BROAD-SPECTRUM MINERAL-VITAMIN TREATMENT TO SUPPORT SMOKING CESSATION

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Abstract

Background: Smoking cessation/quitting smoking is among the most important health-promoting life changes a person can make, and is the most cost-effective disease prevention intervention available. Despite the benefits, many smokers have difficulty quitting using current smoking cessation options and the incidence of smoking relapse is high. Alternative treatments that are safe, effective, relatively inexpensive, and readily available are needed. Broad-spectrum micronutrient (minerals and vitamins) supplements are one such possible alternative. Research on the use of micronutrients in the treatment of substance dependence has existed for half a century. Investigations in to the use of micronutrients to relieve psychological symptoms has grown substantially in the past decade and has now been demonstrated in a number of trials. This thesis presents two randomised control trials to investigate whether a broad spectrum mineral vitamin formula supports smoking cessation. Aim Study One: Study one, a pilot trial, investigated if a broad-spectrum micronutrient formula supports withdrawal, smoking cessation, cigarette/day reduction and associated psychological symptoms. Methods: This pilot study was a single-case multiple-baseline design with replication across participants (*n*=24), nested within an active treatment-placebo double-blind randomized trial. Following a baseline phase of one to three weeks when smoking history, daily cigarette consumption (cigarettes/day), withdrawal, and nicotine dependence were measured, 24 participants were randomized (12/group) to placebo or micronutrient conditions. A four-week pre-quit phase permitted titration up to 12 capsules/day and ensured the metabolic effects of the capsules were established before quitting. In the smoking cessation phase (12 weeks duration), participants registered with Quitline NZ (not including Nicotine Replacement Therapy (NRT)), read the *Quit book*, and continued to consume the 12/day micronutrient or placebo

capsules while attempting to quit smoking from a target quit day. Participants were counted as having a quit success if they were abstinent for ≥three days after their quit day. Quit success was established through self-report at study waypoints (4, 8, and 12 weeks post quit day). Abstinence was counted if a participant had not relapsed (≥three continuous days smoking) from their quit date to the end of the study waypoint. Daily withdrawal measures were taken at weeks 1-4, 8, and 12 post quit. Monthly withdrawal and psychological measures were completed at each study waypoint. Results: The results showed that median withdrawal scores were higher in the placebo group. Drop-out before making a quit attempt was lower in the micronutrient group (0 vs 4) and those taking micronutrients were more likely to make a quit attempt (11 (91.7%) vs 5 (41.7%); Odds Ratio (OR) = 15.4; 95% Confidence Interval (CI) [1.47, 160.98]) and be successful at quitting (≥ 3 days smoke-free) (10 (83.0)% vs 4 (33.3%); OR = 10.0; 95% CI [1.44,69.26]). The micronutrient group had a higher quit rate at four weeks (58.3%) compared to placebo (25.0%), this was not significant (χ^2 (1, *n*= 24) = 2.74, *P*=0.10), and NNT=13. Aim Study Two: Study two, a fully-blinded randomised placebo-controlled trial was designed to further investigate the use of a broad-spectrum micronutrient formula to assist with quitting smoking, reduction of cigarettes/day, withdrawal symptoms, and associated psychological symptoms. Methods: Following the baseline phase (one to two weeks) when smoking history, daily cigarette consumption (cigarettes/day), withdrawal, and nicotine dependence were measured participants (*n*=107) were randomised to placebo (*n*=50) or micronutrient conditions (*n*=57). A four-week pre-quit phase permitted titration up to 12 capsules/day. During the quit phase participants were registered with a public Quitline (not including NRT), read the *Quit book*, and attempted to quit smoking on a target quit day while continuing to consume micronutrients or placebo for 12 weeks. Carbon monoxide levels and self-report confirmed continuous

abstinence at 4, 8, and 12 weeks post-quit. Results: Twenty-two (39%) participants in the micronutrient group and twenty-one (42%) in the placebo group completed the full trial. Micronutrient + Quitline and Placebo + Quitline groups did not differ on the primary outcome of continuous abstinence at 12-weeks post-quit day using intent-to-treat analysis; however, 28% of the micronutrient treated group had quit versus 18% for placebo (OR=1.78, 95%CI [0.71, 4.48]), with NNT=10. Comparison of cigarettes/day between micronutrient and placebo groups showed that those taking micronutrients reported reduced consumption throughout the trial, notably at pre-quit weeks one and four, and at quit phase week four. There were no serious adverse events, masking was successful and there were no substantive group differences in side effects or drop-out rate. Conclusion: The two studies presented are the first RCT's investigating the impact of micronutrients on smoking reduction, finding that micronutrients support quit attempts, and reduced harm through reduction in number of cigarettes smoked relative to placebo. The small sample sizes and high drop-out rate limits confidence in the conclusions and generalizability of the results; however, micronutrients were shown to be comparable to other smoking cessation treatments but with fewer side effects. Future research using larger and longer trials including cost effectiveness and biomarker measures is encouraged.

Declaration

None of the researchers has any financial, professional, or personal relationships with Hardy Nutritionals or any other nutritional, pharmaceutical, or smoking-cessation company or organization.

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List of Abbreviations

ADHD – Attention Deficit Hyperactivity Disorder

ASI – Anxiety Sensitivity Index

ATP – Adenosine triphosphate

AUDIT – Alcohol Use Disorders Identification Test

AUDIT-C – Alcohol Use Disorders Identification Test – Consumption

BAI – Beck Anxiety Inventory

BDI – Beck Depression Inventory

CI – Confidence Interval

CLES – Common Language Effect Size

CO – Carbon Monoxide

CONSORT – Consolidated Standards of Reporting Trials

DASS-21 – Depression Anxiety and Stress Scale-21

DEMF-N – Diener and Emmons Mood Form-Negative

DEMF-P – Diener and Emmons Mood Form-Positive

DEN – Daily Essential Nutrients

DNA – Deoxyribonucleic acid

DQQ – Diet Quality Questionnaire

DSM-5 - Diagnostic and Statistical Manual of Mental Disorders 5th edition

ES – Effect size

FTCD – Fagerstrom Test for Cigarette Dependence

GI – Gastrointestinal

HADS – Hospital Anxiety and Depression Scale

HSI – Heaviness of Smoking Index

ITT – Intent-to-treat

MNWS – Minnesota Nicotine Withdrawal Scale – short form

MPSS – Mood and Physical Symptoms Scale

mtDNA – Mitochondria Deoxyribonucleic acid

MTHR – Methylenetetrahydrofolate reductase

nAChRs – Nicotine acetylcholine receptors

NNT – Number needed to treat

NRT – Nicotine Replacement Therapy

Odds Ratio – OR

P – Participant

PDM – Percent Deviating from the Median

RC+ - Positive Reliable Change

RCI – Reliable Change Index

RCT – Randomised Controlled Trial

RDI – Recommended daily intake

ROS – Reactive oxygen species

RR – Relative Risk

SDI – Socio-Demographic Index

t_1 – Time one

t_2 – Time two

TAU – Treatment as usual

UL – Upper limit

WSWS – Wisconsin Smoking Withdrawal Scale

$\alpha_4\beta_2$ – Alpha-4 beta-2

$\chi 2$ – *Chi*-squared

Chapter 1: Tobacco Smoking

This thesis presents two randomised controlled trials (RCT; study one and two) investigating the effect of a broad-spectrum mineral-vitamin formula on smoking cessation outcomes, consumption of cigarettes, withdrawal and other psychological symptoms in adults who were current smokers. This introductory chapter will provide an outline of tobacco smoking, its prevalence, adverse health outcomes, and economic costs. Addiction, nicotine dependence, and withdrawal are also discussed. Furthermore, current standard smoking cessation interventions and at-risk populations for higher smoking prevalence and lower smoking cessation outcomes are outlined.

1.1 Tobacco Smoking

Tobacco is a plant from the *Solanaceae* family within the *Nicotiana* genus and carries in its leaves quantities of an alkaloid called nicotine (Jiloha, 2010). Tobacco was initially used to treat various problems such as toothache and headache, and in the 18th century it began to be used recreationally (Thielen, Klus, & Müller, 2008). After harvesting and curing, tobacco leaves are manufactured into consumable products, the most common being cigarettes – a small quantity of tobacco wrapped in paper. Cigarette smoking, the most common method of tobacco consumption, is the practice of burning the tobacco inside a cigarette and inhaling the smoke (Thielen et al., 2008). With each puff of a lit cigarette a smoker draws tobacco smoke into their mouth and lungs, thus consuming a range of gases containing many different sized particles of approximately 4000-5000 different chemicals with nicotine the main chemically active and addictive component (Jiloha, 2010).

1.2 Prevalence of Tobacco Smoking

The Global Burden of Disease study including 195 countries estimated in 2015 that the age-standardised prevalence of daily smoking was 25% in men and 5% in woman (95% CI 24, 26 and 5, 6 respectively) (Reitsma et al., 2017). The ten countries with the largest number of smokers together accounted for approximately 64% of the world's daily smokers. China, India, and Indonesia, the three leading countries in total number of male smokers, accounted for 52% of the world's male smokers in 2015. Conversely, the USA, China, and India, were the leading three countries in total number of female smokers, accounted for only approximately 27% of the world's female smokers. The prevalence of daily smokers in low Socio-Demographic Index (SDI) countries (29 countries) was 13% (range 7% to 22%) for men and 2% (range 1% to 7%) for woman in 2015. In low-to-middle SDI countries (30 countries) 20% are daily smokers in men (range 1% to 48%) compared to 5% (range 0.4% to 25%) in woman. Middle SDI countries (34 countries) had an average daily smoking prevalence of 24% in men (range 9% - 47%) and 4% (range 0.4% – 12%) in woman. High to middle SDI countries (55 countries) had a smoking prevalence of 24% in men and 10% in woman (ranges 5% to 44% and 1% to 44% respectively). High income countries (47 countries) had a prevalence rate of 23% in men (range 4% - 46%) and 14% in woman (range 2% to 25%) (Reitsma et al., 2017). Fifty-one countries and territories had significantly higher prevalence in smoking compared to the global average for men; these countries were mainly located in central and eastern Europe and southeast Asia. For women, 70 countries significantly exceeded the global average, largely located in western and central Europe (Reitsma et al., 2017).

With increasing awareness of the adverse health effects of smoking and heightened anti-smoking campaigns, tobacco use has steadily decreased in many developed countries

over the past 20-30 years (Zheng et al., 2014). The global-age standardised prevalence of daily smoking has reduced significantly in both sexes decreasing by 29% (95% CI 26, 31) and 34% (95% CI 30, 39), in men and women respectively, since 1990 (Reitsma et al., 2017). Thirteen countries (Australia, Brazil, China, Denmark, Dominican Republic, Iceland, Kenya, the Netherlands, New Zealand, Norway, Sweden, Switzerland, and the USA) recorded significant annualised rates of decline both between 1990 to 2015, suggesting sustained progress in tobacco control. Since 2005, 53 of 195 (27%) countries and territories recorded significant decreases in age-standardised prevalence of male daily smoking, whereas only 32 (16%) recorded significant reductions for women. Nevertheless, Ng et al. (2014) who analysed data from 187 countries (38,315 observations) estimated that due to population growth the number of current smokers globally in 2014 had increased from 721 million to 967 million since 1980 (Ng et al., 2014).

New Zealand Smoking Prevalence

Aotearoa New Zealand (NZ) is a small, developed country that has had a long standing public health commitment to reducing smoking, not least because indigenous Māori have high rates of smoking and smoking-related death and disease (see www.health.govt.nz). A NZ Ministry of Health (Manatū Hauora) survey (approximately 13,000 respondents) reported that 18% of NZ adults aged 15 years and over were current smokers in 2012-13, with current smokers defined as smoking more than 100 cigarettes in their lifetime and at the time of the survey smoking at least once a month[1] (Ministry of Health, 2014). There were similar rates of current smoking across male and females (19%

[1] There is a difference in definitions of a 'current smoker' between the two surveys of 1996/97 and 2012/13. The definition of 'current smokers' used in the 1996/97 NZHS is 'those who reported that they smoked one or more cigarettes per day' whereas the 2012/13 NZHS defines 'current smokers' as 'those who have smoked more than 100 cigarettes in their lifetime and at the time of the survey were smoking at least once a month'.

and 16% respectively). The survey also reported that approximately 16% of adults (aged 15 years and above) smoked daily (Ministry of Health, 2014).

Current smoking rates in NZ are declining, with the prevalence falling significantly from 2006 (24%) to 2009 (21%), and again in 2012 (18%). However, the decline in smoking prevalence is occurring, at different rates among different population groups, with some declines slower than others. Individuals who identify as NZ European or Other showed a significant decline in tobacco smoking prevalence between 2006-07 and 2012-13. Those who identify as Māori, Asian, and Pacifica have also decreased in prevalence, but this is not statistically different from 2006-07. Māori *c*ontinue to have the highest rates of smoking in NZ; around four in ten Māori adults (39%) were current smokers in 2012-13, a non-significant change since 2006-07 (40%). Pacifica adults have the second highest prevalence in NZ with one in four (24%) identifying as current smokers in 2012-13, a non-significant decline since 2006-07 (26%) (Table 1.1) (Ministry of Health, 2014). Almost one in eight young people aged - 15–19 - years (13%) were current smokers in 2012/13. This represents a significant decline from the 2006/07 prevalence of one in five young people (20%). This age group 15–19 year olds showed the largest relative decline in current smoking prevalence (36%) between 2006 and 2012. In comparison, those aged 65–74 years and 25–34 years showed 27% and 13% relative declines respectively between 2006 and 2012 (Ministry of Health, 2014).

Table 1.1. *Ethnic differences in prevalence of current smoking in NZ.*

Ethnic Group	2006/07 (%)	2012/13 (%)	Relative % change
Māori	42	39	-7
Pacific	27	25	-9
Asian	11	10	-10
European/Other[2]	19	15	-18*

Source: New Zealand Health Survey (Ministry of Health, 2014). *There is a statistically significant difference (p<0.05) between 2006 and 2012.

The Ministry of Health Survey (2014) revealed a gradient in smoking prevalence and neighbourhood deprivation, with 32% of smokers being from the most deprived areas compared to 13% in the least deprived. After adjusting for age, sex, and ethnic group, those who live in the most deprived areas are almost three times more likely to be smokers than people in the least deprived areas (Ministry of Health, 2014).

Sex

As discussed, there are large differences in smoking prevalence among males and females across countries. Women outlive men in all countries in the world, but men have a higher prevalence of smoking than women, and it is estimated that smoking-related deaths account for 40% to 60% of the gender mortality gap (McCartney, Mahmood, Leyland, Batty, & Hunt, 2011). The proportion of NZ females smoking in 2012 (16%) was significantly lower than the proportion of NZ males smoking (19%) (Ministry of Health, 2014). Conversely, there were significantly more Māori female smokers (42%) than Māori male smokers (37%) in 2012/13 (Ministry of Health, 2014). Conversely, significantly more Asian males (16%) than Asian females (4.3%) were smokers.

[2] Other includes individuals that do not identify with New Zealand European, M*ā*ori, Samoan, Cook Island Maori, Tongan, Niuean, Chinese, or Indian.

Mental health

Tobacco use remains high in persons with mental illness (Centers for Disease Control and Prevention, 2013), with these individuals smoking at rates two to three times that of the general population (Dalton, Mellemkjær, Olsen, Mortensen, & Johansen, 2002; Lawrence, Mitrou, & Zubrick, 2009; Lê Cook et al., 2014; McClave, McKnight-Eily, Davis, & Dube, 2010). Mental illness is associated with higher levels of nicotine dependence, intensity of smoking, number of cigarettes smoked, greater withdrawal symptoms, and lower quit rates (Bowden, Miller, & Hiller, 2011; Gierisch, Bastian, Calhoun, McDuffie, & Williams, 2012; Lê Cook et al., 2014; Prochaska, Das, & Young-Wolff, 2017). The Ministry of Health survey revealed that almost a quarter (24%) of NZ smokers reported one or more diagnosed mental health conditions (depression, bipolar disorder, anxiety disorder, an alcohol-related disorder or a drug-related disorder) compared to 15% of non-smokers (Ministry of Health, 2014). People with mental health disorders have a life expectancy of eight years less than the general population and cigarette smoking may contribute to much of this difference (Tam, Warner, & Meza, 2016; Taylor et al., 2014).

Many explanations for the high rate of tobacco use among people with mental illness have been proposed, including biological factors and psychosocial reasons such as a lack of social support, changes in cognitive functioning, anxiety, side effects of medications, and lack of coping skills (Ashton, Miller, Bowden, & Bertossa, 2010). The self-medication hypothesis posits that many smokers report that they smoke to alleviate emotional problems, and feelings of depression and anxiety, to stabilise mood, and for relaxation, as well as to relieve stress (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Taylor et al., 2014). Patients with mental illness may attribute greater benefits and reward value to smoking, may experience more difficult life circumstances compared to people without

mental illness, have higher levels of negative affect (referring to mood states marked by feeling angry, frustrated, irritable, sad, depressed, and distressed), and/or a relative lack of alternative rewards, all factors consistent with higher prevalence of smoking in these individuals (Ashton et al., 2010; Prochaska et al., 2017). Conversely, evidence also indicates that smoking may have a role in the aetiology of depression, anxiety, and schizophrenia, and is a gateway to problematic substance use (Prochaska et al., 2017). Therefore, bi-directional models maintain that smoking and psychiatric symptoms influence each other (Windle & Windle, 2001).

1.3 Adverse health effects

Smoking is associated with an array of adverse health effects, including an increased risk of cardiovascular disease, respiratory disease, stroke, hypertension, and cancer (Talhout et al., 2011; Yeomans et al., 2011). The primary reason for this is that smoking has a carcinogenic effect on tissues (Talhout et al., 2011; Valavanidis, Vlachogianni, & Fiotakis, 2009). High rates of cancers in the mouth, pharynx, and lungs occur as these organs are directly exposed to the smoke. The oesophagus, stomach, and gut are not directly exposed to the smoke, but are exposed to the secretions of the mucous membranes from the mouth and pharynx as they are swallowed after smoking, leading to higher rates of cancers in these organs. Further, substances within tobacco smoke are absorbed from the lungs into the bloodstream and thus circulated to all parts of the body damaging many other organs and further contributing to whole-body adverse health events (Dreyer, Winther, Pukkala, & Andersen, 1997).

Tobacco smoking is the leading cause of preventable premature mortality in the world (Banks et al., 2015; Polosa & Benowitz, 2011). Annually tobacco smoking and

exposure to second hand smoke causes approximately five million global deaths (Ng et al., 2014; Polosa & Benowitz, 2011) with 4500-5000 occurring in NZ (Ministry of Health, 2014). The relative risks of adverse health effects and mortality associated with smoking increase with increased amounts of tobacco smoked per day. A large Australian cohort study (*n*= 204, 953; aged ≥45 years) reported an adjusted relative risk (RR) for premature mortality of 2.96 in all current smokers, with approximately a two-fold increase in mortality for people smoking 14 or fewer cigarettes/day and a four-fold increase in smokers who smoked 25 or more cigarettes per day compared to those who were never smokers (Banks et al., 2015).

1.4 Economic Impact

The economic impact of smoking is extensive, and a large amount of this cost is due to the loss of productivity over a smoker's life, the adverse health effects (smoking-related illness and mortality), and attempts by governments to promote smoking cessation among smokers and to deter commencing smoking among non-smokers, especially adolescents (Ekpu & Brown, 2015; O'Dea, Thomson, Edwards, & Gifford, 2007). The World Bank estimates that approximately 15% of all health care expenditure in high income countries can be attributed to cigarette smoking (Feenstra, Hamberg-van Reenen, Hoogenveen, & Rutten-van Mölken, 2005; Parrott & Godfrey, 2004). Smoking also contributes considerable indirect costs to society and the non-smoking public, including the cost of second-hand smoking and costs to employers due to loss of productivity as a direct result of smoking-related illness (Ekpu & Brown, 2015; Halpern, Shikiar, Rentz, & Khan, 2001)

1.5 Nicotine Dependence

Addiction (or substance dependence) is a complex disease marked by reduced capacity to control drug intake, regardless of the risks and other negative consequences

(Hyman & Malenka, 2001). Drugs of abuse produce their effects through a variety of mechanisms, but all of them recruit the natural reward pathways of the central nervous system (Joffe, Grueter, & Grueter, 2014) and increase dopamine release resulting in feelings of pleasure. Addictive substances create reinforcing feedback that is of a greater magnitude and duration than what is observed in response to natural events, and enhanced learning about a drug's positive experiences increases the likelihood of that drug being used again, with this effect magnified each time the drug is used (Torregrossa, Corlett, & Taylor, 2011). Addiction is a complex bio-behavioural phenomenon with causes and effects that range from molecular mechanisms to social interactions (Polosa & Benowitz, 2011), and as a chronic disease, is often characterised by a cyclical, relapse-laden progression through several phases of maladaptive behaviour (Joffe et al., 2014).

