stomach aches as an adverse event, which may have been related to the micronutrient intervention. All adverse events were transient in nature, and overall, such events had only minor impact on the conduct of the study.

5.6 General Implications

From this study, and the growing research on multi-ingredient nutrient formulas, it is evident that broad-spectrum micronutrients are beneficial in reducing ADHD symptoms and behaviours. Positive treatment effects from the current study include a decrease in ADHD symptoms, and an increase in overall mood and functioning. These results suggest that EMP+ has the potential to become a treatment option for children with ADHD; however, further research is needed to establish the place of such treatment within the treatment options for ADHD. The current study does not imply that micronutrients are a "cure" for ADHD (no known treatment can make that claim), however, micronutrients have been shown to reduce symptom expression with few adverse events.

If the hypothesised mechanisms of action by which micronutrients may work are correct, then correcting inborn errors of metabolism (Kaplan et al., 2007) or improving mitochondrial dysfunction (Gardner & Boles, 2005) by increasing the micronutrient intake essential for optimal functioning will result in reduction in ADHD symptoms in affected individuals. As the current study revealed, micronutrient intervention resulted in a decrease of ADHD symptoms and improvements in general functioning while removing the micronutrient intervention results in a reversal in functioning and increase in ADHD symptoms. Further research investigating the possible mechanisms of action behind this effect is necessary.

Although there is a long history of vitamins and minerals being used for mental health disorders, there is still much debate around their use (Kaplan et al., 2007). There is a growing body of well-designed studies revealing the effectiveness and efficacy of this combination of vitamins and minerals on a variety of mental health disorders (Rucklidge et al., 2014a; 2014b; Kennedy et al., 2010; Gesch, Hammond, Hampson, Eves, & Crowder, 2002). The current

study chose a more complex group of participants, evaluating a number of psychiatric symptoms within the same study to assess the effectiveness of micronutrients as a possible treatment. The findings reveal improvements across a range of symptoms, such as ADHD symptoms, mood, social functioning and general overall functioning, with only minor transitory adverse events.

While the current study does not establish micronutrients as an efficacious treatment, the data are compelling and warrant replication and extension to confirm and better identify the possible changes occurring. The current study supports the use of micronutrients as a treatment to reduce ADHD symptoms and improve overall functioning in children. The micronutrient formula investigated in the current study revealed a continuous control of symptoms when the optimal dosage for each participant was reached, minimal adverse events, and high compliance rates during the study. Participants and their parents/caregivers also reported unexpected improvements in sleep, decreased sugar cravings, tic reduction and improved social relationships. Although follow-up data were unable to identify clear differences between those who chose to stay on and those who came off, it appears long-term micronutrient use may result in fewer difficulties and improved functioning, although more extensive systematic replication is required to ascertain whether this difference is clinically meaningful.

5.7 Future Directions

As the search for alternative treatments for ADHD increases—due to negative side effects experienced with conventional treatment, the percentage of the population for whom standard medications are not effective, and the potential long-term negative effects of stimulants on the developing brain—further research in this area is essential. The research to date on multi-ingredient micronutrient formulas for ADHD is limited, and shows a need for

well-designed studies that are replicable. The exploration of micronutrients as a possible treatment option may provide people who have ADHD with an effective alternative to conventional treatment.

Additional research investigating multi-ingredient micronutrient formulas should explore long-term efficacy and safety of these formulas. This would allow insight into whether benefits are maintained over longer periods, and whether any adverse effects arise after long-term consumption. Safety data on EMP+ to date has shown only minor and transitory adverse events associated with taking this micronutrient formula, and no occurrences of clinically meaningful negative outcomes/effects or abnormal blood tests that could be attributed to toxicity. While it may be difficult to compare different micronutrient formulas, it may be important to further investigate the recommended dosage amount and particular combinations of micronutrients and their use in mental health populations. This may allow specific dosage amounts or formulas to be personalised for the individual based on their specific nutritional needs.