Cigarette smoking expresses a major addiction (Hall, Humfleet, Reus, Muñoz, & Cullen, 2015; Taggar et al., 2015). Approximately one third of those who ever try cigarettes will become addicted (Centers for Disease Control and Prevention, 2013), and the primary reason most smokers have difficulty quitting is because they become addicted to nicotine (West, Ussher, Evans, & Rashid, 2006). Nicotine is the primary active addictive component in tobacco (Lenoir, Tang, Woods, & Kiyatkin, 2013). Pure nicotine is a colourless, volatile, strongly alkaline liquid that turns pale yellow to dark brown when exposed to air, and is highly toxic and potentially lethal. It is chemically responsible for several physiological changes in the body. When a cigarette is lit and tobacco is burnt, nicotine volatilizes and is present in the smoke as free nicotine suspended on microscopic droplets of tar. Nicotine from tobacco smoke enters the blood stream through the lungs and is rapidly carried to different parts of the body; within seconds it crosses the blood-brain barrier and enters the brain (Jiloha, 2010; Polosa & Benowitz, 2011). There it binds to specific receptors in the

brain where it influences cerebral metabolism (Jiloha, 2010). Nicotine activates the same reward pathways as other addictive drugs such as cocaine and amphetamines, but to a lesser degree (Maritz & Mutemwa, 2012). Over time, nicotine use alters the properties of individual neurons, in particular those using acetylcholine as the neurotransmitter at synaptic junctions, and the neural circuits they participate in, and leads to complex states including dependence, tolerance, sensitization, craving, and withdrawal (Polosa & Benowitz, 2011).

Acetylcholine is involved in systems concerned with mental and physical arousal, learning and memory, and several aspects of emotion. Acetylcholine receptors respond to acetylcholine as they recognize the molecule by the position of two electrical charges, one positive and one negative. Nicotine has structural similarity to acetylcholine and this structural similarity makes nicotine molecules interact with acetylcholine receptors (Jiloha, 2010). Unlike acetylcholine, nicotine remains bound to the receptor for much longer and consequently a proportion of receptors are desensitized. Repeated exposure to nicotine leads to an increase in the number of nicotine acetylcholine receptors (nAChRs), and the activation of nAChRs by nicotine can have a number of consequences in the recipient cells, such as the release of various other neurotransmitters including dopamine (Jiloha, 2010). Increases in the levels of dopamine and other neurotransmitters in the brain are responsible for the rewarding effects of nicotine (Maritz & Mutemwa, 2012). Nicotine not only causes damaging effects, it also leads to tolerance and addiction (Benowitz, 2008). Nicotine is also thought to be gateway drug to other drugs of abuse such as cannabis and alcohol (Jiloha, 2010).

The pharmacological basis of nicotine addiction can, therefore, be regarded as a combination of positive reinforcement (via the reward system) leading to enhancement of

mood or functioning, as well as negative reinforcement through escape/avoidance of negative consequences of prior drug use, especially relief from aversive withdrawal symptoms (Jiloha, 2010). Other reasons that motivate smoking are to alleviate emotional problems, to stabilise mood, for relaxation, to suppress appetite, and out of habit/boredom (Taylor et al., 2014).

Nicotine dependence is a strong negative predictor for quit attempts and quit success; the more nicotine-dependent a smoker the less likely they are to attempt to quit or be successful at the quit (Li & Grigg, 2007; Taggar et al., 2015). There is no single definition of nicotine dependence and therefore no universal measure of it. However, two dependence measures are widely used, namely the Fagerström Test for Cigarette Dependence (FTCD) (Fagerstöm, 2011) and the two item Heaviness of Smoking Index (HSI) (Borland, Yong, O'Connor, Hyland, & Thompson, 2010). These measures have been biochemically validated and are widely used in tobacco smoking research (Taggar et al., 2015).

1.6 Cigarette/Nicotine Withdrawal

Abrupt cessation/quitting or reduction of tobacco consumption and, therefore, of nicotine results in a withdrawal syndrome that primarily consists of negative affect and the emergence of aversive withdrawal symptoms (Piasecki, 2006). This negative affect and withdrawal leads to significant distress (Piper et al., 2011) and causes many smokers trying to quit to relapse, i.e., to resume smoking (West et al., 2006). Tobacco withdrawal symptoms are multi-dimensional and consist of several different types of symptoms (Javitz, Lerman, & Swan, 2012), but are all immediately relieved by smoking (Taylor et al., 2014).

Acute tobacco withdrawal usually begins within 24 hours of stopping or cutting down consumption, and peaks 1-4 days after abstinence, and lasts 2-4 weeks (American Psychiatric Association, 2013; Piasecki, 2006). The average pattern of withdrawal has considerable intra- and inter-individual variability, and each person responds somewhat differently when nicotine is withdrawn (Piasecki, 2006). Tobacco withdrawal symptoms listed in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) are: 1) irritability, frustration, or anger, 2) anxiety, 3) difficulty concentrating, 4) increased appetite, 5) restlessness, 6) depressed mood, and 7) insomnia (American Psychiatric Association, 2013). Clinical and anecdotal evidence reports other symptoms of withdrawal including: decreases in heart rate by 5-12 beats per minute, weight increases (of an average of 2-3 kilograms over the first year after quitting), clinically significant mood changes (American Psychiatric Association, 2013; Hatsukami, Hughes, Pickens, & Svikis, 1984), craving for sweet and sugary food, impaired performance on tasks requiring vigilance, increases in constipation, coughing, dizziness, dreaming/nightmares, nausea, and a sore throat (American Psychiatric Association, 2013).

Cigarette Craving

The term craving refers to an intense desire or urge to smoke, and is not part of the DSM-5 criteria for tobacco withdrawal; however, it is considered to be an essential component of the withdrawal syndrome (Piasecki, 2006; Van Zundert, Ferguson, Shiffman, & Engels, 2012). Craving is one of the DSM-5 diagnostic criteria for tobacco use disorder (American Psychiatric Association, 2013) and may be one of the most sensitive predictors for continued smoking and of relapse (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012). Craving typically shows a strong increase in the first week after quitting (Van Zundert,

Ferguson, et al., 2012) and decreases after a lengthy period of abstinence, but may never fully disappear (Piasecki, 2006).

Positive or negative affective states (discussed in section 1.8) can trigger craving to smoke (Brewer et al., 2011) and upward variations in craving are associated with an increased risk of lapse and relapse of smoking (Taggar et al., 2015; Van Zundert, Ferguson, et al., 2012). Strong daily urges to smoke (craving) predict same day or next day relapse, even when baseline urge level is statistically controlled for (Van Zundert, Ferguson, et al., 2012). Those who report less frequent urges to smoke and lower nicotine dependence are more likely to report abstinence at six months (Taggar et al., 2015). Craving is an important target for smoking cessation treatment; however, existing therapies may not assist those trying to quit manage craving adequately (Taggar et al., 2015).

1.7 Smoking Cessation Interventions

Smoking cessation/quitting smoking is among the most important health-promoting life changes a person can make (Bottorff et al., 2014), and is the most cost-effective disease prevention intervention available (Aubin et al., 2008). For instance, the leading cause of death from cigarette smoking is cardiovascular disease and quitting smoking has immediate cardiovascular benefits, reducing the risk of occurrence of coronary events to that of a non-smoker within three years, and reducing mortality from a heart attack by up to 50% over three to five years (Prochaska & Hilton, 2012). Furthermore, those who have smoked cigarettes since early adulthood but stop at 30, 40, or 50 years of age gain approximately 10, 9, and 6 years of life expectancy respectively, compared to those who continue to smoke (Jha & Peto, 2014). Other common reasons for people to want to quit smoking include the financial benefits, family, and lifestyle reasons (Ministry of Health, 2007).

Before reviewing specific smoking cessation interventions, a note on terminology is in order, since despite attempts to classify important outcomes in smoking cessation research, variations in the key definitions remain. In general, and in this thesis, the term *lapse* means a slip back to smoking after a period of abstinence. A lapse is an isolated event that is followed by the renewal of abstinence (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012). A *relapse* refers to a period of several days (three or more) of continuous smoking after a period of abstinence or an attempt at abstinence (Brown, Lejuez, Kahler, Strong, & Zvolensky, 2005; Piasecki, 2006). Initiators of a lapse and relapse include withdrawal symptoms, negative affect, urge/craving for cigarettes, increases in alcohol consumption, the presence of other smokers, and being in situations where cigarettes are readily available. A lapse may also alleviate the withdrawal symptoms, and a lapse is therefore a major risk factor for relapse (Piasecki, 2006). *Continuous abstinence* requires an ex-smoker to be totally abstinent from smoking from a specified day (quit date) or after a specified grace period (up to two weeks after the target quit day) until a follow-up end point (a variable period specified study-by-study) to be counted as a treatment success. Most studies allow for isolated lapses without a relapse after cessation (Piasecki, 2006). *Point prevalence* is also used as a measure of prolonged abstinence; it is a measure of whether a person has had "even a puff" in a specific time-period prior to follow-up, typically the past seven days. Key endpoints/ follow-ups in clinical trials for determining treatment success are 3, 6, or 12 months after a quit date (Cinciripini et al., 2013; Piasecki, 2006; Walker et al., 2011).

Not all smokers will reach the gold standard goal of complete abstinence; therefore, reduction in the number of cigarettes/day is also frequently reported. Many smokers are

able to maintain smoking reductions after a relapse, and there is evidence to suggest that smoking reduction is associated with an increase in cessation rates in some (Broms, Korhonen, & Kaprio, 2008; Farkas, 1999; Lindson-Hawley, Aveyard, & Hughes, 2012), but not other studies (Hughes, Cummings, & Hyland, 1999; Hughes, Lindgren, Connett, & Nides, 2004; Meyer, Rumpf, Schumann, Hapke, & John, 2003). A Cochrane review of 10 RCTs (N=3760) concluded that neither reduction or abrupt quitting had superior abstinence rates, whether all studies were combined (RR 0.94, 95% Confidence Interval (CI) 0.79, 1.13), whether pharmacotherapy was used (RR 0.87, 95% CI 0.65, 1.22), or not (RR 0.97, 95% CI 0.78, 1.21), whether studies included behavioural support (RR 0.87, 95% CI 0.64, 1.17) or self-help therapy (RR 0.98, 95% CI 0.78, 1.23) (Lindson-Hawley, Aveyard, & Hughes, 2012).

Despite the known benefits, many smokers have difficulty quitting and the incidence of smoking relapse is high (Yeomans et al., 2011), with many smokers failing to attempt even 24 hours of continuous abstinence after quit date (Piasecki, 2006). Quitting smoking is a dynamic process often involving sequences of unsuccessful quit attempts before long-term abstinence is achieved (Zvolensky, Stewart, Vujanovic, Gavric, & Steeves, 2009). To quit successfully requires both (i) making a quit attempt, and (ii) maintaining abstinence after that attempt. In general, effective smoking cessation treatments show an advantage over control treatments very soon after quit date, within the 3-10 day window when relapse is at its highest (American Psychiatric Association, 2013; Piasecki, 2006).

NZ, as do many other Western countries, runs comprehensive tobacco control programmes to support smoking cessation, including annual increases in tax on tobacco, mass media campaigns to prompt quitting and reduce smoking initiation, restrictions on tobacco product marketing and sales, and extensive bans on smoking in indoor and some

outdoor environments (Glover, Fraser, & Nosa, 2012; Ng et al., 2014). *The New Zealand Guidelines for Helping People to Quit Smoking* (see www.health.govt.nz) provide updated guidance for smoking cessation support offered in NZ, including using free telephone counselling services and/or smoking cessation medications. The remainder of this chapter discusses current smoking cessation interventions, along with self-quitting (quitting without the support of any assistance or treatment).

Self-quitting

Many smokers attempt to quit smoking without any assistance or treatment, referred to as self-quitting (Chapman & MacKenzie, 2010; Piasecki, 2006). Rates of self-quitting are declining due to the increase in smoking cessation medication and behavioural support, with approximately 50% of smokers who attempt to quit using a cessation aid (Smith et al., 2015). However, this means that half of quit attempters do not use an aid, and this is problematic as rates of success at self-quitting are low. Studies (seven studies, N=1677) suggest that approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence, and only 3-5% of smokers (15 studies, N= >6955) remain abstinent at 6-12 months (Hughes, Keely, & Naud, 2003). A range of smoking cessation interventions are offered to decrease the level of self-quitters and increase global quit success and these are now discussed.

Behavioural Interventions

Behavioural or psychological interventions to aid smoking cessation include self-help materials, brief therapist-delivered interventions, intensive counselling delivered on an individual basis or in a group, and any combinations of these approaches (Stead et al., 2013). These interventions can be delivered in a face-to-face, internet, mobile phone,

and/or telephone format. Lancaster and Stead (2017) reviewed the effect of intensive one to one behavioural interventions on smoking cessation delivered by specialist counsellors. They found that individual counselling was more effective than a minimal contact control (brief advice, usual care, or provision of self-help materials) when pharmacotherapy was not offered to any participants (RR 1.57, 95% CI 1.40, 1.77; 27 studies, N= 11,100). Furthermore, there was evidence for a benefit of intensive counselling when all participants received pharmacotherapy (NRT; RR 1.24, 95% CI 1.01, 1.51; 6 studies, N=2662). There was also a small benefit of more intensive counselling compared to brief counselling (RR 1.29, 95% CI 1.09, 1.53; 11 studies, N=2920) (Lancaster & Stead, 2017).

Quit lines

Telephone counselling services (quit lines) for smoking cessation, are an easily accessible and effective treatment delivery method (Toll et al., 2015), and are available in many countries in the world through state and/or national health plans (Wadland et al., 2007). The support offered by quit lines typically includes mailed materials, recorded messages, call-back counselling, and some quit lines, including NZ, provide free or discounted nicotine replacement therapy (NRT) (Cummins, Bailey, Campbell, Koon-Kirby, & Zhu, 2007; Stead, Perera, & Lancaster, 2007). Proactive telephone support for smoking cessation increases long-term (conventionally 12-months) abstinence rates, and including telephone support with medication interventions increases abstinence rates compared to medication alone (McRobbie et al., 2008). A Cochrane review pooled nine-trials (N >24,000) among smokers who contacted quit lines, and found that quit rates were higher in those who received multiple sessions of proactive counselling (participants were called back) reported a RR of 1.37 (95% CI 1.26, 1.50). Fifty-one trials (N =30,246) were reviewed to test the effect of telephone counselling for people who had not called a quit line, some of whom

might not have been actively planning to quit. The results suggested a modest benefit of proactive telephone counselling (RR 1.27, 95% CI 1.20, 1.36) (Stead, Hartmann-Boyce, Perera, & Lancaster, 2013). Furthermore, twelve studies (N =30,182) compared an intervention involving multisession (>five sessions) proactive telephone counselling with a control condition that provided self-help materials or brief counselling at a single call. The results showed evidence of a benefit from the additional support (RR 1.38, 95% CI 1.28, 1.49) when compared to brief support (Stead et al., 2013). The results suggest that rates abstinence are increased with more intensive telephone support when compared to brief support (one or two calls).

Quitline NZ is a free quit smoking telephone helpline launched in 1999 by the NZ Ministry of Health. Callers can request a quit pack containing practical quit-smoking advice and information including the *Quitbook*, register on the Quitline programme for ongoing advice and support, and get exchange vouchers (Quitcards) for a four to eight week supply of subsidised (NZ$5) NRT (patches, gum, lozenges). Borland et al. (2012) reported that 12% of quitters in NZ used Quitline between 2011-12, and this was the highest rate of quit line use out of the 15 countries (Australia, Canada, China, France, Germany, Ireland, Malaysia, Mexico, Netherlands, New Zealand, South Korea, Thailand, UK, Uruguay and USA, N= 24,523) in the International Tobacco Control Policy Evaluation Project (ITC), versus approximately 10% in Australia, 9% in the USA, 6% in UK (Borland et al., 2012). In 2014 the Ministry of Health reported that Quitline was used by one in six (16%) recent quit attempters (Ministry of Health, 2014).

Four week self-report continuous abstinence rates for all callers using Quitline NZ were reported to be 30% in 2013 (*n*= 1251) (Quitline NZ, 2013). Research using Quitline usual care as a control group in NZ adults reported three-month continuous abstinence

rates of 21% and 26% (Walker et al., 2011; Walker et al., 2012) and six-month rates of 15-19% (*n*=551, *n*= 704, *n*=705 respectively) (Bullen et al., 2010; Walker et al., 2011; Walker et al., 2012). Biochemical confirmation (Walker et al., 2011) or not (Bullen et al., 2010; Walker et al., 2012) did not appear to effect abstinence rates. Borland and colleagues randomised 1578 adult Australian smokers to receive self-help materials, computer-generated advice, or computer generated advice plus telephone counselling (via Quit Victoria, an Australian Quitline). At the three-month follow-up they reported a point-prevalence rate post-randomization of 21% (chi squared = 17; $p<0.001$) versus 12% for the control groups (not biochemically confirmed). However 24% of this group purchased and used NRT during their quit attempt (Borland, Balmford, Segan, Livingston, & Owen, 2003). A meta-analysis of 10 RCTs (N = 8225) using telephone counselling (Mottillo et al., 2009) reported an odds ratio (OR) of quitting of 1.58 (95% CI 1.15, 2.29) for telephone counselling compared to a control group at 6 and 12 month follow-ups.

Aukati Kai Paipa

Aukati Kai Paipa is a smoking cessation approach developed by Māori for Māori and is predominately delivered by Māori health organisations as well as hospital and community based clinics. It is whanāu-focused (family-focused), operating in a whanāu setting utilising strong local ties, and adopts a holistic approach to health. NRT is typically combined with support. Support consists of a Māori approach to health addressing all elements of wellbeing, and regular follow-up (McRobbie et al., 2008). A pilot programme, primarily targeting Māori woman (aged 18 and over; *n* = >3200) and their whanāu provided free NRT in the form of patches or gum, and counselling delivered by Māori quit coaches over a period of up to 12-months. They reported positive results for Aukati Kai Paipa with a six-month self-reported point-prevalence quit rate of 26% and 12-month point-prevalence quit

rate of 23% (Ministry of Health, 2003). The cost of delivering Aukati Kai Paipa was calculated to be approximately $4310 to $5715 per person (Ministry of Health, 2003).

Mobile phone-based interventions

The International Telecommunications Union estimated that there were more than seven billion mobile subscriptions in 2015, approximately 96.8 per 100 inhabitants of the world. Mobile phones are increasingly useful for health information and healthcare delivery around the world, and text messaging has been used for health service appointment reminders, preventive activities, and medication adherence (Free et al., 2013). Smoking cessation services are using mobile phones to deliver support, particularly in conjunction with other services (Abroms, Whittaker, Free, Van Alstyne, & Schindler-Ruwisch, 2015). Whittaker and colleagues reviewed the current research on the use of mobile phones in smoking cessation to determine whether mobile phone-based smoking cessation interventions increase cessation in people who want to quit (Whittaker, McRobbie, Bullen, Rodgers, & Gu, 2016). They included randomised and quasi-randomised trials, with participants of any age who wanted to quit smoking. Twelve studies (N =11, 885), of which the majority used text messaging, were analysed using their most rigorous six month data, some studies providing continuous abstinence measures or repeated measures of point prevalence, others only providing seven-day point prevalence. The pooled RR was 1.67 (95% CI 1.46, 1.90) supporting the use of mobile-based interventions when compared to usual care. The evidence supports the beneficial impact of using mobile phone-based smoking cessation interventions. However, it should be noted that the majority of the included studies used text messaging in high-income countries with good tobacco control policies. Caution should be taken when generalising the efficacy outside of this type of intervention (text messaging) and context (high income countries) (Whittaker et al., 2016).

Internet-based interventions

The internet has the potential to deliver behaviour change interventions (Japuntich et al., 2011). The Internet can be accessed in people's homes, on their phones, in libraries and through other public access points, such as Internet cafes and information kiosks. It is available all day every day, including in areas where there are limited resources for a smoking cessation clinic (e.g., some rural or deprived areas and low-income countries). Internet-based interventions can also be individualised similarly to that of one-to-one counselling (Muñoz et al., 2006), and therefore have a lot of potential to be used for smoking cessation interventions.

Taylor et al. (2017) reviewed 67 RCTs that investigated any type of smoking cessation internet intervention, with no exclusions based on age or gender. Eight trials (N =6786) compared a tailored and interactive internet intervention compared to a non-active control in adults for abstinence at six-months. Results showed an effect in favour of the internet-based intervention (RR 1.15, 95% CI 1.01, 1.30). Five trials (N =3806) compared a non-tailored internet-based intervention to an active control. The pooled effect favoured the control; however, the results were not statistically significant with the CI crossing the null (RR 0.92, 95% CI 0.78, 1.09). Five studies evaluated an internet programme plus behavioural support compared to a non-active control (N =2334). These studies indicated a positive effect of the intervention (RR 1.69, 95% CI 1.30, 2.18). Four studies evaluated the Internet plus behavioural support compared to active control. None of the studies detected a difference between trial arms (RR 1.00, 95% CI 0.84, 1.18, N =2769). Seven studies compared an interactive or tailored internet intervention, or both, to an Internet intervention that was not tailored/interactive. Pooled results favoured the interactive or tailored programme, but the estimate crossed the null (RR 1.10, 95% CI 0.99, 1.22, N =

14,623). Three studies compared tailored with non-tailored internet-based messages, compared to non-tailored messages. The tailored + non-tailored messages produced higher cessation rates compared to control, but the estimate crossed the null (RR 1.17, 95% CI 0.97, 1.41, N =4040). Taylor and colleagues concluded that internet-based interventions that were interactive and tailored to individual responses led to higher quit rates than usual care, however the results should be interpreted with caution due to some of the pooled results not showing a significant difference to the control groups.