Further research that may be of benefit are trials that compare the micronutrient intervention to the current empirically supported treatments (i.e., stimulant medication and behavioural interventions), as well as a comparing a micronutrient intervention to placebo. It would be imperative that these studies assess long term outcomes, particularly on brain development, as research has identified a gap in long-term consequences of stimulant exposure on the developing brain (Andersen, 2005), but preliminary results show trends towards positive long term outcomes with micronutrients (Popper, 2014). It would also be of interest to compare micronutrient treatment plus behavioural interventions to behavioural treatments alone and micronutrients alone. In pursuit of this objective, a randomised double-blind placebo-controlled trial is currently being conducted, at the University of Canterbury, Christchurch, investigating EMP+'s successor formula, Daily Essential Nutrients (DEN) in

children with ADHD. EMP+ was reformulated as DEN to increase absorption of vitamin B12 and folate, higher levels of vitamin D, thiamine, riboflavin, vitamin B6 and pantothenic acid were added, the inclusion of vitamin K, and formulated to reduce gastrointestinal upset, making it easier to take on an empty stomach.

Future research investigating long-term compliance will also be of benefit. It was reported that, particularly with EMP+, the large number of capsules required and the high cost associated with EMP+ can act as a barrier to adoption and maintenance of the treatment. It is also important to note that the positive results found in the current study, and previous research with EMP+, is often reported as gradual, not immediate as found with stimulants, so the benefits received may be more difficult to associate with consumption of the micronutrient formula. fMRI techniques may also be useful in identifying any change in brain activity associated with micronutrient treatment, as well as providing a way to document possible mechanisms of action of the treatment on neural circuitry.

More recently, research has investigated gastrointestinal functioning and the impact that this can have on the expression of psychological symptoms (Jackson et al., 2012; Niederhofer & Pittschieler, 2006). An unhealthy gastrointestinal system may affect the absorption of essential vitamins and minerals. Future research may consider combining probiotics alongside micronutrient formulas to ensure nutrient absorption and therefore maximise the treatment response. Rucklidge and Kaplan (2013) anticipate that healthy gastrointestinal functioning will become increasingly important in maximising intervention response through enabling optimal absorption of essential nutrients.

5.8 Conclusions

ADHD is a chronic disorder that causes significant difficulties for the child, their family, and the community, that persists into adulthood for a sizable majority of children with

ADHD (Barkley et a., 1991; Biederman et al., 2004; Brown, 2000; Kollins et al., 2001, Spencer, Biederman, & Mick, 2007). Research has shown that the current treatments available are ineffective for at least 30% of those with ADHD (Zachor et al., 2009; Chabot et al., 1996). There is growing popularity for the use of alternative treatments for psychiatric illnesses, including ADHD. The current study is the first to explicitly investigate the effectiveness of micronutrients as a treatment for children with ADHD, using a single case ABABA reversal design. The effectiveness of the micronutrient formula for the treatment of ADHD symptoms in children was investigated and compared to a reversal phase, when participants discontinued taking the micronutrients.

Significant differences in ADHD behaviours were found when taking the micronutrients compared to when the micronutrient treatment was withdrawn. Both parent- and self-report measures revealed a clear on/off pattern: a decrease in ADHD behaviours and improvement in overall functioning when taking the micronutrients and a reversal when the micronutrients were withdrawn. Although significant differences were not found for teacher ratings of ADHD behaviours, there was a slight improvement in the overall distress and social impairments reported. Group differences were found for those who came off the micronutrients compared to those who chose to stay on the micronutrients at the six-month follow-up. This was particularly evident in ratings of the participants' ADHD severity, overall functioning, and overall clinical impression, with medium to large effect sizes signifying a meaningful difference between the two groups. However, group mean differences—between participants who were on the micronutrients at 6 months post-trial and those who discontinued use of the micronutrients—were not statistically significantly different from each other.