Incentives

Material or financial incentives are widely used in an attempt to precipitate or reinforce behaviour change, including smoking cessation (Cahill, Hartmann-Boyce, & Perera, 2015). Previous research has shown that providing financial incentives can increase enrolment in to smoking cessation programmes (Volpp et al., 2006, Hennrikus et al., 2002, Donnatelle, Prows, Champeau, & Hudson., 2000). Cahill and colleagues (2015) reviewed RCTs allocating adults in workplaces, groups within workplaces, or communities to receive incentives to quit smoking versus controls. The incentives included lottery tickets or prize draws, cash payments, vouchers for goods and groceries, and in six trials the recovery of money deposited by those taking part. The OR for quitting with incentives at the longest follow-up (six months or more) compared with controls was 1.42 (95% CI 1.19, 1.69; 17 trials; N =7715). However only three studies demonstrated significantly higher quit rates beyond six-months post receiving the incentives versus controls (Cahill, Hartmann-Boyce, & Perera, 2015). Recently, Lasser, Quintilani, & Truong (2017) conducted a RCT with 352 adults randomised to usual care or patient navigation and financial incentives, delivered over six months. At 12-months post-randomization 11.9% of the navigation + financial incentives

group had quit smoking versus 2.3% of the control (OR 5.8, 95% CI 1.9, 17.1). Therefore, based on the current research it appears as though incentives boost smoking cessation while they are in place, with limited research that they may lead to improvements six-months post incentives.

Pharmacotherapy Interventions

Pharmacotherapies (i.e., the consumption by an individual of a specific drug or drug combination sanctioned by the health system) are often presumed to work by the drug induced reduction of withdrawal symptoms (Piasecki, 2006). More than 50% of quit attempters in high-income countries (Australia, Canada, United Kingdom and United States) sought pharmacotherapy in 2007 to support a quit attempt and less than 30% in NZ (Borland et al., 2012). Pharmacotherapy smoking cessation interventions are discussed below.

Nicotine Replacement Therapy (NRT)

NRT is the most common medication used to assist smoking cessation (Polosa & Benowitz, 2011). There are six commonly used NRT products (patches, gum, sublingual tablets, inhalers, lozenges, and nasal spray) (McRobbie et al., 2008) but the nicotine patch is the most commonly used (Piper et al., 2009). Differences between the formulations from NRT (e.g., lozenges *vs* gum) could influence withdrawal symptoms or the urge to smoke, but there is little evidence that one nicotine product is more effective than another (Polosa & Benowitz, 2011). Combination NRT (using two simultaneously) is associated with higher abstinence rates than single NRT use (Cahill et al., 2014; Stead, Perera, Bullen, Mant, & Lancaster, 2008). It is recommended that NRT should be used for 8 to 12 weeks, but heavily dependent smokers and those finding it hard to quit may need to use it for longer (McRobbie et al., 2008).

NRT's mechanism of action is to partially replace the nicotine that was acquired through tobacco smoking, and this aids smoking cessation by weakening the reinforcing effects of nicotine, reducing the severity of withdrawal and craving (Polosa & Benowitz, 2011). NRT does not completely remove withdrawal symptoms because the delivery of NRT nicotine differs from the rapid and high levels of nicotine achieved through tobacco smoking (Benowitz, 1993).

NRT approximately doubles the chance of achieving long-term abstinence (Polosa & Benowitz, 2011). A recent Cochrane review analysed 133 trials with 64,640 participants comparing any type of NRT to a placebo or a non-NRT control group. The RR for any form of NRT relative to control was 1.55 (95% CI 1.49, 1.61) (Hartmann-Boyce, Chepkin, Ye, Bullen, & Lancaster, 2018). The OR reported by another Cochrane review for NRT compared to placebo (quit rate 17% versus 10%) was 1.84 (95% CI 1.71, 1.99; 150 studies; N >51,000) at a six-months post-quit (Cahill et al., 2014). Wu, Wilson, Dimoulas, and Mills (2006) analysed 70 trials that compared NRT to controls at 1 year and found an OR of 1.7 (95% 1.6, 1.9, N=28,343). The results were consistent when examining all placebo-controlled trials (49 RCTs, N =25,512, OR 1.8, 95% CI 1.6, 2.0), NRT gum (33 RCTs, N =12,245, OR 1.60, 95% CI 1.4, 1.9) or patch (23 RCTs, N =11,108, OR 1.6, 95% CI 1.4, 1.9). NRT also reduced smoking at 3 months (59 RCTs, N =25,294, OR 1.99, 95% CI, 1.8–2.2).

NRT is considered safe for most patients, with a relatively low rate of discontinuation because of adverse events. Wu and colleagues analysed 70 placebo controlled-trials using NRT (N =28,343). Although there was inadequate information for pooling they found that the following adverse events were reported significantly more often in the NRT group: mouth and throat irritation, skin irritation, nausea/vomiting, coughing, hiccoughs,

dyspepsia, watering of eyes, headaches, heart palpations, sneezing, sleep disturbances and dream abnormalities, insomnia, rhinitis, vertigo, taste disturbances, and muscle aches (Wu et al., 2006). Hartmann-Boyce et al., (2018) reported that adverse events from using NRT were related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. Attempts to quantitatively analyse the incidence of various adverse effects were hindered by variation in reporting the nature, timing, and duration of symptoms. The odds ratio (OR) of chest pains or palpitations for any form of NRT relative to control was 1.88 (95% CI 1.37, 2.57, 15 trials, N =11,074); however, chest pains and palpitations were rare in both groups and serious adverse events were extremely rare. Warnings for NRT include a history of myocardial infarction within six weeks of starting, uncontrolled hypertension, severe cardiac dysrhythmia, unstable angina, and pregnancy (McRobbie et al., 2008; Polosa & Benowitz, 2011). Despite these warnings, NRT is reported to be safe in smokers with cardiovascular problems. Furthermore, there is little to no withdrawal discomfort when patients discontinue NRT (Polosa & Benowitz, 2011).

Bupropion Hydrochloride

Bupropion hydrochloride (bupropion) was initially developed and marketed as an antidepressant medication and was later found to be effective as a smoking cessation aid and marketed as *Zyban* or *Wellbutrin* (Cinciripini et al., 2013). There are three mechanisms suggested by which antidepressants may support smoking cessation. First, nicotine withdrawal may produce depressive symptoms or precipitate a major depressive episode, and antidepressants may relieve these symptoms. Secondly, nicotine may have antidepressant effects that maintain smoking and anti-depressant medication may substitute for this. Lastly, some antidepressants may act on specific neural pathways or receptors underlying cigarette addiction (Hughes, Stead, Hartmann-Boyce, Cahill, &

Lancaster, 2014). Whatever the specific mechanism, bupropion acts to reduce severity of withdrawal symptoms, and may also have other actions to help smokers quit (McRobbie et al., 2008). Among possible mechanisms of action, bupropion is a weak inhibitor of the neuronal uptake of norepinephrine and dopamine (Hurt et al., 1997). Further, the method of action of bupropion involves inhibition of neuronal reuptake of dopamine and a weak nicotinic acetylcholine receptor antagonist effect (less dopamine release) and this may play a role in the reported reduction in severity of nicotine cravings and withdrawal symptoms (Cinciripini et al., 2013; Polosa & Benowitz, 2011). Physicians recommend taking bupropion hydrochloride one week before quitting allowing accumulation of blood levels of bupropion hydrochloride and its active metabolites (Polosa & Benowitz, 2011).

Hughes and colleagues (2014) concluded that there was high quality evidence that when used as the sole pharmacotherapy, bupropion significantly increased smoking cessation (44 trials, N =13,728, RR 1.62, 95% CI 1.49, 1.76) (Hughes et al., 2014). Furthermore Cahill et al., (2014) showed an OR for bupropion versus placebo of 1.82 (95% CI 1.60, 2.06; 45 trials, N =12,097). A meta-analysis of 11 trials using bupropion reported an OR of 2.13 (95% CI 1.72, 2.64; N =5148) at three months and two trials reported an OR of 1.56 (95% CI 1.20, 2.21; N =548) at one-year when compared to placebo-control groups (Wu et al., 2006). There was insufficient evidence that adding bupropion (12 trials, N =3487, RR 1.2, 95% CI 0.9, 1.5) to NRT provides additional long-term benefits over NRT alone (Hughes et al., 2014). Anthenelli et al. (2016) in a double-blind study randomised adult smokers to receive either varenicline (*n*=1005), bupropion (*n*=1001), nicotine patch (*n*=1013), or placebo (*n*=1009) for 12-weeks. Of the total sample 4028 were from a non-psychiatric cohort and 4116 from a psychiatric cohort (met DSM-IV criteria for a psychiatric disorder). They

reported that those receiving bupropion achieved higher abstinence rates than those on placebo (OR 2.1, 95% CI 1.8, 2.5).

Common reported adverse side effects while taking bupropion include insomnia (30-40% of patients) and dry mouth (approximately 10%) (Hughes et al., 2014). Other adverse events reported significantly more in bupropion groups compared to placebo are gastrointestinal upset, and constipation (Wu et al., 2006). Rates of discontinuation because of adverse events range from 7% - 12% (Polosa & Benowitz, 2011). The prescribing information for bupropion also carries a 'black box' warning that antidepressants can increase the risk of suicidal ideation and behaviour in people with certain psychiatric disorders (Polosa & Benowitz, 2011). Hughes and colleagues' review did not detect a significant increase in the rate of serious adverse events amongst participants taking bupropion, although the 95% CI narrowly missed statistical significance (33 trials, N =9631, RR 1.30, 95% CI 1.00, 1.69). There is a risk of about 1 in 1000 of seizures associated with bupropion use. Bupropion has been associated with suicide risk, but whether this is causal is unclear (Hughes et al., 2014). Anthenelli et al. (2016) did not report any differences between groups for neuropsychiatric events and reported the most frequent adverse side effect in the bupropion group to be insomnia (12%). A serious adverse event meta-analysis of the bupropion studies demonstrated no increase in neuropsychiatric or cardiovascular events compared to placebo (Cahill et al., 2014).

Other antidepressants

A Cochrane review assessed the safety and efficacy of other antidepressant medications to aid smoking cessation (Hughes et al., 2014). These medications included doxepin; fluoxetine; imipramine; lazabemide; moclobemide; nortriptyline; paroxetine; S-Adenosyl-L-Methionine (SAMe); selegiline; sertraline; St. John's wort; tryptophan;

venlafaxine; and zimeledine. There was moderate quality evidence, limited by a small number of trials and participants, that nortriptyline significantly increased cessation when used as the sole pharmacotherapy (six trials, N =975, RR 2.03, 95% CI 1.48, 2.78). There was insufficient evidence that adding nortriptyline (4 trials, N =1644, RR 1.21, 95% CI 0.94, 1.55) to NRT provides additional long-term benefits over NRT alone. Cahill and colleagues (2014) reviewed 10 studies (N =2,194) that investigated the efficacy of nortriptyline. They found that nortriptyline increased the chance of quitting (RR 2.03; 95% CI 1.48, 2.78). Nortriptyline has the potential for side effects, including dry mouth, constipation, nausea, and sedation, and it can be dangerous in overdose (Hughes et al., 2014). but none have been seen in the few trials completed.

A Cochrane review by Hughes and colleagues (2014) reported that there was no evidence of a significant effect for selective serotonin reuptake inhibitors (SSRIs) on their own for smoking cessation when compared to controls (RR 0.93, 95% CI 0.71, 1.22, N = 1594; 2 trials fluoxetine, 1 paroxetine, 1 sertraline) or in conjunction with NRT (3 trials of fluoxetine, N =466, RR 0.70, 95% CI 0.64, 1.82). Significant differences were also not reported for monomine oxidase inhibitors (RR 1.29, 95% CI 0.93, 1.79, N =827; 1 trial moclobemide, 5 trials selegiline), the atypical antidepressant venlafaxine (1 trial, N =147, RR 1.22, 95% CI 0.64, 2.32), the herbal therapy St John's wort (hypericum; 2 trials, N =261, RR 0.81, 95% CI 0.26, 2.53), or the dietary supplement SAMe (1 trial, N =120, RR 0.70, 95% CI 0.24, 2.07) (Hughes et al., 2014).

Varenicline tartrate

Varenicline tartrate (varenicline) marketed as *Champix* or *Chantix*, was launched in 2006 (Polosa & Benowitz, 2011) after it was approved for marketing as a pharmacological aid for smoking cessation (Ware et al., 2013). Varenicline is a partial agonist selective for

$\alpha_4\beta_2$ nAChRs (Polosa & Benowitz, 2011; Ware et al., 2013) with dual effects; these are partial stimulation of nAChRs without creating the full effect of nicotine, and blocking the nAChRs, which prevents nicotine reaching the receptors (Polosa & Benowitz, 2011) (i.e., it reduces the severity of withdrawal and simultaneously reduces the rewarding effects of nicotine). Varenicline inhibits the surges of dopamine release that are believed to be responsible for the reinforcement and reward associated with tobacco use (Prochaska & Hilton, 2012). These effects provide relief from craving and withdrawal symptoms (Polosa & Benowitz, 2011).

Two RCTs reported that after one-year, healthy smokers had approximately 2.5 greater odds of quitting with varenicline compared to placebo, and 1.7 times greater odds compared to bupropion (Gonzales et al., 2006; Jorenby et al., 2006). Cahill, Lindson-Hawley, Thomas, Fanshawe, & Lancaster (2016) reviewed 39 trials that investigated the use of varenicline. The RR for abstinence at six months or longer for varenicline compared to placebo was 2.24 (95% CI 2.06, 2.43, 27 trials, N =12,625). The pooled RR for varenicline compared to bupropion at six months was 1.39 (95% CI 1.25 to 1.54, 5 trials; N =5877) and the RR was 1.25 (95% CI 1.14 to 1.37, 8 trials, N =6264) for varenicline versus NRT (Cahill et al., 2016). A Cochrane review reported an OR of 2.88 (95% CI 2.40 to 3.47, 24 trials; N = 4,102) for varenicline compared to placebo (quit rate 28% versus 12%) at a follow-up of six-months (Cahill et al., 2014). Varenicline was also shown to be superior to both NRT (OR 1.57, 95% CI 1.29 to 1.91) and to bupropion (OR 1.59, 95% CI 1.29 to 1.96) (Cahill et al., 2014). Wu et al. (2006) pooled four trials to compare the effect of varenicline versus placebo and increased odds of quitting using varenicline were reported at one-year (OR 2.96, 95% CI 2.12, 4.12) and at three months (OR 3.75, 95% CI 2.12, 4.12). Pooled results from four trials comparing bupropion to varenicline showed significantly lower quitting with bupropion than

with varenicline (N =1810, RR 0.68, 95% CI 0.56 to 0.83) (Hughes et al., 2014). Anthenelli et al. (2016) reported that varenicline-treated participants achieved higher abstinence rates than those on placebo (OR 3.61, 95% CI 3·07, 4.24), nicotine patch (OR 1.68, 95% CI 1.46, 1.93), and bupropion (OR 1.75, 95% CI 1.52, 2.01).

McKee et al. (2011) conducted a meta-analysis of 17 double-blind RCTs to examine the sex differences in the efficacy of varenicline for smoking cessation (*n*=6710, 34% females). For those who were randomised to placebo, women were more than 30% less likely to quit when compared to men (point-prevalence OR 1.3, 95% CI 1.1, 1.6 and continuous abstinence OR 1.4, 95% CI 1.0, 1.8). For those who used varenicline, similar rates of abstinence for men and women were reported at six months post quit day. However, the effect size for varenicline was significantly larger for women than for men when sex was included as a moderator in the analysis. Varenicline was 46%, 34%, and 31% more effective for women in point-prevalence at 12 weeks, continuous abstinence at 12, and 24 weeks respectively. No differences in abstinence rates were found between men and women at the one year follow-up. Therefore, the meta-analysis concluded that varenicline was more effective for women for short and intermediate outcomes, and it may have potential in supporting to reduce the sex disparity in rates of smoking cessation.

The most common side effects reported from varenicline are nausea, insomnia, gastrointestinal upsets, and headache (Polosa & Benowitz, 2011; Wu et al., 2006). Varenicline has been associated with an increased risk of sleep disorders, abnormal dreams, depression, and fatigue (Thomas, Martin, Knipe, Higgins, & Gunnell, 2015). Anthenelli and colleagues reported that the overall incidence of neuropsychiatric adverse events was similar across the four treatment groups (varenicline, bupropion, nicotine patch, and

placebo), ranging from 3.7% to 4.5% (Anthenelli et al., 2016). The most common adverse event in the varenicline was nausea (25%) (Anthenelli et al., 2016).

Unlike other pharmacotherapies, varenicline is associated with gradually increasing cessation rates over 12 weeks of treatment, presumably due to the antagonism of nicotine resulting in reduced satisfaction from smoking (Polosa & Benowitz, 2011). A meta-analysis of 14 varenicline RCTs found no difference between varenicline and placebo for the outcome of serious adverse events; however, there was one incident of suicidal ideation in a varenicline group that was considered to be varenicline-related (Cahill et al., 2014). Thomas et al. (2015) reported through a meta-analysis (39 RCTs, N =10,761) that participants prescribed varenicline compared to placebo had no increased risk of suicide or attempted suicide, suicidal ideation, depression or death, however, varenicline was associated with an increased risk of sleep disorders (OR 1.63, 95% CI 1.29 to 2.07), insomnia (OR 1.56, 95% CI 1.36 to 1.78), abnormal dreams (OR 2.38, 95% CI 2.05 to 2.77), and fatigue (OR 1.28, 95% CI 1.06 to 1.55) but a reduced risk of anxiety (OR 0.75, 95% CI 0.61 to 0.93). Singh and colleagues conducted a meta-analysis (14 RCTs, N=8216) of the safety of varenicline in regards to cardiovascular events and concluded that the varenicline increased the risk of serious adverse events by 72% (OR=1.72, 95% CI 1.09, 2.71) (Singh, Loke, Spangler, & Furberg, 2011). Prochaska and Hilton (2012) conducted a meta-analysis of all published RCT of varenicline and found that there was no significant differences in serious adverse cardiovascular events between placebo and varenicline within 30 days of discontinuation. Thus, there remain unresolved questions about the safety of varenicline, with the majority of research reporting no increase in adverse effects. Further research is needed to determine whether varenicline has serious long term adverse effects.

Cytisine

Cytisine was developed as a treatment for cigarette dependence in Bulgaria in the 1960's and is a partial agonist that binds to the nicotinic acetylcholine receptor (Cahill et al., 2016; Walker et al., 2014). There is also heightened interest in cytisine in New Zealand, where it is found in the seeds of the native Kowhai tree, widely used in traditional Māori healing (Cahill et al., 2016). Cahill and colleagues pooled the results from two trials of cytisine (N =937) and found that more participants taking cytisine quit smoking when compared with placebo (RR= 3.98, 95% CI 2.01, 7.87) (Cahill et al., 2016). Furthermore, Walker and colleagues (2014) compared cytisine with NRT in 1310 people using an open-label, noninferiority trial in NZ. At one month abstinence from smoking was reported for 40% who received cytisine and 21% who received NRT (RR 1.3, 95% CI 1.1, 1.5). They also found that more people quit using cytisine at six months (22% versus 15%; RR 1.4, 95% CI 1.1, 1.8) (Walker et al., 2014). In pre-specified analyses conducted according to sex Walker and colleagues reported significantly higher one-month continuous abstinence in women when compared to men (RR 1.55 (95% CI 1.26, 1.90) versus RR 1.05 (95% CI 0.84, 1.30), *p*=0.011). The cytisine trials analysed by Cahill et al., (2016) did not identify more adverse events in the intervention group when compared to controls, but self-reported adverse events over 6 months occurred more frequently in the cytisine group (288 events among 204 participants) than in the group receiving NRT (174 events among 134 participants). Adverse events were primarily nausea, vomiting and sleep disorders (Walker et al., 2014).

Combined pharmacotherapy and behavioural interventions

Many clinical practice guidelines recommend that healthcare providers should offer people who want to quit smoking both behavioural support interventions and pharmacotherapy on the basis that they will have an additive, combined effect (Stead,

Koilpillai, & Lancaster, 2015). Stead and colleagues (2016) reviewed trials that combined pharmacotherapy (including NRT, varenicline, bupropion, cytisine, or nortriptyline) with behavioural support (tailored materials, brief advice, in person or telephone counselling) and compared the outcomes against a control group that received either usual care or a brief cessation component (i.e., advice to quit but no other behavioural support or medication common to the intervention). Based on 52 studies there was evidence for a benefit of combined pharmacotherapy and behavioural treatment compared to usual care, brief advice, or less intensive behavioural support (RR 1.83, 95% CI 1.68, 1.98; N =19,488). The pooled estimates for the efficacy of 43 trials that recruited participant's in healthcare settings (RR 1.97, 95% CI 1.79, 2.18; N =13863) was higher than the eight trials recruiting from community based recruitment (RR 1.53, 95% CI 1.33, 1.76; N =4906) (Stead, Koilpillai, Fanshawe, & Lancaster, 2016).