The results of the current study provide evidence that a broad-based micronutrient formula has potential as a treatment option for children with ADHD, and gives support to

previous research indicating the effectiveness of micronutrient treatment for a range of psychiatric symptoms. This research found medium to large effect sizes comparable to medication trials without the adverse events typically found and reflects the importance for researchers and clinicians to remain open to multiple treatment options, including micronutrients, when treating psychiatric illness. Individual benefits from this study suggest that future research investigating broad-based micronutrient interventions as a treatment for mental health disorders is warranted. Replication of the current findings would strengthen the evidence base and may result in the support required for the use of micronutrients as an evidence-based treatment for psychiatric illness.

Chapter 6: References

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Chapter 7: Appendices

Appendix A: EMPowerplus Capsule Ingredient List

1 cap		4 caps		8 caps		15 caps		
384.0	IU	1536.0	IU	3072.0	IU	5760	IU	Vitamin A
40.0	mg	160.0	mg	320.0	mg	600	mg	Vitamin C
96.0	IU	384.0	IU	768.0	IU	1440	IU	Vitamin D
24.0	IU	96.0	IU	192.0	IU	360	IU	Vitamin E
1.2	mg	4.8	mg	9.6	mg	18	mg	Vitamin B1
0.9	mg	3.6	mg	7.2	mg	13.5	mg	Vitamin B2
6.0	mg	24.0	mg	48.0	mg	90	mg	Vitamin B3
1.4	mg	5.8	mg	11.5	mg	21.6	mg	Vitamin B5
2.4	mg	9.6	mg	19.2	mg	36	mg	Vitamin B6
96.0	ug	384.0	ug	768.0	ug	1440	ug	Vitamin B9
60.0	ug	240.0	ug	480.0	ug	900	ug	Vitamin B12
72.0	ug	288.0	ug	576.0	ug	1080	ug	Vitamin H
88.0	mg	352.0	mg	704.0	mg	1320	mg	Calcium
0.9	mg	3.7	mg	7.3	mg	13.74	mg	Iron
56.0	mg	224.0	mg	448.0	mg	840	mg	Phosphorus
13.6	ug	54.4	ug	108.8	ug	204	ug	Iodine
40.0	mg	160.0	mg	320.0	mg	600	mg	Magnesium
3.2	mg	12.8	mg	25.6	mg	48	mg	Zinc
13.6	ug	54.4	ug	108.8	ug	204	ug	Selenium
0.5	mg	1.9	mg	3.8	mg	7.2	mg	Copper
0.6	mg	2.6	mg	5.1	mg	9.6	mg	Managnese
41.6	ug	166.4	ug	332.8	ug	624	ug	Chromium
9.6	ug	38.4	ug	76.8	ug	144	ug	Molybdenum
16.0	mg	64.0	mg	128.0	mg	240	mg	Potassium
24.0	mg	96.0	mg	192.0	mg	360	mg	dl-phenylalanine
12.0	mg	48.0	mg	96.0	mg	180	Mg	Glutamine

16.0	mg	64.0	mg	128.0	mg	240	mg	citrus bioflavanoids
3.0	mg	12.0	mg	24.0	mg	45	mg	grape seed
36.0	mg	144.0	mg	288.0	mg	540	mg	choline bitartrate
12.0	mg	48.0	mg	96.0	mg	180	mg	Inositol
2.4	mg	9.6	mg	19.2	mg	36	mg	ginkgo biloba
4.0	mg	16.0	mg	32.0	mg	60	mg	Methionine
1.4	mg	5.5	mg	11.0	mg	20.7	mg	germanium sesquioxide
160.0	ug	640.0	ug	1280.0	ug	2400	ug	Boron
2.0	ug	7.8	ug	15.7	ug	29.4	ug	Nickel
79.6	ug	318.4	ug	636.8	ug	1194	ug	Vanadium
111.0		444.1		888.2		1665.3		Proprietary Total

Appendix B: Parental Information Sheet and Consent Form

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

INFORMATION SHEET: April 6th 2011

Title of research project: Investigation into the effect of a nutritional supplement on mood and behaviour in children with Attention-Deficit/Hyperactivity disorder (ADHD) with mood dysregulation: a pilot study using single case ABAB design.