Stead and colleagues (2015) reviewed 47 studies (N >18,000) to evaluate the effect of increasing the intensity of behavioural support for people using smoking cessation medication compared to either treatment alone. All but four studies provided more than four sessions of support. Most trials used NRT. There was evidence of a small but statistically significant benefit for intensive support combined with pharmacotherapy (RR 1.2, 95% CI 1.1, 1.2), with no statistical difference between NRT and bupropion. No significant effects for nortriptyline (two trials) and varenicline (one trial) combined with behavioural support were shown. This suggests that increasing the intensity of behavioural support with the aid of pharmacotherapy for people trying to make a quit attempt typically leads to a small increase in the proportion that are abstinent at 12 months (Stead, Koilpillai, & Lancaster, 2015).

Electronic Cigarettes

Electronic cigarettes (e-cigarettes) are battery-powered electronic devices that heat a solution of humectants, nicotine (in most cases), and flavourings (in many cases), to deliver an aerosol that the user inhales (Kalkhoran & Glantz, 2016) and no tobacco is necessary for it to operate. Most e-cigarette users report using them in an attempt to stop smoking, with fewer than 1% of never-smokers using them regularly (Brose et al., 2015).

A meta-analysis reported on 15 cohort studies (N =24,496), three cross sectional studies (N =15,625) and two clinical trials (N =757) assessing smoking cessation in e-cigarette users compared to control groups and reported 28% lower odds (OR=0.7, 95% CI 0.6, 0.9) of smoking cessation among those who used or had used e-cigarettes (Kalkhoran & Glantz, 2016). Bullen and colleagues (2016) conducted a Cochrane review to investigate the safety and efficacy of using e-cigarettes to help people achieve smoking abstinence. They reviewed three RCTS, two of which compared nicotine e-cigarettes to non-nicotine e-cigarettes (N =662). The results showed that participants using a nicotine e-cigarettes were more likely to have abstained from smoking for at least six months compared with participants using placebo e-cigarettes (RR 2.3, 95% CI 1.1, 5.0; placebo 4% versus e-cigarette 9%). One study compared e-cigarettes to NRT (nicotine patch) found no significant difference in six-month abstinence rates, but the confidence intervals do not rule out a clinically important difference (RR 1.26, 95% CI 0.68, 2.34; N = 584) (Bullen et al., 2013). Further RCTs that compare e-cigarettes to other forms of smoking cessation will determine the safety and efficacy of these devices as a smoking cessation intervention long-term (Rahman, Hann, Wilson, Mnatzaganian, & Worrall-Carter, 2015; Hartmann-Boyce et al., 2016).

Of the 24 included studies involving e-cigarettes (three RCTs and 21 cohort studies) in the Cochrane review, none reported serious adverse events considered to be related to the use of e-cigarettes (follow-up up to two years). The most frequently reported adverse side effects were mouth and throat irritation, of which most disappeared over time (Bullen et al., 2016).

Costs of smoking cessation interventions

Due to the differences in effect sizes based on the current body of literature it is difficult to obtain reliable estimates of current cost effectiveness for current smoking cessation interventions. However, the approximate cost of smoking cessation interventions deserves mention. Based on calculations from the 2012 WHO study of 126 countries the approximate cost per person attempting to quit of the following pharmacotherapies are estimated as: NRT = NZ$2.50 to $12.40/day, varenicline = NZ$7.20/day, bupropion = NZ$3.40-$7.90/day, cytisine = $1.00 to $1.50/day, and nortriptyline $1.40/day (World Health Organization, 2013). Cytisine and nortriptyline are considerably cheaper in comparison to other smoking cessation options. Therefore there may be potential for these treatments to be used more in countries with lower average incomes and where smoking cessation programmes are not supported by insurance plans or by a national health service (Cahill et al., 2016). Furthermore, in many regions, it may be considerably cheaper to continue smoking than to embark upon a course of pharmacotherapy for smoking cessation. In 2011 in China a packet of cigarette cost between USD $0.15 and USD $0.73, compared with a course of NRT (USD $230), bupropion (USD $123), or varenicline (USD $327). Similarly, a pack of 20 cigarettes in India costs around USD $1.10, compared with USD $150 for a course of NRT, USD $100 for bupropion and USD $200 for varenicline. Cytisine is

currently available in Poland for the equivalent of USD $15 for a course of treatment, and in Russia for the equivalent of USD $6 as an over-the-counter medication.

1.8 Differences in Smoking Cessation Outcomes

Rates of smoking cessation are not linear across all individuals, with significant differences observed across gender and between people with and without mental illness. These differences are discussed below.

Sex

As mentioned there are large differences in smoking prevalence among males and females across countries, with men generally having a higher prevalence of smoking than women (McCartney et al., 2011). However, clinical trials report that women are less likely to successfully quit smoking than men, with no difference reported in the number of quit attempts (Bohadana, Nilsson, Rasmussen, & Martinet, 2003; Collins et al., 2004; Smith et al., 2015). A double-blind RCT examined whether the male *versus* female smoking cessation outcome was influenced by baseline smoking rates when participants (196 men and 204 women) were randomised to receive different combinations of NRT therapy. Men had significantly higher FTCD scores at baseline (6.4 versus 6.0, p=0.02) and women had higher behavioural dependence (Glover–Nilsson Smoking Behavioural Questionnaire 1.27 versus 1.06, p<0.001). They reported significant differences in continuous abstinence rates (p<0.05) with men more likely to quit than women regardless of treatment group and quit rates of 42.3% vs. 30.9% at 12 weeks, 30.1% vs. 17.6% at 6 months, and 23.0% vs. 10.8% at 12 months (Bohadana et al., 2003). This observed difference was supported by Collins et al. (2004) who randomised 314 women and 241 men to receive 10 weeks of bupropion or a placebo control. They reported an end of treatment quit rate (10 weeks post-

randomization) of 51% in men versus 40% in woman (chi squared = 6.56, *p*=0.01), and a six month post-randomization quit rate of 31.5% in men and 22.3% in women (chi squared = 12.79, *p*=0.0004). Smith and colleagues analysed data from the International Tobacco Control Four Country Survey conducted in the UK, USA, Canada, and Australia to examine gender differences in smoking cessation among 8,904 participants. Among those who made a quit attempt, women had 31% lower odds of successfully quitting smoking than men at a 30-day follow-up (OR = 0.7, 95% CI 0.5, 0.9), despite no significant gender difference in the likelihood of making a quit attempt (Smith et al., 2015). The NZ Ministry of Health reported that NZ males were more likely than females (62% vs 54%) to have quit for at least a week, after adjusting for age differences (Ministry of Health, 2014).

Possible explanations for the sex difference in smoking cessation outcomes include women's greater concern about weight gain, possibly greater difficulty with negative mood associated with quitting, and greater need for social support during a quit attempt (Bohadana et al., 2003). Women are more likely to report the use of smoking cessation medication than men (Smith et al., 2015), therefore the difference in cessation outcomes favouring males is clinically meaningful in regards to how we continue to develop smoking cessation aids, since it clearly suggests that smoking cessation programmes need to reflect these known sex differences.

Mental Illness

Most smokers, both with and without mental illness, report that they want to quit but continue to smoke as it provides them with perceived mental health benefits (Taylor et al., 2014). In contrast, individuals with mental illness also often report a fear that quitting will increase their symptoms; fortunately, most people do not experience an increase in psychiatric symptoms specific to their illness when they stop smoking (McRobbie et al.,

2008). Persons with mental illness may encounter greater difficulty with tobacco cessation (Addington, El-Guebaly, Campbell, Hodgins, & Addington, 1998; Lasser et al., 2000; Ziedonis & George, 1997) and more intensive smoking cessation interventions appear to be beneficial for this population, including multi-session support and medication (McRobbie et al., 2008). Further research to identify interventions to address mechanisms specific to people with mental illness should be a priority for tobacco control policy (Lê Cook et al., 2014). Despite the higher use of cigarettes and the potential challenge of quitting smoking for individuals with a mental illness, their motivation to quit is high and comparable with the general population (Acton, Prochaska, Kaplan, Small, & Hall, 2001; Nahvi, Richter, Li, Modali, & Arnsten, 2006; Prochaska et al., 2017; Prochaska, Fletcher, Hall, & Hall, 2006).

1.9 Mood and Tobacco Smoking

Negative affect, referring to mood states marked by feeling angry, frustrated, irritable, sad, depressed, and distressed, is widely believed to be a motive for smoking and may explain some of the aforementioned differences in smoking cessation in those with mental illness; however, the relationship between the two is complex (Piasecki, 2006). Positive affect refers to mood states of feeling happy, joyful, pleased, and of enjoyment (Diener & Emmons, 1985). Greater depressive symptoms and low positive affect prior to a quit attempt, and negative changes in depressive symptoms and positive affect following quitting are associated with poor smoking cessation outcomes (Kahler et al., 2015). Nicotine dependence is a complex process, developed in part from the formation of associative memories of both positive (e.g., after a good meal) and negative (e.g., feeling stressed) affective states (Brewer et al., 2011). Thus, cues that are judged positive or negative can induce positive or negative affective states and trigger craving to smoke.

Smokers learn to connect negative affect relief to smoking through repeated experience. Negative affect becomes a conditioned cue to smoke, understood cognitively as an expectancy (e.g., “cigarettes help me deal with anxiety and worry”) (Weinberger & McKee, 2012) and experiential confirmation of the expectancy functions as a (negative) reinforcement for smoking. Therefore, smokers commonly report a desire for relief from negative affect as a chief reason for smoking, and often attribute relapses to acute negative affect (Piasecki, 2006). Many studies have demonstrated a positive association between tobacco use and depressive disorders (Edwards, Maes, Pedersen, & Kendler, 2011), suggesting that the risk of major depression increases with increasing levels of nicotine dependence, or vice versa (Edwards et al., 2011). Negative affect or depressed mood is also considered a hallmark of nicotine withdrawal, and increases in negative affect after quitting appear in both adults and adolescents (Van Zundert, Ferguson, et al., 2012).

1.10 Alcohol and Tobacco Smoking

Nicotine and alcohol are two addictive drugs that have significant impact on public health; they are both prevalent and lead to significant health risks (Berg, Piper, Smith, Fiore, & Jorenby, 2015). Furthermore, alcohol and nicotine abuse are the largest type of polysubstance abuse reported (Van Skike et al., 2016). Approximately 40% of NZ smokers have drinking patterns that are considered potentially hazardous (alcohol consumption that carries a risk of harming the drinker's physical or mental health), compared to 14% of non-smokers (Ministry of Health, 2014). Estimates based on clinical samples of adults with alcohol use disorders have revealed that 50-95% are current smokers (Van Skike et al., 2016; Van Zundert, Kuntsche, & Engels, 2012). Analysis of data from 1376 respondents of the NZ Health Survey revealed that High Alcohol Use Disorders Identification Test (AUDIT) scores (8

or more) are associated with smoking, especially in people that are younger, male, and Māori (Wilson, Weerasekera, Kahler, Borland, & Edwards, 2012). Relative to non-smokers, tobacco smokers are more likely to binge drink, consume two times more alcohol, and are 10-14 times more likely to have an alcohol use disorder (Van Skike et al., 2016). Higher levels of alcohol intake are associated with higher levels of smoking and are also associated with lower rates of quitting (Wilson et al., 2012). Lapse and relapse are strongly associated with alcohol use, as smokers report a higher craving to smoke and more enjoyment of their cigarette when drinking compared to not drinking (Van Zundert, Kuntsche, et al., 2012).

Evidence suggests that alcohol consumption decreases after a smoking quit attempt. Karlamangla, Zhou, Reuben, Greendale, and Moore (2006) found that smoking cessation was associated with a lower probability of heavy drinking (RR= 3.4, 95% CI 2.8, 4.0) compared to no change in smoking habits in US adults. Berg et al. (2015) followed 1301 participants daily for two weeks prior and after a quit attempt. They reported that participants significantly decreased their alcohol intake post-quit, with mean pre-quit alcohol use at 0.73 (Standard Deviation (SD) = 0.9, range 0-4.3) drinks per day; excluding the 482 non-drinking participants the average was 1.16 (SD =0.9, range 0.1-4.29) drinks per day. The average post-quit alcohol consumption was 0.6 (SD =0.88, range 0-6.6) drinks per day; excluding those who did not drink at all, average alcohol use post-quit was 0.95 (SD =0.94, range 0.1-6.6) drinks per day. For the whole sample there was a significant reduction in drinks per day at two weeks post-quit when compared to baseline ($t(1300) = 6.98$, $p<0.001$) and for the sample that excluded non-drinkers ($t(697) = 6.87$, $p<0.001$).

The risk of mortality increases with combined use of tobacco and alcohol (Toll et al., 2015), therefore it is important to consider combining the effort to reduce both alcohol

intake and smoking (Van Skike et al., 2016). Previous research has found that adding alcohol interventions to smoking cessation treatment improved quit rates among hazardous drinkers (Kahler et al., 2015). Wilson et al. (2012) suggested that the NZ Government could consider potential benefits for advancing tobacco control via cost effective and evidence-based interventions that reduce alcohol related harm, and consider additional funding support for health services to allow them to address heavy drinking and smoking cessation together.

As mentioned above, on the balance of evidence, varenicline appears to currently be the most efficacious treatment for smoking cessation. There is also evidence to support the use of varenicline to support decreasing alcohol consumption. Mitchell and colleagues (2012) reported a double-blind study that randomized 99 participants to receive varenicline or placebo for 12 weeks. Participants were eligible if they smoked 10 or more cigarettes and consumed ≥7 for women or ≥14 for men alcoholic drinks per week. They reported significant difference in cigarettes per week for those in the varenicline group versus the placebo group from weeks 3 to 11 ($\chi^2 = 182.23$, $p < 0.001$). There was also a significant difference in drinks per week between completers in the varenicline and placebo groups from weeks 3 to 11 ($\chi^2 = 35.32$, $p < 0.001$) (Mitchell, Teague, Kayser, Bartlett, & Fields, 2012). Litten et al. (2014) in a double-blind study randomised 200 adults meeting criteria for alcohol dependence to receive either varenicline or placebo and a computerized behavioural intervention for 13 weeks. The varenicline group had significantly lower weekly percent of heavy drinking days (37.9 versus 48.4, p=0.03, Cohen's d=0.31), drinks per day (4.4 versus 5.3, p=0.03, Cohen's d=0.29), drinks per drinking day (5.8 versus 6.8, p=0.03, Cohen's d=0.26), and alcohol craving (8.2 versus 9.0, p=0.01, Cohen's d=0.33) when compared to placebo. The varenicline group

also reported smoking fewer cigarettes per day compared to placebo (7.4 versus 11.7, *p*=0.002, Cohen's *d*=0.73) (Litten et al., 2013).

Hurt and colleagues investigated the use of varenicline in adults, who smoked an average of 10 or more cigarettes per day, and had alcohol dependence or abuse as assessed by the Mini-International Neuropsychiatric Interview and the physician investigator, were currently drinking, and interested in quitting smoking. Participants were randomly assigned to varenicline (*n*=16) or placebo (*n*=17) for 12-weeks, with follow-up at six months. The 7-day point prevalence smoking abstinence rate at the end of treatment (12 weeks) was significantly higher in the varenicline than the placebo group (*n*=7 (44%) vs *n*=1 (6%); *p* =0.01). Prolonged smoking abstinence was also significantly higher with varenicline than placebo at end of treatment (*n*=6 (38%) vs *n*=1 (6%); *p* =0.03). At the end of study (24 weeks), the 7-day point prevalence smoking abstinence rate (*n*=5 [31%] vs 0%; *p* =0.02) and prolonged smoking abstinence (*n*=4 (25%) vs 0%; *p*=0.04) were both significantly higher with varenicline than with placebo. Over the first 16 days after the target quit date, nicotine craving was significantly lower in those receiving varenicline than placebo (average difference, −1.79; 95% CI 2.59, 0.99; *p*< .001). At the end of treatment, average drinks per drinking day was significantly lower with varenicline than placebo (mean (SD), 5.7 (3.9) vs 9.0 (5.3); treatment effect estimate, −2.8; 90% CI −6.6, −1.0). At the end of study, the average drinks per drinking day was also significantly lower in the varenicline group than the placebo group (mean (SD), 5.0 (3.8) vs 7.6 (4.3); treatment effect estimate, −2.3; 90% CI −5.0, −0.4) (Hurt et al., 2018).

Summary

Cigarette smoking is the practice of burning tobacco contained in a cigarette and inhaling the smoke. Approximately 20% of the global population (>15 years) and 18% of the NZ population are current smokers. Overall the prevalence of cigarette smoking is decreasing, but not equally across all ethnic groups, genders, and nationalities. Smoking is associated with an array of adverse health effects, but individuals continue to smoke because nicotine contained in tobacco smoke is highly addictive and causes an adverse withdrawal syndrome upon cessation.

Current smoking cessation interventions include counselling, NRT, and pharmacotherapy, singly and in combination, but many smokers still do not quit with such treatments. Furthermore, the cost per person per day of these treatments varies widely among countries and health systems, and the ratio of the costs of these different treatments, with their different levels of efficacy, to the benefits of quitting are hard to typify. In NZ, Quitline provides free telephone counselling and supplies a prescription for two months of heavily subsidised NRT. NRT doubles an individual's chance of staying smoke free long-term. Other pharmacotherapies (varenicline and bupropion), achieve quitting and abstinence rates equal to or exceeding NRT but many smokers (>70%) do not successfully quit even with such treatments. Pharmacotherapy can be expensive, requires medical prescription and supervision, and may have problematic side effects. Alternative treatments that are safe, effective, relatively inexpensive, and readily available are needed. Broad-spectrum micronutrients (minerals and vitamins) supplements are one such possible alternative, and mineral and vitamin supplements for the treatment of psychiatric symptoms and addictions are discussed in Chapter 2.

Chapter 2: Broad-spectrum Micronutrients

Researchers, public health authorities, and consumers will continue to seek treatments for smoking cessation because of its high prevalence and the adverse health effects it causes. This chapter provides an overview of one such alternative, namely broad-spectrum micronutrient supplementation, and why it may be applicable to this population. Research on the use of micronutrients in the treatment of substance dependence has existed for half a century, and investigations in to the use of micronutrients to relieve psychological symptoms has grown substantially in the past decade and has now been demonstrated in a number of trials. This chapter will review the literature on the use of micronutrients as a treatment of substance dependence, and to relieve associated psychological symptoms in adults. This will be followed by a discussion of potential mechanisms of action for the therapeutic effect of micronutrients on mental health.

2.1 Micronutrients

Micronutrients are conventionally considered to include vitamins, minerals, amino acids, and antioxidants and have a primary function in human metabolism, the maintenance of health, and the prevention of disease (Ames, 1998). Adequate intakes of micronutrients are essential in maintaining the body's homeostasis, and its physiological functioning for normal growth and development. At least 30 micronutrients are essential to the body's functioning and cannot be synthesised by the body, making intake via dietary sources critical (Shergill-Bonner, 2013).

Although the human brain only accounts for 2 to 2.7% of body weight, it requires 25% of the body's primary energy supply (glucose) and 19% of the blood supply at rest, and

this increases by 50% and 51% respectively in response to cerebral activity (Haller, 2005). The brain is dependent on a stable supply of both glucose and oxygen for the maintenance of cellular integrity and information processing. In addition to the high requirements of glucose and oxygen, the brain also requires a range of micronutrients for metabolism and chemical transmission (Sinn & Howe, 2008). Micronutrients are involved in many aspects of brain function, from the global functions such as energy metabolism, to more specific functions, for example being the co-enzymes for neurotransmitter functioning (Haller, 2005). Every neurotransmitter goes through many metabolic steps to ensure synthesis, reuptake, and breakdown, each of these steps requires an enzyme - a biological catalyst – and enzyme function and synthesis are dependent on multiple co-enzymes. Co-enzymes include a variety of vitamins and minerals. Availability of the co-enzymes may limit the rate at which neurotransmitter synthesis and other critical brain metabolism is carried out (Kennedy et al., 2010).

Unfortunately, a significant proportion of the world's population suffers from micronutrient deficiencies, particularly in developing societies where low dietary intake of micronutrients is common among most of the population (Schlebusch et al., 2000). Alleviating deficiencies through diet or supplementation is likely to lead to major improvements in general health and an increase in longevity, at a low cost (Ames, 1998).

Supplementation is a term used to describe the ingestion of micronutrients usually in the form of pills, capsules, or syrups, independently of normal food consumption, and has the advantage of being able to supply an optimal amount of specific micronutrients to the body (Allen, De Benoist, Dary, & Hurrell, 2006). Recommended daily intakes (RDI) of micronutrients in the normal diet and upper limits (UL) have been formulated from observational studies in healthy populations and laboratory estimates of tissue and blood

status to assist with determining the optimal ingestion of extra nutrients (Shergill-Bonner, 2013). The RDI is defined by the Australian Government (2005) as *"the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97-98 percent) the healthy individuals in a particular life stage and gender group"* and the UL is *"the highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population"*. Variations in recommendations may occur due to different methods used to assess requirements, different age, sex, the presence of chronic disease, pregnancy, or specific dietary conditions (Shergill-Bonner, 2013). However, as intake increases above the UL the potential risk of adverse effects increases (Australian Government, 2005).