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

Other investigators: Heather Gordon, Assoc Prof Neville Blampied, Dr David Ritchie

What is the purpose of the study?

Your child is invited to participate in a study that will evaluate a nutritional supplement in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) with mood dysregulation. 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 some symptoms of ADHD, as shown in an open-label trial with adults with ADHD 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 not presently on psychiatric medications for their attention, hyperactivity, impulsivity and/or mood problems. Approximately 10 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 mood instability to stabilize their 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 some symptoms of ADHD. 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 member's 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 first intervention phase. The preferred method of administration 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 them taking it. It is up to your child how best to take the supplement. Before your child begins taking the capsules they will be shown a short video on different ways to swallow capsules. They will then practice swallowing by using hard lollies and recording which ways they prefer to have their head when swallowing. We will ask them to monitor prefer head positions over a number of days.

Once your child is ready to begin, your child will take *up to* 15 gelatin capsules per day, divided however you like, but preferably in 3 doses of 5 capsules each. Your child will begin by taking 4 capsules of EMP+ each day, increasing to 8 capsules on the 4th day and then after the initial 4 weeks this may be increased up to 15 capsules depending on your child's initial response to the capsules as well as any side effects he/she may be experiencing. 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. After 8 weeks, the capsules will be discontinued for 4 weeks, resumed for a further 8 weeks and then stopped for 4 weeks. This on-off-on-off procedure is called an ABAB case study design. 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 6 months, there will be weekly appointments for the first three weeks followed by fortnightly appointments for the rest of the duration of the study with one of the primary investigators. These appointments will take place in person at a work space provided by the University of Canterbury or over the phone. At your appointments, this person will review the physical and mental health of your child, will ask about any problems they are having, and will complete a number of assessment tools evaluating their overall functioning. At every appointment, we will also ask you to complete questionnaires about your child regarding overall level of functioning. You will also be asked to keep a daily diary of any unusual events in your child's life, and any capsules that you know have not been taken. At the end of the first 4 weeks, a re-assessment will be done, to determine whether or not to increase your child's dosage.

A short neuropsychological test will be completed with your child to assess memory, learning and reaction times before the trial begins. This testing will be repeated after the second period on the capsules.

We will also ask your child's teacher to complete a few questionnaires about your child on a monthly basis. This allows us to assess changes your teacher may observe.

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 they need to complete the course of the drug. 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 they have completed their 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).

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 in two ways: 1) 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, and 2) Your child will provide us with a blood sample (20ml or 4 teaspoons) at the beginning and the end of the first 8 weeks to ensure that all systems are functioning normally. The laboratory we will send you to, are very experienced with working with children. They will offer your child a spray or cream to numb the area where blood will be taken. These samples will provide us with haematological and biochemistry screening, thyroid function tests, serum lipids, prolactin and glucose, clotting screen, iron, magnesium, calcium and copper levels. While risks associated with blood tests are usually minimal, bruising can occur with blood tests. The results of laboratory testing will need to be sent to us with a copy to your general practitioner such that they can be reviewed accordingly.

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 right 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 38 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.

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. The blood tests will help us determine whether the nutrients are having any effects on your child.

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 for their illness using prescribed 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 you needed a pain killer for a headache, it would be safer for you 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 yourself 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, you 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 patients with attention and/or mood problems.

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 them stop, you are certainly free to do so. This decision will not influence their 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. 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 ADHD, including medications and behavioural therapy. 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 yourself 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 are happy to discuss any of the results found from the present study with you and discuss the scales that we have used as well as the questionnaires upon the completion of your child's participation. We would need your permission and signed consent to send these test scores to another professional involved in your child's care as 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, 364-2987ext7959, 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
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

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, chrondroitin, 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.

EMPowerplus Capsule Ingredient List (Current)

1 cap		4 caps		8 caps		15 caps		
384.0	IU	1536.0	IU	3072.0	IU	5760	IU	Vitamin A
40.0	mg	160.0	mg	320.0	mg	600	mg	Vitamin C
96.0	IU	384.0	IU	768.0	IU	1440	IU	Vitamin D
24.0	IU	96.0	IU	192.0	IU	360	IU	Vitamin E
1.2	mg	4.8	mg	9.6	mg	18	mg	Vitamin B1
0.9	mg	3.6	mg	7.2	mg	13.5	mg	Vitamin B2
6.0	mg	24.0	mg	48.0	mg	90	mg	Vitamin B3
1.4	mg	5.8	mg	11.5	mg	21.6	mg	Vitamin B5
2.4	mg	9.6	mg	19.2	mg	36	mg	Vitamin B6
96.0	ug	384.0	ug	768.0	ug	1440	ug	Vitamin B9
60.0	ug	240.0	ug	480.0	ug	900	ug	Vitamin B12
72.0	ug	288.0	ug	576.0	ug	1080	ug	Vitamin H
88.0	mg	352.0	mg	704.0	mg	1320	mg	Calcium
0.9	mg	3.7	mg	7.3	mg	13.74	mg	Iron
56.0	mg	224.0	mg	448.0	mg	840	mg	Phosphorus
13.6	ug	54.4	ug	108.8	ug	204	ug	Iodine
40.0	mg	160.0	mg	320.0	mg	600	mg	Magnesium
3.2	mg	12.8	mg	25.6	mg	48	mg	Zinc

13.6	ug	54.4	ug	108.8	ug	204	ug	Selenium
0.5	mg	1.9	mg	3.8	mg	7.2	mg	Copper
0.6	mg	2.6	mg	5.1	mg	9.6	mg	Managnese
41.6	ug	166.4	ug	332.8	ug	624	ug	Chromium
9.6	ug	38.4	ug	76.8	ug	144	ug	Molybdenum
16.0	mg	64.0	mg	128.0	mg	240	mg	Potassium
24.0	mg	96.0	mg	192.0	mg	360	mg	dl-phenylalanine
12.0	mg	48.0	mg	96.0	mg	180	Mg	glutamine
16.0	mg	64.0	mg	128.0	mg	240	mg	citrus bioflavanoids
3.0	mg	12.0	mg	24.0	mg	45	mg	grape seed
36.0	mg	144.0	mg	288.0	mg	540	mg	choline bitartrate
12.0	mg	48.0	mg	96.0	mg	180	mg	Inositol
2.4	mg	9.6	mg	19.2	mg	36	mg	ginkgo biloba
4.0	mg	16.0	mg	32.0	mg	60	mg	methionine
1.4	mg	5.5	mg	11.0	mg	20.7	mg	germanium sesquioxide
160.0	ug	640.0	ug	1280.0	ug	2400	ug	Boron
2.0	ug	7.8	ug	15.7	ug	29.4	ug	Nickel
79.6	ug	318.4	ug	636.8	ug	1194	ug	vanadium
111.0		444.1		888.2		1665.3		Proprietary Total

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

PARENTAL CONSENT FORM

Title of research project: Investigation into the effect of a nutritional supplement on mood and behaviour in children with Attention-Deficit/Hyperactivity disorder (ADHD) with mood dysregulation: a pilot study using single case ABAB design.

Principal Investigators: Dr. Julia Rucklidge, Heather Gordon, Assoc Prof Neville Blampied and Dr David Ritchie

I have read and I understand the information sheet dated April 6th 2011 for people taking part in the study designed to assess the impact of micronutrients on behaviour and mood in children with ADHD. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I believe that (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's medical records being reviewed as part of the research process YES/NO

I consent to my child supplying blood samples as indicated YES/NO

I consent to my child's teacher being contacted and completing questionnaires about my child's behaviour at school YES/NO

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.