Recent research has demonstrated the efficacy of micronutrient supplementation above the RDI but below the UL as beneficial in the treatment of various psychological symptoms (Kimball, Mirhosseini, & Rucklidge, 2018; Lothian, Blampied, & Rucklidge, 2016; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2017; Sole, Rucklidge, & Blampied, 2017). The remainder of this chapter will review research investigating the use micronutrient treatments in adults for substance dependence and psychological symptoms that are often associated with cigarette smoking. It will then consider the potential physiological mechanisms that support a micronutrient treatment approach in the treatment of psychological symptoms.

2.2 Micronutrients and substance dependence

The lifestyle of addiction often corresponds with diet neglect and the tendency to consume foods high in sugars, and low in proteins, vitamins, and minerals. Numerous studies have reported on the adverse effects of alcohol, illicit drug use, and cigarette

smoking on nutritional status (Albert, Butters, Rogers, Pressman, & Geller, 1982; Alkerwi et al., 2017; Cowan & Devine, 2008; Elnimr, Hashem, & Assar, 1996; Islam, Hossain, & Ahsan, 2001; Lumeng & Li, 1974; Prayurahong, Migasena, Pongpaew, Vudhivai, & Busapathumrong, 1991; van den Berg, van der Gaag, & Hendriks, 2002). Over half a century of research has provided a strong biological rationale for the use of nutrients in the treatment of substance dependence. The literature includes numerous case reports and pilot studies (Beasley et al., 1991; Libby & Stone, 1978; Mathews-Larson & Parker, 1987; Scher, Rice, Kim, DiCamelli, & O'Connor, 1976; Smith, 1974), alongside a group of controlled studies, suggesting that high dose micronutrient interventions can improve abstinence rates and withdrawal symptoms. This section includes a summary of the trials in the investigation of a micronutrient treatment on withdrawal.

Free and Sanders (1978) conducted a six-month pilot study investigating the use of high dose ascorbic acid (vitamin C) in the treatment of narcotic drug withdrawal symptoms in adults. At the point of intake, participants were able to choose to be in one of three groups; 186 participants received medications for symptom relief, 30 received high dose ascorbic acid alone, and 11 received a combination of ascorbic acid and medications. At the end of the six-month protocol, results showed that the ascorbic acid procedure was more effective than the medications in alleviating narcotic withdrawal symptoms, and that the combination of both showed the greatest reduction in symptoms. With an average of 2 symptoms reported in the ascorbic acid group (6.5 at baseline), 1 in the combination group, (9 at baseline), and 6.5 in the symptomatic medication group (6.5 at baseline). The results should be interpreted with caution as no qualitative analyses were provided.

Guenther (1983) randomised 50 male adult participants to receive 63 days of conventional therapy for alcohol dependence and 55 to a combination therapy (conventional treatment + diet modifications, vitamin and mineral supplements, and nutrition education classes). At the six-month discharge the groups did not differ in measures of anxiety, depression, or general health (p>0.05). However, 38% of the group receiving conventional therapy remained abstinent, compared to 81% of the group receiving nutritional and conventional therapy combined, this difference was statistically significant (z=4.28, p<0.001).

Replogle and Eicke (1989) investigated the use of micronutrients to reduce depression and anxiety during alcohol detox. They randomised 44 male participants, who had been voluntarily admitted to a residential alcohol program to receive 21 days of micronutrients (vitamin C, niacin, vitamin B6, vitamin E) or placebo capsules. There were no group differences in measures of depression. However, the micronutrient group showed significant reductions in anxiety when compared to the placebo group at the end of the 21-day detox. Participants in the micronutrient group significantly (p<0.05) decreased by 11 and 3 points in the State Anxiety Index and State Trait Index respectively, versus no decrease and an increase of 1 in the placebo group.

In the 1980s, Blum and colleagues (1988) conducted the first known double-blind RCT, using nutritional formulas containing amino acids, minerals, and vitamins (they referred to these as “neuronutrients” or “neuroadaptagens”) to treat cocaine addiction (Blum et al., 1988). They randomised participants to three groups: Tropamine (n=24; five amino acids, 12 vitamins and minerals), SAAVE (n=14; five amino acids and vitamin B6), or a control (n=16; no supplement), during a 30-day inpatient cocaine detox. They reported a significant differences (p =0.014) in both drop-out against medical advice in participants

randomised to the Tropamine (1/24, 4.2%) formula compared to SAAVE (4/14, 28.6%) and control (6/16, 37.5%) at the 30-day follow-up (Blum et al., 1988). They also reported that the Tropamine group scored the lowest on the Drug Hunger Index at each follow-up when compared to SAAVE and control, with significant differences reported during the first 10 days of treatment for Tropamine and SAAVE compared to control (Student-Newman-Kuels multiple comparison statistics p=0.015 and p=0.007). Treatment staff and physicians also qualitatively reported that the patients randomised to Tropamine and SAAVE displayed decreases in agitation, outside focus, and drug hunger/craving after as early as five days on the treatment. The beneficial effects of SAAVE and Tropamine was supported in research by Brown, Blum, and Trachtenberg (1990) who demonstrated that 10-weeks of SAAVE and Tropamine significantly reduced relapse rates and enhanced recovery in 30 driving-under-the-influence offenders with either alcohol or cocaine related problems. Follow-up on both SAAVE and Tropamine groups after 10 months revealed a 73% and 53% overall recovery rate, respectively.

Another study administered Ascorbic acid (vitamin C) and vitamin E combined with conventional medication to 40 participants with heroin addiction and compared their withdrawal syndrome to 30 participants who received conventional medication-alone. They found that more participants in the control group (57%) expressed a withdrawal syndrome classified as major compared to the vitamin-treated group (17%, chi-squared 15.5, p<0.005) (Evangelou et al., 2000).

2.3 Cigarette Smoking and Micronutrients

The adverse effects of smoking on nutritional status are well-documented in the smoking cessation literature (Alkerwi et al., 2017), however there is limited research that

has investigated the manipulation of diet or the use of micronutrients to support smoking cessation. The remainder of this section reviews studies that have reported on the beneficial effects of micronutrients to reduce withdrawal symptoms and promote cessation from smoking.

Tryptophan, an amino acid, may have antidepressant properties because it increases levels of serotonin (Hughes, Stead, & Lancaster, 2007). Bowen, Spring, and Fox (1991) hypothesized that tryptophan's serotonin enhancing action, in conjunction with high carbohydrate diet might relieve the negative effects of nicotine withdrawal. Participants (*n*=16) received tryptophan and were instructed to follow a high carbohydrate diet + low protein diet, and were compared to participants (*n*=15) who received placebo pills and instructions to follow a low carbohydrate diet. Participants in both groups also received two-hour weekly group therapy sessions. Two weeks after their quit date, 75% (12/16) of those receiving tryptophan and high carbohydrate instructions were abstinent versus 47% (7/15) of the placebo and low carbohydrate diet group, although this difference was not statistically significant ($p > 0.05$) (Bowen et al., 1991). These data suggest that a serotonin-enhancing substance shows promise for use as an addition to existing smoking cessation interventions.

One case study (Harrison, Rucklidge, & Blampied, 2013) used a single case reversal (off-on- -off) design to investigate a broad-spectrum micronutrient formula in the treatment of ADHD symptoms in an adult. They documented on-off control of psychological symptoms as micronutrients were consumed (for 10 and 16 weeks) or withdrawn (for 10 weeks), and simultaneous on-off craving and decreases in the use of cannabis and cigarettes, despite the addictions not directly being targeted in the treatment protocol. During both "on" phases,

the participant quit cigarettes while taking the micronutrients. This case study used EMPowerplus, a 36-ingredient vitamin-mineral formula, and one of the most researched multi-ingredient formula for the treatment of psychiatric disorders (Harrison et al., 2013). This study is the first study reporting on the use of a broad-spectrum micronutrient to support smoking cessation.

In summary, the existing body of literature tentatively suggests that micronutrient treatment improves psychological functioning, reduces withdrawal symptoms, enhances program retention, and increases the chance of remaining abstinent when trying to quit drugs and cigarette smoking. The research investigating the outcomes of using micronutrients to assist with becoming abstinent from addictive substances and cigarette smoking is limited due to small sample sizes, limited control groups, and blinding. Additional large RCT studies are warranted. Nevertheless, withdrawal from smoking is associated with numerous adverse psychological symptoms, some of which have been relieved with micronutrient supplementation and this is discussed in the next two sections of this chapter.

2.4 Single micronutrient interventions for psychological symptoms

Many researchers have investigated the use of single nutrients (e.g., folate, zinc, vitamin D) for the treatment of psychological symptoms (Haller, 2005; Kaplan & Leung, 2011). This single nutrient approach has produced some promising results, although symptom improvements are often modest (see; Popper, Kaplan, and Rucklidge (2017) for a review). This modest symptom improvement is not surprising as most nutrient risk factors for psychological symptoms are related to a combination of nutrients (Kaplan, Crawford, Field, & Simpson, 2007). Humans have evolved to need many nutrients in combination for a variety of functions, and no single nutrient appears to show more therapeutic potential than

any other (Kaplan et al., 2007), therefore, a more efficacious treatment for psychological symptoms may be one containing a broad-spectrum of micronutrients.

2.5 Multi-ingredient micronutrient interventions for psychological symptoms

Over the last decade there has been a considerable amount of research conducted investigating the use of multi-ingredient/broad-spectrum micronutrient formulas for the treatment of psychological symptoms. Below is a review of RCTs using micronutrient supplements for a range of symptoms that are often associated with withdrawal from nicotine and cigarette smoking, suggesting that the use of a broad-spectrum micronutrient is a reasonable approach to take to address the psychological symptoms associated with nicotine withdrawal.

Mood Symptoms

As discussed above, quitting or reducing cigarette smoking can result in withdrawal symptoms that consist of negative affect or low mood (Piasecki, 2006), and this can trigger cravings to smoke (Brewer et al., 2011). Poor mood has been associated with a deficiency of a number of essential vitamins and minerals (Harris et al., 2011). Benton, Haller, and Fordy (1995) randomized 209 young (17-27 years) healthy university students to take either a high dose of nine vitamins (A, thiamine, riboflavin, B6, B12, C, E, folic acid, and niacin) or a placebo for one year under a double blind procedure. At the end of the 12 months female participants (n=99) reported significant improvements in scores on the General Health Questionnaire (Gender x Treatment X Time interaction (F(3,354)=2.81, p<0.05) when compared to placebo, with males (n=110) showing no significant difference (p>0.05). Female participants taking the vitamins reported feeling “more composed” (gender x treatment x time interaction F(3,348) = 2.65, p<0.05) on the Profile of Mood States when

compared to the females taking the placebo capsules, with no significant difference in males. All participants taking the vitamin formula reported themselves as feeling "more agreeable" on the POMs when compared to taking the placebo (treatment x time interaction $F(3,348)=3.18$, $p<0.02$).

A double-blind RCT randomized 225 hospitalized elderly patients suffering from various acute illnesses to receive six-weeks of a micronutrient formula containing 12 vitamins (A, C, D, E, B_1, B_2, B_6, B_{12}, folic acid, niacin, biotin and pantothenic acid) and 11 minerals (potassium, magnesium, calcium, phosphorous, chloride, iron, zinc, iodine, copper, manganese and selenium) or treatment as usual (TAU; normal hospital diet) (Gariballa & Forster, 2007). The patients who received a micronutrient formula displayed significantly (repeated measures analysis adjusting for baseline depression scores $p=0.021$) fewer signs of depression on a 15-item geriatric depression scale compared to the TAU group, with a mean group difference of 1.35 (95% CI, 0.43, 2.27). The positive effect of the supplement on depressive symptoms was seen in all patients including those with no symptoms of depression, mild depression, and severe depression.

Gosney, Hammond, Shenkin, and Allsup (2008) conducted a double-blinded RCT examining the effect of a micronutrient supplement (selenium, folate, and vitamin C) on mood symptoms in 73 nursing home patients over the age of 60. Among those with abnormal Hospital Anxiety and Depression Scale (HADS) depression scores at baseline (≥8), those in the active treatment group showed a significant increase in selenium levels ($t(9)=2.94$, $p= 0.009$) and a significant decrease in depression scores (Wilcoxon signed ranks test $Z =2.15$; $p= 0.016$) after 8 weeks. However, in the placebo group, selenium levels were unchanged ($t(6)=0.24$, $p = 0.41$) and HAD depression scores did not show significant change (Wilcoxon $Z = 1.02$, $p= 0.15$) (Gosney et al., 2008).

Kennedy et al. (2010) assessed the cognitive and mood effects of a high dose B-complex vitamin and mineral supplement (Berrocca™) compared to placebo in 215 healthy males in a placebo-controlled, double-blind, parallel groups trial. At the end of the 33-day treatment period participants who received the vitamin/mineral formula had significantly greater improvements in ratings of stress ($F(1205)= 5.24$, $p<0.05$) and general health ($F(1205)= 4.52$, $p<0.05$) as compared to those who received the placebo. Overall trends of mood scores (Profile of Mood States) also improved, however, narrowly failed to reach a statistically significant difference compared to placebo ($F(1196)= 3.77$, $p=0.054$). However, analysis of the mood subscales showed a significant increase in self-reported 'vigour' ratings ($F(1196)= 6.03$, $p<0.05$).

Harris and colleagues randomised 50 healthy men aged 50 to 69 years to a high dose multivitamin, mineral, and herbal supplement (Ulitivite™) or a placebo for eight weeks (Harris et al., 2011). They reported a significant group difference in the General Health Questionnaire scores ($t(47)=2.51$, $p=0.016$) and alertness scores on the visual analogue mood scale ($t(47)= 2.2$, $p=0.03$), with the change in the multi vitamin group being higher than the placebo group. There was also a significant treatment effect x time for the total Depression Anxiety Stress Scale-42 (DASS-42) score ($z=2.1$, $p=0.03$), revealing significant symptom reductions in the multivitamin group.

Sarris et al. (2012) asked semi-structured, open ended questions to explore the subjective experience of taking a once-daily multivitamin (Swisse Ultivite; $n=55$) compared to placebo ($n=59$) in a 16-week double-blind, randomised, placebo-controlled, parallel groups trial. In response to a question asking participants about any positive effects of the treatment, more participants in the micronutrient group (60%) qualitatively reported at least one positive experience compared to those in the placebo group (51%). The two main

statistically significant themes identified in the multivitamin group over the placebo group were an increase in energy and mental alertness (p= 0.022), and an increase in mood and mental/emotional wellbeing (p= 0.027) (Sarris et al., 2012).

Lewis et al. (2013) evaluated the efficacy of a vitamin B complex (Max Stress B) for improving depressive and anxiety symptoms using the Beck Depression and Anxiety Inventories (BDI and BAI). They randomised 60 adults who had a diagnosis of major depression or another form of depressive disorder to receive the vitamin B complex or a placebo control (double-blinded). Results revealed that both groups showed significant improvements in BDI and BAI scores from baseline to a 60-day follow-up. The vitamin B complex group showed greater improvements in BAI (mean difference 4.2 versus 3.4); however, the change was not significant (p>0.05). Conversely, the placebo group showed greater improvements in BDI, with both groups showing a significant improvement (mean difference 7.5 versus 7.9, p<0.05). However, the participants who received the vitamin B complex achieved a more continuous decrease throughout the 30 to 60-day study protocol, with the placebo showing no improvement.

Research suggests that there is a correlation between impaired B-vitamin metabolism and elevated homocysteine levels, leading to a heightened risk of depressive disorders (Mech & Farah, 2016). Mutations or minor variations in the genes coding for B-vitamin metabolism can lead to deficient co-enzyme production and lower than optimal levels of neurotransmitters (e.g., serotonin, norepinephrine, and dopamine) (Mitchell, Conus, & Kaput, 2014). The most common of these gene polymorphisms are the methylenetetrahydrofolate reductase (MTHFR) variants (Mech & Farah, 2016). Mech and Farah (2016) randomised participants with major depressive disorder and were positive for MTHFR polymorphism to receive either a placebo (n=160) or a broad-spectrum

micronutrient (three forms of vitamin B9, thiamine, magnesium, and zinc) in a double-blind study. They demonstrated that those in the micronutrient group decreased in homocysteine levels (Cohen's *d* effect size = 0.88) compared to an increase in the placebo group. The micronutrient group was also scored significantly lower on the Montgomery-Asberg Depression Rating Scale at the eight-week follow-up when compared to placebo (Cohen's *d* effect size = 0.81) (Mech & Farah, 2016).

In summary, there is now a substantial body of research that supports the use of micronutrient supplements to improve mood symptoms. However, this research relies heavily on the use of B-vitamin complexes and mean differences are not always consistently statistically significant. Furthermore, there is a lack of RCTs with clinical samples, diminishing the generality of the results. Further research in to the use of a broad-spectrum micronutrient for the treatment of mood symptoms is needed, in particular with large sample sizes (or more replications), long term follow-ups, and recruitment of clinical samples.

Stress and anxiety

As also noted above, many smokers report that they smoke to alleviate feelings of anxiety and to relieve stress (Taylor et al., 2014). Stress is a person's physiological, psychological, and behavioural response when seeking to adapt to internal and/or external pressures associated with change. Deficiencies in micronutrients can result in a diminished ability to cope with stress, and during times of high stress, essential micronutrients become depleted because of dietary increased demand for basic nutrients (Schlebusch et al., 2000). Furthermore, stress-related behaviours (e.g., cigarette smoking, alcohol consumption, poor nutritional habits, excessive caffeine intake) and symptoms of these behaviours (e.g. withdrawal and anxiety) have a negative effect on micronutrient status (Huskisson, Maggini,

& Ruf, 2007), and may compromise stress management mechanisms. Multiple RCTs have demonstrated the use of micronutrient supplements for the reduction of stress and anxiety symptoms.

Carroll, Ring, Suter, and Willemsen (2000) investigated the effects of a vitamin and mineral supplement (Berocca™) on psychological well-being. They double-blind randomized 80 healthy adult males (18-42 years), to take either the micronutrient supplement or a placebo for 28 days. The micronutrient supplement resulted in consistent and significant increases in the General Health Questionnaire (2.1 score increase, $F(1,74)=4.1$, $p<0.05$) compared to decreases in the placebo group (1.2 score decrease). They also reported reductions in anxiety (1.1 score decrease, $F(1,73)= 3.9$, $p=0.05$) and perceived stress (1.3 score decrease, $F(1,74)= 6.2$, $p<0.05$) compared to an increase in placebo groups (0.2 and 1.9 score increase for anxiety and stress respectively). The group receiving the supplement also reported being less tired ($F(1,73)=3.5$, $p=0.06$) and more able to concentrate ($F(1,73)= 7.49$, $p<0.05$) following treatment compared to the placebo group (Carroll et al., 2000).

Schlebusch et al. (2000) conducted a double-blind RCT with 300 adults with high stress levels across two centres in South Africa, to examine the effects of a taking a micronutrient formula (Berocca™) compared to a placebo for 30-days on stress. Although both groups showed improvements, the micronutrient group showed more pre-to-post improvements (decreases) in the Berocca Stress Index (20.6 versus 15.6, $p=0.03$), the Hamilton Anxiety Rating Scale (6.74 versus 4.60, $p=0.01$), and the Psychological General Wellbeing Schedule (16.4 versus 11.7, $p=0.01$) (Schlebusch et al., 2000).

A small body of research has also examined the use of micronutrients to support psychological symptoms following natural disasters. Rucklidge, Johnstone, Harrison, and Boggis (2011) followed 16 adults with ADHD who were taking a broad-spectrum

micronutrient (EMPowerplus) following a magnitude 7.1 earthquake in Christchurch NZ that caused property damage and on-going disruption to services such as water, power and sewage, compared to a group of adults with ADHD (*n*=17) who were not taking the micronutrients. Before the earthquake, the two groups did not differ in measures of depression, anxiety, and stress. However, at two -weeks post-earthquake the micronutrient, but not the control group, reported significantly less depression (percentage decrease from baseline 66.6%, Cohen's *d* =0.73, versus 30.2%, Cohen's *d* =0.45), anxiety (76.3%, Cohen's *d* =0.84, versus 12.9%, Cohen's *d* =0.11) and stress (55.1%, Cohen's *d* =1.00, versus 8.6% Cohen's *d* =0.16). Five months after the initial 7.1 earthquake, Christchurch experienced a devastating 6.3 magnitude aftershock, which killed 185 people and caused widespread destruction to the City. Subsequently, Rucklidge et al. (2012) randomised 91 adults who had heightened psychological symptoms (depression, anxiety, stress, trauma symptoms) at three-five months post-earthquake to either two doses (four capsules or eight capsules) of a broad-spectrum micronutrient (CNE™) or a high dose vitamin B complex (Berocca Performance™; one pill/day). A non-randomized control group (*n*=25) also completed questionnaires. All three treatment groups experienced significant decreases in psychological symptoms over the four weeks of the trial ($p<0.001$). However, participants taking the higher dose of CNE™ reported significantly greater improvement in mood, anxiety, and energy ($p<0.05$). The CNE™ group were more likely to report being "much" to "very much" improved (52% versus 17%) and more likely to continue taking CNE post-trial (OR=5.2, $p<0.05$) compared to the Berocca™ group. In 2013, there was a devastating flood in southern Alberta, Canada. Subsequently, Kaplan, Rucklidge, Romijn, and Dolph (2015) randomised 56 participants with heightened levels of depression, anxiety, or stress to one of three groups; Vitamin D (one pill/day), a Vitamin B-complex (one pill/day), or a broad-

spectrum micronutrient formula (four capsules/day). At the end of the six-week trial, participants taking the B-complex and the broad-spectrum micronutrient showed significantly greater reductions in stress and anxiety compared to those consuming Vitamin D, with large between group effect sizes (Cohen's *d* range 0.76 to 1.08). Thus, the current research supports the use of micronutrients to alleviate stress and anxiety symptoms. This may be particularly important in times of withdrawal and learning new behaviour post-quitting.