Appendix C: Consent to Contact Teacher Form

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Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Teacher Consent Form

Title of Research Project: Effect of a nutritional supplement on mood and functioning in children with ADHD

Principal Investigator: Dr. Julia Rucklidge

I _____

Name of participant's parent/guardian

Hereby consent to the disclosure or transmittal to or the examination by Dr. Julia Rucklidge of **Teacher Rated Forms** completed at

_____

Name and address of school

by _____ **in respect of** _____,

Name of Teacher **Child's name**

_____ .

Date of birth

_____

Name of parent/guardian

_____

Signature of participant's parent/guardian

Date: _____

Appendix D : Child Information Sheet and Assent Form

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 Attention Deficit/Hyperactivity Disorder (ADHD). About 10 children will be in this study.*

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

- You will visit the University for activities and questions once a week or every other week for a total of 6 months
- You will take a vitamin and mineral formula every day for 2 months. Then you will have a month off the vitamins and minerals. 2 more months on the vitamins and minerals and 1 final month off of them
- We will need you to give a small amount of blood before we begin

We need the blood tests to make sure that you are nice and healthy!

Will the study help you?

- The pills in this study have helped some adults with Attention Deficit/Hyperactivity Disorder (ADHD) but it may or may not help you
- We do not know if your ADHD will get better because you take part in this study although we do hope that it does
- This study may find out things that help out other children who have ADHD

Who will see the information collected about you?

- The information collected about you during this study will be kept locked up. Only the people doing research will know it

Will any part of the study hurt?

- The vitamin and mineral formula you take **may** make you feel upset to your tummy or give you a sore head
- This is important to know so please tell your parent if you feel any of these things
- When blood is drawn from your arm (this will happen two times) you will feel a pinch from the needle and this may leave a black and blue spot on the skin where the needle touched your arm

Do you have to be in the study?

- **No.** And no one will be mad if you don't want to
- 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??

You can ask questions you may have about the study now or if you think of them later you can ring us or have your parent ring

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 Signature Printed Name Date

☐ I have solicited the assent of the child.

_____

Parent Signature Name of Parent(s) Date

_____

Researcher explaining study
Signature Printed Name Date

Appendix E: Schedule of Events

	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24
***Screening**:*													
K-SADS	X												
WASH-U K-SADS	X												
***Neuro**:*													
CPT-II	X				X		X				X		X
***Scales**:*													
CLINICIAN													
CGI	X	X	X	X	X	X	X	X	X	X	X	X	X
CGAS	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X
CDRS	X	X	X	X	X	X	X	X	X	X	X	X	X
PARENT													
CPRS-R:L	X				X		X				X		X
ADHD-RS-IV	X	X	X	X		X		X	X	X		X	
CMRS-P	X	X	X	X	X	X	X	X	X	X	X	X	X
SDQ	X		X		X		X		X		X		X
TEACHER													
CTRS-R:L	X				X		X				X		X
SDQ	X				X		X				X		X
CHILD													
MYMOP adaptation	X	X	X	X	X	X	X	X	X	X	X	X	X
Side Effects Q		X	X	X	X	X	X	X	X	X	X	X	X

Appendix F: Recommended Upper Limits

EMPowerplus Capsule Ingredient List (Current)

1 cap		4 caps		8 caps		15 caps		Upper limit for children 8-12 years/day based on NZ guidelines	
384.0	IU	1536.0	IU	3072.0	IU	5760	IU	50,000IU (based on extrapolation from adult studies)	Vitamin A
40.0	mg	160.0	mg	320.0	mg	600	mg	No UL set but 1000mg recommended	Vitamin C
96.0	IU	384.0	IU	768.0	IU	1440 36	IU ug	80 ug	Vitamin D
24.0	IU	96.0	IU	192.0	IU	360 240	IU mg	300mg for adults (extrapolated to 180 mg for children but not based on any data)	Vitamin E
1.2	mg	4.8	mg	9.6	mg	18	mg	No UL set	Vitamin B1 (thiamine)
0.9	mg	3.6	mg	7.2	mg	13.5	mg	No UL set	Vitamin B2 (riboflavin)
6.0	mg	24.0	mg	48.0	mg	90	mg	500mg	Vitamin B3 (niacinamide)
1.4	mg	5.8	mg	11.5	mg	21.6	mg	No UL set	Vitamin B5 (calcium pantothenate)
2.4	mg	9.6	mg	19.2	mg	36	mg	100mg for adults	Vitamin B6 (pyridoxine hydrochloride)
96.0	ug	384.0	ug	768.0	ug	1440	ug	1mg (if taken without B12, otherwise, much higher)	Vitamin B9 (folic acid)
60.0	ug	240.0	ug	480.0	ug	900	ug	No UL set	Vitamin B12 (Cyanocobalamine)
72.0	ug	288.0	ug	576.0	ug	1080	ug	No UL set	Vitamin H (biotin)
88.0	mg	352.0	mg	704.0	mg	1320	mg	2500mg	Calcium
0.9	mg	3.7	mg	7.3	mg	13.74	mg	40mg	Iron
56.0	mg	224.0	mg	448.0	mg	840	mg	4000mg	Phosphorus
13.6	ug	54.4	ug	108.8	ug	204	ug	600 ug	Iodine
40.0	mg	160.0	mg	320.0	mg	600	mg	350mg but due to risk of diarrhoea on its own; however, required for absorption of calcium so if taken with calcium can tolerate higher. Diarrhoea has not be a commonly reported side effect	Magnesium
3.2	mg	12.8	mg	25.6	mg	48	mg	25mg but set to avoid problems with copper metabolism (which is included)	Zinc
13.6	ug	54.4	ug	108.8	ug	204	ug	280 ug	Selenium
0.5	mg	1.9	mg	3.8	mg	7.2	mg	10mg for adults (extrapolated to 5mg for children but not based on data)	Copper
0.6	mg	2.6	mg	5.1	mg	9.6	mg	Low acute toxicity, no UL set	Manganese
41.6	ug	166.4	ug	332.8	ug	624	ug	No UL set	Chromium
9.6	ug	38.4	ug	76.8	ug	144	ug	1100 ug	Molybdenum

16.0	mg	64.0	mg	128.0	mg	240	mg	No UL set	Potassium
24.0	mg	96.0	mg	192.0	mg	360	mg	10g	dl-phenylalanine
12.0	mg	48.0	mg	96.0	mg	180	mg	600mg	glutamine
16.0	mg	64.0	mg	128.0	mg	240	mg	No UL set	citrus bioflavanoids
3.0	mg	12.0	mg	24.0	mg	45	mg	No UL set	grape seed
36.0	mg	144.0	mg	288.0	mg	540	mg	1000mg	choline bitartrate
12.0	mg	48.0	mg	96.0	mg	180	mg	No UL set	Inositol
2.4	mg	9.6	mg	19.2	mg	36	mg	No UL set	ginkgo biloba
4.0	mg	16.0	mg	32.0	mg	60	mg	3g	methionine
1.4	mg	5.5	mg	11.0	mg	20.7	mg	No UL set	germanium sesquioxide
160.0	ug	640.0	ug	1280.0	ug	2400	ug	20mg	Boron
2.0	ug	7.8	ug	15.7	ug	29.4	ug	600mcg	Nickel
79.6	ug	318.4	ug	636.8	ug	1194	ug	10mg	vanadium
111.0		444.1		888.2		1665.3			Proprietary Total

Appendix G: Follow-up Consent Letter

Dear _____,

Thank you again for taking part in our research investigating the effect of micronutrients on mood and ADHD behaviours. As it has been six months since we last saw you, we are interested in the long term effectiveness of the micronutrients and would like to invite you to be part of this research as well. If you and your child are interested in being part of this research, whether or not currently taking the micronutrient, please be in contact with myself or Heather and we will organise a brief meeting where we discuss how the last six months have been. As with the initial research, you will be reimbursed for your time with a $10 petrol voucher.

We look forward to hearing from you.

Yours sincerely,

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