Insomnia

Sleep is essential to human functioning (Lothian et al., 2016) and insomnia (difficulty sleeping) is a core smoking withdrawal symptom. There are no known RCTs that have investigated the use of nutrient supplements to treat insomnia (See Appendix I for fuller explanation of single case designs). However, one recent multiple-baseline open label study investigated the use of a broad-spectrum micronutrient (Daily Self Defence) in 17 adults diagnosed with insomnia. Throughout the eight week trial, consumption of the micronutrient formula resulted in improvements in insomnia symptoms (Cohen's *d* =3.45), mood (Cohen's *d* =1.33), stress (Cohen's *d* =2.53), and anxiety (Cohen's *d* =1.36), with large effect sizes observed in the reduction of mean insomnia severity ratings (Lothian et al., 2016). This research suggests that micronutrients can improve sleep, mood, stress, and anxiety symptoms, but further single-case replications and larger sample RCTs are needed to investigate the efficacy of micronutrients to improve insomnia over a placebo control.

Irritability

Currently, there are no RCTs investigating the use of broad-spectrum micronutrients in the reduction of irritability in adults. However, there is research supporting the use of micronutrients to reduce antisocial behaviors. Gesch, Hammond, Hampson, Eves, and

Crowder (2002) gave 231 adult prisoners adequate (in terms of established nutritional norms) intakes of vitamins, minerals, and essential fatty acids (26 ingredients) or a placebo (in a double-blind study) and compared disciplinary offences before and after supplementation. The group receiving the nutritional supplement showed a reduction from baseline in their rate of offending by 35%, whereas the group receiving placebo only showed a 7% reduction (p<0.001), and those receiving the nutritional supplement committed an average of 26% (95% CI 16.3, 53.9) fewer offences compared to those receiving placebo(p<0.001) (Gesch et al., 2002). This study was replicated in detail by Zaalberg, Nijman, Bulten, Stroosma, and Van Der Staak (2010), where 221 prisoners (aged 18 to 25 years) received nutritional supplementation that was virtually identical to Gesch and colleagues' formulation or placebo for 1 to 3 months. Findings were comparable to Gesch and colleagues', with a 34% decrease in staff-reported incidents of aggressive and rule-breaking behaviours (mainly alcohol or drug use) in the group receiving nutritional supplementation, compared with a 14% increase (p=0.017) in the placebo group. Other assessments however reported no significant reductions in aggressiveness and psychiatric symptoms.

Cost of Daily Essential Nutrients

Due to the variety in combinations of nutrients used in the studies discussed it is difficult to report on the cost of the formulas studied. However, the cost of the broad-spectrum micronutrient used in the current research – Daily Essential Nutrients (DEN) – at 12 capsules/day is NZ$4.71 per day. With cigarettes in NZ costing an average of NZ$1.26 per/cigarette (see www.smokefree.co.nz), DEN is more cost-effective for any quitter who has smoked at least four cigarettes per day, or for an individual who cuts down to no more than four cigarettes per day. Furthermore, it is assumed (more controlled research is

required to confirm) that DEN (or other nutritional supplement) will only need to be taken during the initial weeks of the quit attempt. Thereafter, the financial benefits of not smoking will not be offset by the cost of the supplement.

The research reviewed in this section supports the use of multiple micronutrient formulas to facilitate the reduction of some of the psychological symptoms that are associated with smoking withdrawal symptoms. A logical next step in this discussion is to review the potential mechanisms of action for the therapeutic effect of micronutrient supplements on psychological symptoms.

2.6 Physiological mechanisms of the beneficial effect of micronutrients on psychological symptoms and withdrawal

The mechanisms of action for the beneficial effects of broad-spectrum micronutrients assisting with psychological symptoms, including withdrawal and becoming abstinent from addictive drugs are not fully known. Many theories have been proposed as to why micronutrients might effect change on psychological symptoms. Reviewed here are potential mechanisms of positive effects of nutrient supplementation on psychological symptoms and withdrawal, including the effect of smoking on nutritional status, reducing inflammation in the gastrointestinal (GI) tract and oxidative stress, correcting mitochondria dysfunction and inborn errors of metabolism, and addressing deficient methylation processes. These mechanisms are not mutually exclusive or exhaustive; they may be completely compatible and explain co-existing pathways by which vitamins and mineral influence the psychological symptoms of withdrawal and support one to achieve abstinence.

Cigarette smoking nutritional implications

The effects of cigarette smoking on a variety of adverse diseases and health outcomes is well-documented (see chapter one); however, smoking also causes direct

effects on levels of macro- and micronutrients in the body (Preston, 1991). As discussed in chapter one, tobacco smoke contains numerous compounds and gases, many of which are oxidants. Antioxidants constitute vitamins, minerals, fibres, fatty acids, and amino acids (Pisoschi & Pop, 2015) (e.g. Vitamin E, vitamin C, B-carotene and selenium), and are involved in cellular anti-oxidant defence systems. Smoking has been shown to lower the level of vitamin C and B-carotene, and cadmium found in tobacco decreases the bioavailability of selenium. Tobacco smoke also acts antagonistically to zinc. Vitamin E may be at suboptimal levels in the tissues of smokers. Furthermore, compounds from tobacco smoke have been shown to reduce levels of several B-vitamins (Preston, 1991). The nutritional status of smokers may be further compromised by an inadequate diet (Dallongeville, Marecaux, Fruchart, & Amouyel, 1998; Traber, Van Der Vliet, Reznick, & Cross, 2000). Imbalances in nutrients may have a role in many of the pathological conditions attributed to smoking and withdrawal symptoms upon cessation. Taken together, the research suggests that smokers have both lower intakes of antioxidants and are exposed to increased oxidative stress.

The microbiome and inflammation

It would be hard to consider any mechanisms of the beneficial effects of micronutrients on functioning, without first considering that at least 90% of the cells in and on our bodies are microbial cells, predominantly bacteria. These cells make up our microbiome (also known as the gut flora, microflora and microbiota). Microbial cells have a variety of functions: to protect the intestinal barrier defence system, digest food, extract nutrients that we need, and synthesize these nutrients (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Most of these microbial cells reside in the GI tract. The GI tract is an organ system that takes in food, digests it to absorb nutrients, and expels the remaining waste (Ouwehand, Isolauri, & Salminen, 2002).

Any imbalance in gut bacteria, termed dysbiosis, can have various negative consequences for the host, such as an over-growth of already-present microorganisms, a decrease in the production of short chain fatty acids, an increased susceptibility to intestinal pathogens, and can be a pre-disposing factor for the translocation of bacteria from the intestines to the interior of the body (Bailey et al., 2011). This translocation of bacteria is often referred to as “leaky gut”. Leaky gut stimulates the immune system and causes inflammation (Bailey et al., 2011; Maes et al., 2013).

Depression is associated with increased activation of inflammatory responses (Berk et al., 2013) and the increased production of proinflammatory cytokines (Dowlati et al., 2010). Pro-inflammatory cytokines can also contribute directly to the development of depressive symptoms (Dantzer, 2012; Dietrich-Muszalska et al., 2012), leading to the debate of whether inflammation causes depression, or depression causes inflammation. Longitudinal data suggests that this relationship is complex, with depression sometimes preceding elevations of inflammation biomarkers, or the opposite - the biomarker elevation precedes the onset of depression (Dantzer, 2012). Inflammatory processes have also been demonstrated in bipolar disorder (Hamdani, Tamouza, & Leboyer, 2012) and psychosis (Borovcanin et al., 2012).

Increases in the inflammatory response can make one more susceptible to stress (Bailey et al., 2011), a common withdrawal response after cessation from smoking. This relationship is also a complex one, as stress exposure significantly changes the structure of bacteria in the gut, further aggravating any initial stress response (Bailey et al., 2011; Knowles, Nelson, & Palombo, 2008). Gut dysbiosis can be caused by a variety of other mechanisms including the use of broad-spectrum antibiotics, a poor diet, the modern very clean environment, the innate act of breathing (Kaplan, Rucklidge, Romijn, & McLeod,

2015), and notably for this research, cigarette smoking. Cigarette smoke and nicotine causes an increase in inflammatory cells in the colon and inflammation in the GI tract due to oxidative stress (Cope & Heatley, 1992; Lei et al., 2015; Verschuere, De Smet, Allais, & Cuvelier, 2012).

In summary, inflammation can negatively affect brain function and exacerbate psychological symptoms. The association between dysbiosis and inflammatory activation is a robust one, but there are many potential causative agents for chronic activation. A regular smoker may already have higher levels of gut dysbiosis and inflammation due to increased oxidative stress, and this is likely to be exacerbated upon the stressful event of quitting and the subsequent withdrawal.

Oxidative Stress

Oxidative stress happens in even the most balanced body systems. It occurs because normal metabolism (i.e., the innate act of breathing) generates reactive chemical molecules that are pro-inflammatory, called reactive oxygen species (ROS). Through the promotion of oxidation, the ROS govern cellular signalling, which then stimulates inflammatory processes (Lei et al., 2015). Inflammatory responses are what enable us to fight infection, and they trigger ROS in the process of that fight. It would be a mistake to categorize inflammation and oxidative stress as harmful, given that both are an essential part of a balanced system and enable us to maintain health in the face of infection (Kaplan, Rucklidge, Romijn, & McLeod, 2015).

Oxidative stress and ROS-induced damage, however, are also relevant to psychological symptoms. Stress can elevate oxidative stress and in turn ROS, and this can damage cell structures (Mitochondria, DNA, RNA, and proteins) (Kaplan, Rucklidge, Romijn, & McLeod, 2015). ROS-induced damage can contribute to programmed cell death

(apoptosis), neurodegenerative diseases such as Alzheimer's and Huntington's, and is also relevant to mental disorders (Lei et al., 2015). Elevations in biomarkers for oxidative stress have been reported for many different types of mental disorders, including ADHD (Ceylan, Sener, Bayraktar, & Kavutcu, 2012), bipolar disorder (Andreazza et al., 2008), schizophrenia (Dietrich-Muszalska et al., 2012) and as mentioned, in cigarette smokers. Inflammation influences oxidative stress, and both are inevitable consequences of normal metabolism, (Lei et al., 2015) therefore the next logical question is, what influences oxidative stress? For the answer to this question we need to discuss the mitochondria.

Mitochondria and Mental Health

Mitochondria are cellular organelles which have a fundamental function of producing the bodies energy source adenosine triphosphate (ATP) (Gardner & Boles, 2011), and have evolved in humans to manage inflammation and oxidative stress (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Mitochondria possess their own genome and Deoxyribonucleic acid (DNA), namely mtDNA, this is small and only accounts for 0.3% of total cellular DNA. The mtDNA encodes enzymes that are involved in two processes (electron transport chain and Krebs cycle) that produce ATP. Many cofactors required for proper enzymatic function in the Krebs cycle and electron transport chain are dependent on the availability of dietary nutrients. The electron transport chain is efficient in generating energy but requires oxygen to do so, and errors in reactions involving oxygen can generate ROS. ROS can damage mitochondria and cause DNA mutations. The mtDNA is particularly susceptible to ROS-induced damage due to its proximity to the electron transport chain. Furthermore, mtDNA has less efficient repair and protective systems than nuclei DNA, which results in mutations accumulating at a rate 10 to 16 times faster than nuclei DNA (Gardner &

Boles, 2011). Mutations in mtDNA affect enzyme functioning, decreasing energy production, and causes mitochondrial disease and dysfunction.

Mitochondrial disorders result in decreased production of cellular energy (ATP) and the management of oxidative stress and inflammation (Harrison et al., 2013). All tissues in the body are dependent on the electron transport chain process, and mitochondria are in all our cells, therefore mitochondria dysfunction can affect virtually every organ and system in the body (Gardner & Boles, 2011). Given that brain tissue requires high levels of ATP for metabolism, and the susceptibility of mtDNA to oxidative stress and mutation, it is not surprising that investigators are proposing that mitochondrial dysfunction is a causal pathway to consider in mental disorders. Research has demonstrated that ATP production is compromised in bipolar disorder (Young, 2007), ADHD (Russell et al., 2006), autism spectrum disorder (Rossignol & Frye, 2012), and depression (Gardner & Boles, 2011). When all steps of cellular metabolism and energy production are combined for consideration, it appears as if virtually all known minerals, vitamin, amino acids, and essential fatty acids are involved (Kaplan, Rucklidge, Romijn, & McLeod, 2015). For that reason, it is reasonable to consider using a broad spectrum of nutrients to optimize mitochondrial function, and subsequently increase energy production and decrease oxidative stress and inflammation.

Inborn errors of metabolism

Another potential mechanism pathway that deserves mention are inborn errors in metabolism, as they may reduce neurotransmitter functioning and contribute to psychological symptoms in idiosyncratic ways. Inborn errors of metabolism are a group of disorders each of which results from deficient activity of a single enzyme in a metabolic pathway (El-Hattab, 2015). Inborn errors in metabolism can have many detrimental effects on the brain, including reducing co-enzyme reactions and neurotransmitter functioning

(Kaplan et al., 2007). At least one third of all gene mutations result in the corresponding enzyme having a decreased binding affinity for the co-enzyme (Ames, Elson-Schwab, & Silver, 2002). Approximately 50 human genetic diseases that are due to defective enzymes can be remedied by the supplementation of high doses of the vitamin or mineral component of the corresponding co-enzyme, which partially restores enzymatic activity (Ames et al., 2002). It is possible that brain imbalances, for example psychological symptoms and withdrawal, represent the same type of dysfunction and can be remedied in the same way. That is, psychological and withdrawal symptoms are the result of decreased co-enzymes being available for optimal neurotransmitter functioning, and the individual requires higher (perhaps pharmacological) amounts of micronutrients for normal metabolic functioning to be restored (Kaplan et al., 2007). Micronutrient treatment should theoretically provide the brain with sufficient co-enzymes, so that even enzymes with considerably reduced activity in metabolism can become supersaturated with the necessary co-enzymes and near-normal function is restored (Harrison et al., 2013).

Deficient methylation processes

Methylation reactions represent another interface between nutrients and genetic expression. Methylation is simple in terms of mechanism - it is the process of adding a methyl group to a molecule; however, it has huge and complex impacts on physiological functioning (Kaplan et al., 2007). There are hundreds of methylation processes: they switch on genes, activate enzymes, and regulate the amount of proteins generated by genes. DNA transcription cannot occur without methylation, nor can the synthesis of neurotransmitters (Kaplan et al., 2007).

Several studies have suggested that low levels of methylation are associated with depression, fatigue, autism spectrum disorder, and other neurological diseases (Botez,

Young, Bachevalier, & Gauthier, 1979; Bottiglieri et al., 2000; Ciernia & LaSalle, 2016; Jakovcevski & Akbarian, 2012; Kato & Iwamoto, 2014; Mischoulon & Fava, 2002; Schmidt et al., 2012; Stuffrein-Roberts, Joyce, & Kennedy, 2008). Evidence also suggests that psychological stress impairs methylation processes, resulting in altered availability of micronutrients for neurotransmitter synthesis and function (Kaplan et al., 2007; Yang et al., 2006).

Furthermore, the impact of cigarette smoking can persist for extended periods following cessation, and may involve changes in DNA methylation. Wan et al. (2012) analysed genome-wide methylation data (*n*=1434) and identified 15 sites that were significantly associated with cigarette smoking, suggesting the existence of site-specific methylation changes in response to smoking, which may contribute to the long-term risks associated with cigarette smoking that persist after abstinence.

Nutrition plays an important role in methylation, as many dietary micronutrients such as folate and vitamin B12 are important methyl donors and co-factors, therefore an inadequate supply of micronutrients can disrupt methylation (Scott, Molloy, Kennedy, Kennedy, & Weir, 1994; Stevens, Rucklidge, & Kennedy, 2017). Supplementation with micronutrients during the stress of withdrawal may correct deficiencies and increase the supply of methyl donors restoring adequate methylation (Stevens et al., 2017), moderating the stress of withdrawal.

Conclusion

The mechanisms reviewed in this section represent a summary of the current body of research for understanding the use of micronutrients to reduce withdrawal and improve psychological functioning. A variety of broad-spectrum micronutrient formulas have been researched, making the comparisons across studies challenging. It is unclear if one formula

can be replaced by another and produce the same or similar effects. Despite this, the research is generally consistent that micronutrient combinations are beneficial for psychological functioning and withdrawal symptoms. None of the aforementioned studies have investigated the efficacy and safety of the use of high dose micronutrient formulas long-term. Further research using large sample RCT double-blind designs with reported effect size measures and long-term follow-up are needed, particularly in the area of micronutrient and addiction research.

There are multiple pathways to consider for the use of micronutrients to support psychological functioning during withdrawal, and these pathways may occur in isolation or simultaneously. Further research in the field of nutritional psychiatry is needed to resolve these questions, however, the beneficial effects of micronutrients may well contribute to optimizing brain functioning during and after withdrawal. Any insufficiency in the neural availability of critical enzymes and co-factors, perhaps exacerbated by nutritional deficiencies, illness, injuries, lifestyle, stress, and individual differences in metabolic efficiency, may be particularly significant when coping with stress and withdrawal symptoms and while learning new patterns of behaviour post-quitting.

2.7 Rationale and Aim of Current Research

Current tobacco cessation products increase the chance of quitting. However, relapse rates for quit attempters remain high. Treatments that are safe, effective, relatively inexpensive, and readily available are needed, either on their own or in conjunction to other treatments. A small body of literature shows potential for the use of micronutrients to be used as a treatment for substance dependence. Further investigation into the effects of broad-spectrum micronutrients for the treatment of smoking cessation will provide a

clearer picture of this relationship. The current research aims to investigate the efficacy and safety of a broad-spectrum micronutrient to support smoking cessation in adults who want to quit smoking. The studies were designed so that, first, any effects of the broad spectrum micronutrient on smoking per se was assessed prior to the quit attempt, and second, there was a placebo control for the effects of expectancy related to the micronutrient treatment.

Chapter 3: Study 1: Mineral-Vitamin Treatment for Smoking Cessation: A Pilot Double-Blind Randomised Placebo-Controlled Trial

The following chapter presents a pilot study investigating a smoking cessation treatment involving the consumption of a broad-spectrum mineral-vitamin formula, Daily Essential Nutrients (DEN; see Appendix II for ingredient list and the dose used in this study and compared with the recommended dietary allowance), in conjunction with Quitline NZ support and advice. DEN is similar to the formula used by Harrison et al. (2013) (i.e., EMPowerplus), and is one of the most studied micronutrient formulas. Simpson et al. (2011) 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). However, 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).

Aims and Hypotheses

Based upon the tentative theory outlined in the previous chapter explaining how micronutrient supplementation may improve brain function, and on the limited research supporting the use of nutritional supplements to relieve withdrawal symptoms and assist with quitting addictive drugs, I hypothesised as follows:

1) *The intensity of withdrawal symptoms following a quit attempt would be less for the micronutrient + Quitline group compared to the placebo + Quitline group, and the intensity of withdrawal would predict likelihood of and/or time to relapse.*

2) *Participants randomized to the micronutrient + Quitline intervention would be more likely to succeed in making an initial quit attempt and be more likely to have remained quit at each study waypoint compared to placebo + Quitline.*
3) *Psychological symptoms of some or all of depression, anxiety sensitivity, stress, and negative mood would increase during a quit attempt, but the magnitude of this increase would be less for the micronutrient + Quitline group compared to the placebo + Quitline group.*

3.1 Method

Design

This pilot study was a single-case multiple-baseline design with replication across participants, nested within an active treatment-placebo double-blind randomized trial. Participants are randomised to a baseline phase of one, two, or three weeks, followed by a four-week pre-quit micronutrient or placebo phase, and then a 12 week micronutrient + Quitline or placebo + Quitline phase. A single-case design was selected for this study following the recommendation of Blampied (2013) that such designs should be used in the early stages of investigation of novel treatments, before any RCT's are conducted. Blampied (2013) argued that single-subject research is ideal for exploring novel questions, since it is truly experimental and can document causal relationships between independent and dependent variables. Single-case designs typically involve multiple participants in a single study (Horner et al., 2005), but without the demand for the large numbers of participants needed in group-based RCT research designs (Blampied, 2013), thus reducing the risks associated with exposure of participants to novel treatments while sparing the allocation of others to inert control conditions.

Eligibility criteria

Inclusion criteria were that participants be adults ≥18 years old, current smokers of ≥three cigarettes/day for the previous 12 months, not currently engaged in smoking cessation, not on psychoactive medication four weeks prior to baseline, and able to come in to the University of Canterbury approximately every four weeks for meetings. Exclusion criteria were being under 18 years old, taking psychiatric medication in the four weeks prior to baseline (combining the formula with psychiatric medications may result in complex interactions and should be monitored closely (Simpson et al., 2011; Popper, 2001)), any illness needing concurrent treatment and/or that may affect participation in the study, and being pregnant or breastfeeding (See Consolidated Standards of Reporting Trials (CONSORT) diagram; Figure 3.1).

Recruitment

Participants were recruited in Canterbury, New Zealand, through advertising on posters at local businesses and posts on social media (Mental Health and Nutrition Research Group's Facebook page) from June 2013 until December 2014. Advertising referred potential participants to a website (http://bit.ly/UCnutritionresearch) where they could access information about the study (including the information sheet, see Appendix III), the contact details of the researchers, and a link to an online eligibility screening survey developed using Qualtrics (http://www.qualtrics.com). The survey contained a summary of the study, demographic information questions (see measures section), previous and current smoking information, history of mental illness, and questions on past and current psychoactive medication use. If a participant was not eligible to participate they were referred to Quitline NZ.

Study Interventions

The micronutrient formula was supplied gratis by NutraTek Health Innovation Inc (Raymond, Alberta, Canada). It is a broad-spectrum micronutrient formula for oral administration, containing 17 minerals, 13 vitamins, four amino acids, and four antioxidants/botanicals (see Appendix I). The contents of the pills were independently tested by SupraNaturals in March 2016 and all quality control samples processed yielded acceptable results. All capsules were used within the expiry date, with no compromise in potency. The placebo formula (also supplied gratis by NutraTek Health Innovations Inc) included a small amount of riboflavin to mimic the urine colour associated with taking micronutrients (see Appendix I). The placebo has demonstrated effective masking in a recent study (Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018). Both capsules were identical in appearance. At the completion of baseline participants were given a four-week supply of placebo or micronutrient capsules, in plain containers with their name, participant number, date received, and date to start taking the capsules on the container. Participants titrated up to the full dose of 12 capsules/day (in routine use, NutraTek Health Innovation Inc recommends consuming between 12-15 capsules/day to enhance mental and physical well-being) over seven days, taking four capsules three times daily with food and plenty of water for the remainder of the trial. Based on previous clinical experience, expectation was that participants would typically experience a slow and gradual effect from the capsules within four weeks, therefore the pre-quit phase ensured that the metabolic effects of the micronutrients were established before quitting was attempted, and permitted any effects of the micronutrients or placebo alone on smoking and related symptoms to be detected. This phase then functioned as a second baseline for the quit attempt.

A printed copy of the *Quit Book* was supplied to all participants and read through with the researcher before their quit attempt. The *Quit Book* (see; www.quit.org.nz) explains each step of Quitline's five step program; 1) Set a Quit date, 2) Know your reasons for quitting, 3) Know your triggers, 5) Stay Quit. Step 4, the use of NRT, was removed for this study. The first day of the quit phase was the participant's target quit day, a day where they attempted to stop smoking. Participants continued to consume 12 capsules/day during the quit phase, receiving a four-week supply at each study waypoint meeting (weeks 4, 8, and 12 post-quit day).The participant was instructed to contact Quitline if they had a cigarette (lapse), no other behavioural support was provided. The quit phase intervention for this study was micronutrient + Quitline or placebo + Quitline for 12 weeks; however, for ease to the reader the two groups are referred to as micronutrient and placebo. At the end of the quit phase participants came to the laboratory to complete study waypoint questionnaires, hand in left over capsules, discuss that Quitline can continue to support them, and receive advice on how to purchase the capsules commercially should they wish to continue taking them. Participants were informed as to their randomly allocated condition at the end of data analysis and the plain English summary of the results (with further results sent on request).

Randomisation, allocation, and blinding

An independent research assistant randomly assigned participants to a baseline of one, two, or three weeks and in a 1:1 ratio to micronutrient or placebo capsules with www.randomization.com using block randomisation (blocks of four). Opaque envelopes labelled with a participant number contained the specified baseline length for each participant. The envelopes were opened and the blind for baseline length was broken after the participant consented to take part in the study. A collaborating pharmacist received a

list of participant numbers with their associated randomised condition allocation, but the randomisation sequence was concealed from all researchers involved in the study until the end of data analyses. All capsules (i.e., containing micronutrient or placebo) were pre-packaged by the pharmacist in plain containers and labelled with the participant number. A sealed envelope was contained within each pill package only to be opened in an emergency (e.g., the participant's health deteriorated significantly), permitting the blind to be broken in an emergency for only that one participant. A separate randomization sheet labelled with A and B groups (micronutrient or placebo) was kept by a research assistant and at the end of data collection this list was given to the researcher (PR) to permit analysis of the results.

Concomitant medication

Non-psychiatric medications (e.g., oral contraceptives, antidiabetic drugs, and statins) were allowed case-by-case.

Withdrawal criteria

Participants were able to withdraw voluntarily from the study or the primary investigator may discontinue a participant from the study. The primary investigator may discontinue or withdraw a participant from the study for the following reasons: pregnancy, an adverse event associated with the intervention, medical condition(s) or other situation(s) occur such that continued participation in the study would not be in the best interest of the participant, and if the participant meets exclusion criteria (either newly developed or not previously recognised). A participant is considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by researchers (after three attempts on mobile, email, and phone call). If participants wanted to stop their participation they were asked to come in to the University to complete study way-point questionnaires. Relapse from smoking (≥three days smoking) signalled the end of participation in the study,

participants were asked to complete study waypoint questionnaires and were recommended to contact Quitline NZ for advice.

Baseline assessments

Meetings (approximately one hour) with each individual participant were held at the University of Canterbury Mental Health and Nutrition Research laboratory in the Psychology Department. At the baseline meeting participants were given a full description of the study, and had an opportunity to ask any questions before giving written consent (Appendix IV). At the end of consent participants received their participant number and baseline length (one, two, or three weeks), and used a computer in the laboratory to complete baseline questionnaires through Qualtrics. After the questionnaires were completed using Qualtrics participants received instructions to complete the daily diary (Figure 3.2) every day for their assigned baseline (one, two, or three weeks). This phase provided baseline assessments (discussed below) of cigarettes/day, withdrawal symptoms, nicotine dependence, and psychological health and well-being, and any baseline occurrence of side effects potentially associated with the consumption of micronutrients.

Demographic information. Participant's age, gender, and ethnicity were obtained at baseline.

Smoking History. Participants reported the age they first puffed a cigarette and began regular smoking, and how many times they had attempted to quit smoking (for more than 24 hours).

Fagerström Test for Cigarette Dependence (FTCD). The FTCD is a six-item questionnaire that assessed baseline levels of cigarette dependence, with scores ranging from zero (least dependent) to 10 (most dependent) (Fagerström, 2011; Horner et al., 2005). A score of six

or higher is recognised as establishing cigarette dependence and a score of seven or higher as high dependence (Yeomans et al., 2011); Cronbach's alpha=0.64 (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994).

Mood and Physical Symptoms Scale (MPSS). The MPSS measures symptoms of withdrawal and was completed using the daily diary (Figure 3.2) during the baseline phase (1,2, or 3 weeks). The core items of the MPSS consist of five single-item ratings of depressed mood, irritability, restlessness, hunger, and poor concentration. All items are rated on a five-point scale from applying "not at all" to "extremely", with the total score ranging from 0-25. In addition to these five ratings, the MPSS contains two six-point sub-scales (0-5) to measure time spent craving cigarettes and strength of the cravings. The MPSS only uses one item to assess each withdrawal symptom keeping the scale as brief as possible and suitable for the daily self-report diary; Cronbach's alpha=0.78 (West & Hajek, 2004).

Cigarettes/day. For the baseline phase participants recorded any cigarette smoking (a cigarette is lit and at least one puff taken) in the daily diary (Figure 3.2).

Date:
Please record the amount of cigarettes you inhale (even if it is just a puff it counts as one cigarette).

Please show for each of the items how you have been feeling over the past 24 hours (circle one number for each item).

	Not at all	Slightly	Somewhat	Very	Extremely
Depressed	1	2	3	4	5
Irritable	1	2	3	4	5
Restless	1	2	3	4	5
Hungry	1	2	3	4	5
Poor concentration	1	2	3	4	5

How much of the time have you felt the urge to smoke in the past 24 hours? (circle one number).

All the time	Almost all the time	A lot of the time	Some of the time	A little of the time	Not at all
5	4	3	2	1	0

How strong have the urges been? (circle one number).

Extremely strong	Very strong	Strong	Moderate	Slight	No urges
5	4	3	2	1	0

Figure 3.1. *Daily Diary given to the participants for use throughout the trial.*

Depression Anxiety Stress Scale-21 (DASS-21). DASS-21 is a 21-item questionnaire consisting of three self-report scales designed to measure negative emotional states of depression,

anxiety, and stress (Lovibond & Lovibond, 1995). Participants used a four-point severity scale to rate the extent to which they have experienced each state in the week prior to baseline. Each of the three DASS-21 sub-scales contain seven items, and scores for depression, anxiety, and stress subscales were calculated by summing all the scores for relevant items and doubling the outcome to align with DASS-42 scores (range 0-42). Cronbach's alpha scores = 0.88 for depression, 0.82 for anxiety, and 0.90 for stress (Henry & Crawford, 2005).

Anxiety Sensitivity Index (ASI). The ASI is a 16-item measure developed to assess a person's beliefs about the social and somatic consequences of anxiety symptoms. These beliefs contribute to fear learning, avoidance behaviour, and anxiety disorders. Participants self-reported how much each item was consistent with their usual way of thinking in the two weeks prior to baseline from zero (very little) to four (very much). Total scores range from 0-64; Cronbach's alpha= 0.71-0.75 (Reiss, Peterson, Gursky, & McNally, 1986).

Diener and Emmons Mood Form (DEMF). Positive and negative affect/mood were assessed at baseline using the nine items of the DEMF. The sum of four specified items gives a positive affect score (DEMF-P) and the sum of the remaining five gives a negative affect score (DEMF-N); Cronbach's alpha= 0.89 for DEMF-P and 0.84 for DEMF-N (Diener & Emmons, 1985).

Side effects. Participants were asked about presence/absence of side-effects potentially associated with the consumption of nutrients (e.g., headache, nausea, stomach aches, dry mouth) and to report any other possible effects/concerns. These were followed up and monitored by the researcher (PR).

Primary outcome

Minnesota Nicotine Withdrawal Scale- short form (MNWS). Changes in scores on the MNWS at each study waypoint provided the primary outcome measures. The MNWS-short form measures withdrawal symptoms of craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite/weight gain, depression, and insomnia by rating each symptom from zero (not present) to four (severe). The sum of the eight scores gives an overall rating of withdrawal symptoms severity (range 0-32). The MNWS has been validated in multiple smoking cessation studies (Donny et al., 2015; Ebbert et al., 2014; Zvolensky et al., 2009); Cronbach's alpha= >0.8 (Toll, O'Malley, McKee, Salovey, & Krishnan-Sarin, 2007). Participants completed the MNWS-short form at baseline, at the end of the pre-quit four week phase (pre-quit four weeks), and at 4, 8, and 12 weeks post target quit day during the smoking cessation phase.

Secondary outcomes

Mood and Physical Symptoms Scale (MPSS). Participants monitored changes in daily withdrawal symptoms via the MPSS using their daily diary in weeks 1-4, 8, and 12 of the quit phase.

Cigarettes use. For the first and last week of the pre-quitting phase participants recorded any cigarette smoking in the daily diary (Figure 3.2). A participant was counted as having a quit attempt if they quit smoking for ≥24 hours, and a quit success if they were abstinent for ≥three days after their quit day. Participants reported cigarette use/lapse during the quit phase by using the daily diary (weeks 1-4, 8 and 12), by contacting the researcher through email or text (on weeks that did not require completion of daily diary), or by self-report at study waypoint meetings. Smoking relapse was monitored with self-report (not

biochemically confirmed) at each meeting, *"Have you had a cigarette in the past four weeks?"*, participants were instructed to contact the researcher if they smoked for three days in a row throughout the quit phase, this counted as a relapse. Continuous abstinence (quit rate) was defined counted if a person did not relapse from the target quit day to the specified study waypoint.

Psychological measures. Changes in psychological symptoms during the pre-quit and quit phase were measured using the DASS-42, ASI, and DEMF. Participants completed the questionnaires at each study waypoint using Qualtrics computer software.

Side effects. Participants were asked about presence/absence of side-effects at each study waypoint. Any reported side effects were followed up and monitored by the researcher (PR). If any adverse effects were reported they would have been discussed with the consultant psychiatrist (Prof. Mulder) to determine whether further investigation was required. Prof. Rucklidge was consulted on all aspects of the project, and was aware of any foreseeable risks. The trial would of been terminated if serious adverse effects known to be caused by the nutrients occurred.

Compliance to capsule intake. Capsules were counted at the end of the study for the four weeks prior to each study waypoint. If a participant consumed ≥80% of their capsules they adhered to capsule protocol.

Sample Size

In a single-case multiple-baseline design with replication across participants the minimum number of phase repetitions needed to meet the standard advanced by Horner et al. (2005) is three, but four or more is recognized as desirable (Kratochwill et al., 2010). With

12 replications per study arm (24 participants in total), this project more than meets these design quality requirements.

Statistical Analysis

The researcher (PR) was blinded to the treatment conditions throughout data analysis. The intent-to-treat (ITT) sample included all participants who consented to participate in the study (*n*=24) regardless of whether they were fully compliant with study protocol. No interim analyses were conducted. Frequencies of the categorical variables of quit/not quit, dropped-out/continuing, and side-effects/no side effects at specified study waypoints were analysed using *chi*-squared ($\chi 2$) tests with odds ratios (OR) and 95% Confidence Intervals (CI), using IBM SPSS Statistics version 20.

Primary Outcome. The primary outcome measure defined *a priori* was changes in MNWS scores at each study waypoint when compared to baseline and pre-quit for those in the ITT sample who provided data (i.e., those who did not drop-out), with MNWS median scores, range of scores, and sample size calculated for the micronutrient and placebo groups separately at each study waypoint. Individual Effect size (ES) measures were calculated using Percent Deviating from the Median (PDM), otherwise known as Percent Exceeding the Median (i.e., as percent below or above the median depending on the direction of therapeutic change) (Parker, Vannest, & Davis, 2011). The PDM approach is appropriate for the calculation of effect size of a single-case experimental design to support the analysis of visual data (Ma, 2009). The null hypothesis of the PDM approach is that if the treatment has no effect, the data points in the treatment phase would fluctuate around the baseline median. Ma (2009) suggested that PDM is based on the assumption that if the intervention is effective, data points will fall predominately on the therapeutic side of the median. PDM

is recommended for use in instances when there is some variability over time or a significant outlier is present in the baseline data (Lenz, 2013). Ma (2009) reported that PDM in the range 70-90% indicated a moderate treatment effect and PDM >90% a large effect. Since median data were used to calculate the ES for individuals, medians were also used as measures of central tendency for the groups as well.

Visual analysis of individual change in MNWS scores were additionally undertaken using modified Brinley plots using SigmaPlot 14 Software (Blampied, 2017). Brinley plots were originally used to analyse group data from cognitive psychology experiments (Brinley, 1965). Subsequently, modified Brinley plots have been used to summarize changes over time and in identifying systematic effects of an intervention when modified to display each individual's data (Blampied, 2017; Rucklidge & Blampied, 2011). The way modified Brinley plots display data is as a scatter-plot that uses orthogonal X-Y coordinates with the same origin and scale. Time one (t_1; baseline) scores for each participant are normally plotted on the X-axis and time two (t_2; treatment/intervention phase) scores on the Y-axis. If there are no systematic differences between the conditions the individual data points will lie on or around the 45-degree diagonal line of no change (i.e., X=Y); however, if there are systematic differences between the conditions the points will deviate from the line. When a higher score indicates greater impairment/deterioration, points that fall above the line indicate greater impairment and scores fall below the line indicate improvement. When a higher score indicates improved functioning, points that fall above the line indicate improvement and points that fall below the line indicate greater impairment. Where clinical cut-off scores for a measure exist, these can be added as horizontal and vertical lines, such that it is immediately apparent which individuals have changed from clinical to non-clinical status over time (Rucklidge & Blampied, 2011).

A key question in interpreting modified Brinley plots is to interpret any change over time – how much change is required to be evidence of a clinically or practically meaningful change? (Blampied, 2017). A sophisticated measure of change over time uses the Reliable Change Index (RCI) (Jacobson & Truax, 1991). The RCI permits the detection of change that is reliable (assuming a null hypothesis of zero change) because it exceeds the margin of measurement error defined as $\pm 1.96 S_{Diff}$ where S_{Diff} is the standard error of measurement of the difference scores (derived from the standard error of measurement; see below). There are a number of formulae for calculating the RCI, depending on particular assumptions about the psychometric properties of the measure (see; Wise (2004) for a review), but the Jacobson and Truax (1991) formula has been widely used:

$$RCI = (x_1 - x_2)/S_{diff}$$

$$\text{and } RCI_{(0.05)} = S_{diff} \times 1.96$$

where x_1 and x_2 are an individual's scores at t_1 and t_2; $S_{diff} = \sqrt{2(S_E)^2}$; $S_E = s_1 \sqrt{1 - r_{xx}}$; s_1 is the standard deviation of the normal population, a control group, or the pre-treatment group (taken from the research studies above from where Cronbach's alpha was obtained); and r_{xx} is the reliability of the measure (preferentially Cronbach's alpha). Jacobson and Truax (1991) showed that the RCI can be used to compute upper and lower bounds demarcating a rectangular band of uncertainty about the modified Brinley plot diagonal. Individuals whose data points lie within this band have not shown reliable change (i.e., change is unlikely to be due to measurement error alone) but those lying outside can be considered as demonstrating reliable change, which may be classified as reliable improvement or reliable deterioration depending on the direction of change relative to the measure.

Secondary outcomes

Baseline information and smoking history. Baseline information was reported for all ITT participants (*n*=24) as an average for each group, *t*-tests and χ2 analyses were conducted to identify any significant group differences at baseline, using $p \leq 0.05$.

MPSS Scores. Median and range was calculated for each daily diary collection study waypoint and ES measures were calculated using PDM.

Drop-out. A drop-out was counted if the researcher could not contact the participant (lost to follow-up) or if the participant said they no longer wanted to take part in the trial (withdrawal).

Quit Attempts and quit success. Frequency of quit attempts (≥24 hours continuous abstinence), and quit rates at three days (quit success), and weeks 4, 8, and 12 were compared between groups by χ2. Percentage of quit success at four-weeks was compared with Quitline's continuous quit rate (Quitline NZ, 2013).

Cigarettes/day. Cigarettes/day during baseline and pre-quit for participants who made a quit attempt were analysed visually using time-series graphs. Median and range was calculated at each study waypoint and ES measures were calculated using PDM.

Psychological symptoms. Median and range was calculated for the DASS-21, ASI, and DEMF scores at each study waypoint with PDM effect size in the direction of therapeutic change.

Side effects and capsule compliance. Differences in capsule compliance and side effects were calculated using χ2 tests.

Data management

All study data is to be contained in locked storage systems; either a password protected computer system at the University of Canterbury or on a web-based data

collection system (www.canterbury.qualtrics.com) for electronic documents, while hard copies will be kept in secure filing cabinets at the university.

Renumeration

Participants received a NZ$10 petrol voucher at every second face-to-face meeting to help cover travel costs.

Ethical Considerations

The University of Canterbury Human Ethics Committee approved the study (HEC 2013/55) and the trial was registered with Australia New Zealand Clinical Trials Registry: ACTRN12613001188729.

3.2 Results

Recruitment for study one was from 01/06/2013 until 22/12/2014. The last data collection from a face-to-face interview was 2/06/2014 and data was locked on the 15/07/2014. The flow of participants through the study is shown in Figure 3.2. Thirty-seven participants were assessed for eligibility of which 37 were excluded. Randomisation did not achieve comparable groups with regards to baseline length, with more participants in the micronutrient group randomised to a two week baseline, and more participants in the placebo group to a three week baseline (Figure 3.2). Two participants were lost to follow-up during the baseline phase. The placebo group had more participants withdraw during the pre-quit phase compared to the micronutrient group. Overall retention rates were 60% (6 out of 12) in the placebo group and 75% (9 out of 12) in the micronutrient group (Figure 3.2).

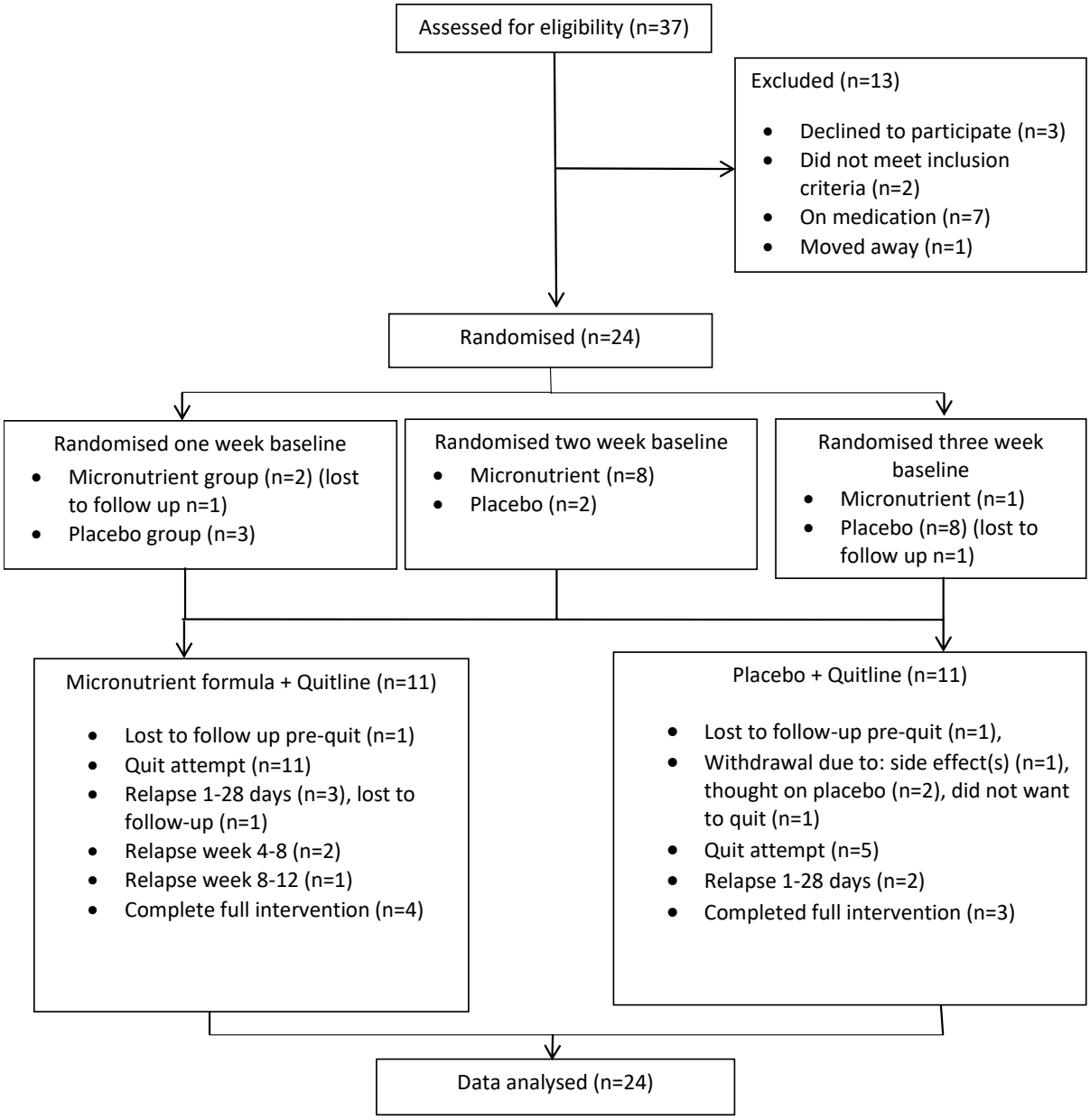

Figure 3.2 *Consolidated Standards of Reporting Trials (CONSORT) diagram.*

Demographic and Smoking information

In the event that participants reported two ethnicities, ethnicity was randomised according to NZ Statistics Guidelines, under this system, Māori had priority coding, followed by Pacific, then Asian, then other ethnic groups, with people of only European ethnicities last. The average age of participants at baseline in the placebo group was 32.8 years and 31.5 years in the micronutrient group. A majority of the sample (75.0%) were NZ European. Randomization did not achieve comparable study groups for gender ratio, with more males in the placebo group (8 versus 4; $t(11)=2.35$, $p=0.04$), and nor for baseline number of cigarettes/day (14.9 cigarettes/day placebo vs 10.5 cigarettes/day micronutrient; $t(23)=5.09$, $p<0.001$). Average nicotine dependence (FTCD) was high (≥7) in both groups. Participants in the placebo group had previously made an average of 3.2 quit attempts and the micronutrient group had made on average 2.3 attempts (Table 3.1.).

Table 3.1. *Demographic characteristics and smoking information of the Intention-to-treat sample (n=24).*

	Placebo Group (*n*=12)	Micronutrient Group (*n*=12)	Total (*n*=24)
Gender			
Male, *n* (%)	8*	4*	12 (50%)
Age (years) (SD)	32.8 (13.87)	31.5 (12.74)	32.2 (13.0)
range	20-63	18-63	18-63
Ethnic origin, *n,* (%)			
NZ European (%)	8	10	18
NZ Māori (%)	2	1	3
Other (%)	2	1	3
Smoking Information			
Average cigarettes/day (SD)			
in baseline	14.9 (8.4)*	10.5 (5.7)*	13.0 (7.7)
range	6.0-45.0	2.5-18.5	2.5-45.0
Age first puffed cigarette, years (SD)	14.8 (2.7)	13.6 (2.0)	14.2 (2.8)
range	10-18	9-17	9-18
Age when started regular smoking, years (SD)	17.3 (2.2)	16.9 (2.6)	17.0 (1.8)
range	13-20	15-19	13-20
Previous quit attempts (SD)	3.2 (1.2)	2.3 (1.0)	2.7 (2.0)

FTCD Score (SD)	7 (3.4)	8 (4.0)	7.8 (2.5)

*FTCD =Fagerstrom Test for Cigarette Dependence; score range 0-10, ≥6 = dependence, ≥7 high dependence. *significant difference between groups (p<0.05), SD= Standard Deviation*

Primary outcome

MNWS data (with change in sample size, *n*, to account for drop-out and relapse) is shown in Table 3.2. Symptoms later associated with withdrawal were reported prior to quitting (i.e., baseline levels were not zero) and were variable across days and participants, with the median baseline score being slightly higher in the micronutrient group (12.5) compared to placebo (10.5). At the end of the pre-quit phase (pre-quit week four) and at weeks 4, 8, and 12 of the quit phase, the placebo group consistently had higher withdrawal median scores and their lowest scores never dropped as low the median for the micronutrient group. The PDM ES (% below the median) was consistently larger at each time point for the micronutrient group compared to the placebo group, with the overall composite ES (the median of the medians) being 73% for the micronutrient group and 35% for placebo.

Table 3.2. *Sample size (n) at each phase, median and range for Minnesota Nicotine Withdrawal Scale for placebo and micronutrient group with Percent Deviating from the Median (PDM) effect sizes.*

	Baseline	Pre-quit week 4	Week 4	Week 8	Week 12
Placebo					
n	*12*	*7*	*3*	*3*	*3*
Median	10.5	13.5	15.0	10.0	10.0
Range	5.0-29.0	7.0-17.0	13.0-15.0	8.0-17.0	7.0-13.0
PDM%		37%	0%	33%	50%
Micronutrient					
n	*12*	*11*	*7*	*5*	*4*
Median	12.5	10.5	10.0	6.0	5.5
Range	3.0-36.0	2.0-17.0	2.0-17.0	2.0-22.0	2.0-9.0
PDM%		50%	86%	60%	100%

Figure 3.3 presents a series of modified Brinley plots presenting comparisons of MNWS scores at different time points and displaying the RCI boundaries. As noted above, each data point represents the score of a single participant. For each individual data were averaged across the start and finish of the first baseline phase (baseline one and two) and these average baseline values were carried forward on the X-axis in the next plot (mean baseline vs pre-quit baseline). No systematic differences or direction of change was identified between mean baseline scores and pre-quit scores, indicating that data were stable over these phases, therefore pre-quit scores functioned as Baseline for the subsequent quit phase plots. The three modified Brinley plots in the lower row show symptoms relative to the pre-quit phase over weeks 4, 8, and 12 of the quit smoking phase.

In the micronutrient group there was no clear direction of group change for MNWS scores at pre-quit. Post-quit, the majority of participants showed a decrease in withdrawal at each follow-up, i.e., as time abstinent progressed withdrawal decreased, and participants who showed a large increase in MNWS relapsed in the four-weeks thereafter. The majority of the placebo group showed an increase in MNWS at pre-quit. At 4, 8, and 12-weeks post-quit two participants in the placebo group showed a reliable decrease and one participant increased in MNWS. Comparison of the two groups at 12-weeks shows that the majority of the micronutrient group had lower MNWS scores compared to the placebo group.

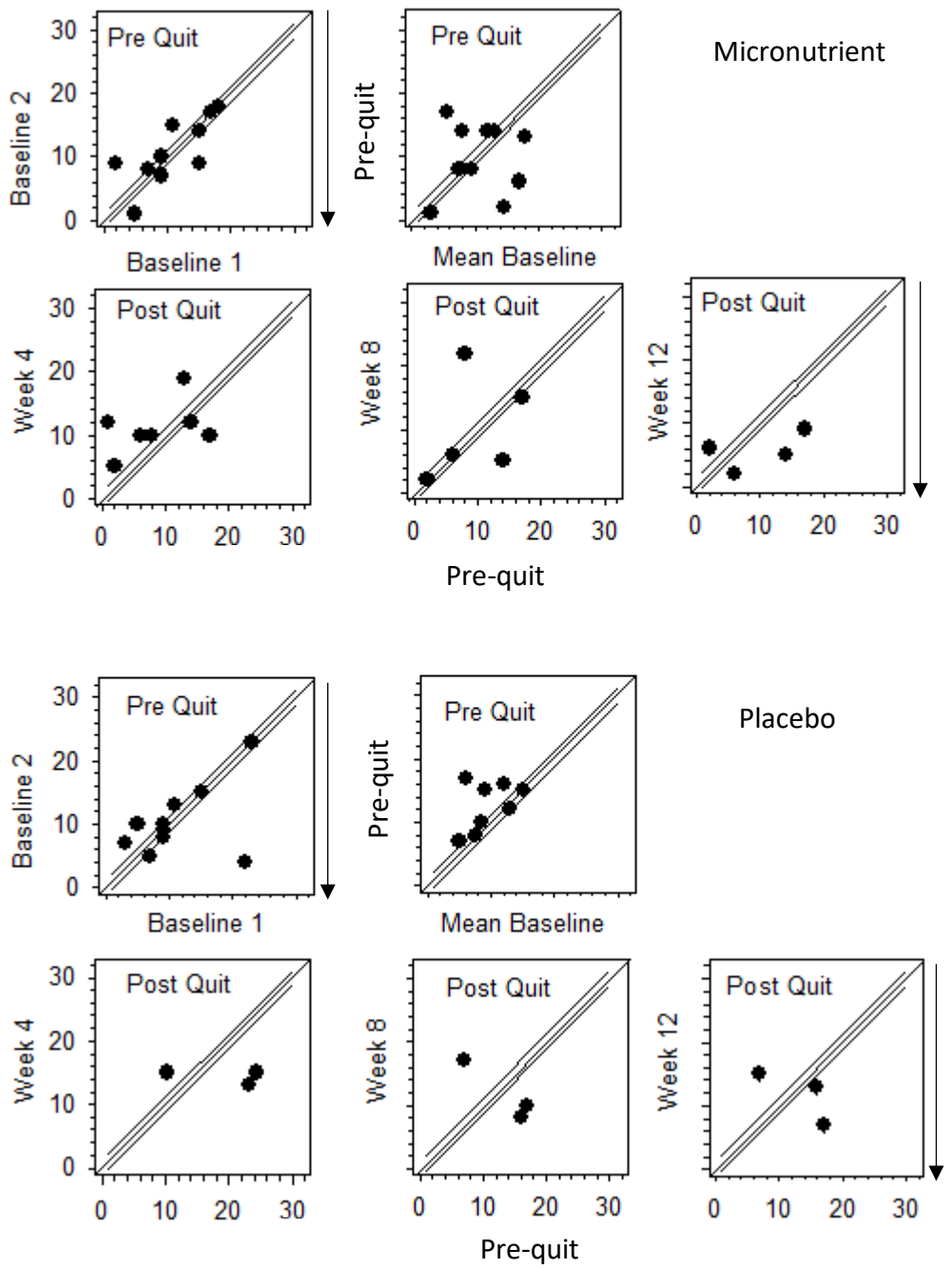

Figure 3.3. *Modified Brinley plots displaying change in participant rated Minnesota Nicotine Withdrawal Scale scores with arrows indicating the direction of desired change. Parallel lines either side of the central diagonal mark the upper and lower boundaries of the Reliable Change Index for the measure.*

Other outcomes

Quit attempts and success

The micronutrient group was associated with significantly more quit attempts compared with placebo (11 vs 5, OR=15.40) and with significantly more quit success overall (10 vs 4, OR=10.00; Table 3.3), with NNT=13 (95% CI 24.8, 44.6). The micronutrient group consistently had higher quit rates compared to the placebo group, however the contrasts between treatment groups were not statistically significant ($p \geq 0.05$). [Note: Due to the small sample size not all the assumptions of the chi-square test are meet (number of observed cases), therefore, Fisher's exact test *p* statistic was calculated.]

Table 3.3. *Comparison of quit attempts and successes at each follow-up between micronutrient and placebo groups for the ITT sample (n=24).*

	Micronutrient (*n*=12)	Placebo (*n*=12)	Odds Ratio	95% CI	Chi squared (*p* fishers exact test)
Quit Attempt	11	5	15.40*	1.47, 160.98	χ^2 (1, *n*= 24) = 6.75, *p*=0.01* (0.03)*
Quit Success	10	4	10.00*	1.44, 69.26	χ^2 (1, *n*= 24) = 6.17, *p*=0.01* (0.04)*
4 Week Quit Rate	7	3	4.20	0.74, 23.91	χ^2 (1, *n*= 24) = 2.74, *p*=0.10 (0.21)
8 Week Quit Rate	5	3	2.14	0.38, 12.20	χ^2 (1, *n*= 24) = 0.75, *p*=0.39 (0.67)
12 Week Quit Rate	4	3	1.50	0.25, 8.84	χ^2 (1, *n*= 24) = 0.20, *p*=0.65 (1.0)

*$p<0.05$ *statistically significant*

The micronutrient group had a higher continuous four-week quit rate compared to the placebo group and Quitline NZ users (43%) reported by Quitline NZ (Quitline NZ, 2013) (Figure 3.4).

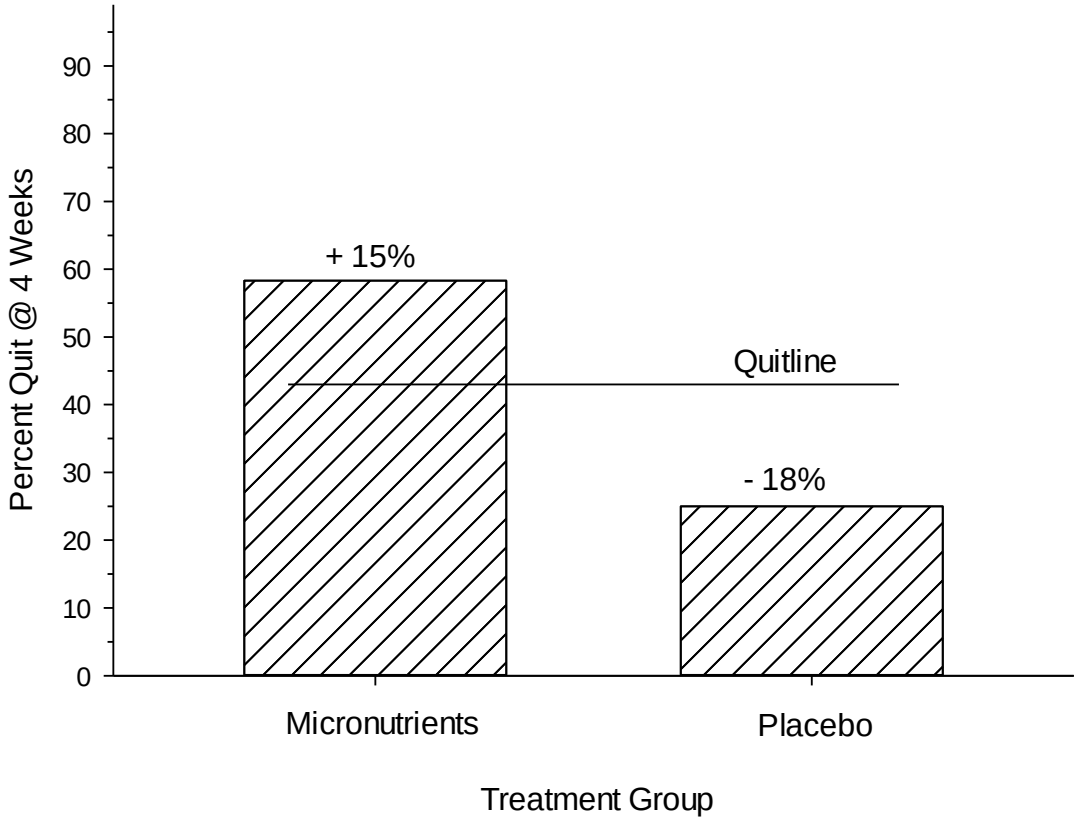

Figure 3.4. *Micronutrient and placebo group four-week continuous quit rate relative to the four-week quit rate for all Quitline New Zealand users reported by Quitline New Zealand (2013).*

MPSS withdrawal scores

Table 3.4 shows individual MPSS median and range scores, with PDM ES in the therapeutic direction (decrease in scores/% below the median) for the micronutrient and placebo participants (P = participant). In the micronutrient group P4 showed an increase in MPSS median scores during the first four weeks of quitting, and then decreased at week 8 and 12. P5 increased in MPSS median scores during the first four weeks of quitting, rating no days lower than the pre-quit median followed by a relapse. P7 had lower median scores during the first four weeks of quitting and week eight; this was followed by a relapse. P8 rated all MPSS withdrawal symptoms as "not at all" during pre-quit, and this was followed by an increase in median scores at each later post-quit point. P13 had the same median

score at pre-quit and during the first four weeks of quitting, followed by a decrease each day during week 8 and 12 (PDM=100%). P15, P19, and P21 increased median MPSS scores during the first four weeks of quitting and then relapsed. P17 had the same median MPSS scores at each study waypoint, showing some variability in the first weeks of quitting ranging in total scores from 5-11. P23 rated MPSS lower each day during the first four weeks of quitting (PDM=100%) when compared to pre-quit, then relapsed.

In the placebo group P3 increased in MPSS median scores during the first four weeks of quitting and during week 12, and decreased scores at week eight. P11 had an increase in median scores during the first four weeks of quitting followed by decreases at weeks 8 and 12. P14 increased MPSS median scores during the first four weeks of quitting and at week eight, this was followed by a decrease at week 12. P20 increased MPSS median score during the first four weeks of quitting compared to pre-quit and this was followed by a relapse. The overall composite ES (the median of the medians) is 30% for the micronutrient group and 5.5% for the placebo group.

Table 3.4. *Mood and Physical Symptoms Scale total median (M), range, and Percent Deviating from the Median (PDM) scores for participants who completed their daily diary during the quit phase.*

	Pre-quit-4 (*n*=14)	Week 4 (*n*=14)	Week 8 (*n*=8)	Week 12 (*n*=7)
	M (range)	M (range) PDM	M (range) PDM	M (range) PDM
Micronutrient				
Participant 4	10 (8-14)	11 (5-17) 30%	9 (7-13) 57%	5 (5) 100%
Participant 5	11 (9-13)	16.5 (15-17)* 0%		
Participant 7	10 (10-11)	7 (6-10) 75%	8 (8) 100%	
Participant 8	5 (5)	7 (5-9) 0%	6 (5-7) 0%	6 (5-7) 0%
Participant 13	10 (6-13)	10 (7-13) 48%	6 (6-8) 100%	5 (5-6) 100%
Participant 15	5 (5)	11 (6-14) 0%		
Participant 17	5 (5)	5 (5-11) 0%	5 (5-6) 0%	5 (5) 0%
Participant 19	8 (5-8)	11 (10-14)* 0%		
Participant 21	9 (7-10)	10 (6-15)* 37%		
Participant 23	9 (6-11)	8 (5-8)* 100%		
Placebo				
Participant 3	9 (8-10)	10 (8-16) 11%	9 (8-13) 50%	10 (8-13) 43%
Participant 11	6 (5-7)	7 (5-10) 11%	6 (6-7) 0%	6 (6-7) 0%
Participant 14	10 (8-12)	15 (13-16) 0%	11 (11-12) 0%	5 (5-6) 100%
Participant 20	11 (7-16)	22.5 (20-24)* 0%		

**relapsed during the phase, incomplete data*

Craving scores. Tables 3.5 and 3.6 shows individual median, range and PDM ES (% below the median) of scores for time spent craving cigarettes and the strength of craving for the micronutrient and placebo groups respectively. In the micronutrient group median craving

scores post-quit for P4, P7, P8, P13 and P23 decreased or remained stable when compared to pre-quit. The individual ES increased for P5, P9, P15, and P21 during the first four weeks of quitting and then these participants relapsed. Craving increased for P17 during the first four weeks of quitting; scores then decreased during week 8 and 12. In the placebo group craving scores for P3 and P11 decreased or remained stable post-quit compared to pre-quit. Craving was stable for P14 then increased during the first four weeks and week eight of quitting, then decreased at week 12. The overall composite ES (the median of the individual's ES) for time craving is 57% for the micronutrient group and 25% for the placebo group, and for strength of craving 52% for the micronutrient group and 25% for the placebo group, i.e., there was a larger effect on craving severity and time spent craving in the micronutrient group than for placebo, indicating a benefit of the micronutrient treatment to decrease craving.

Table 3.5. *Mood and Physical Symptom Scale time spent craving and strength of the cravings subscales median, range, and Percent Deviating from the Median (PDM) scores for participants in the micronutrient group who completed their daily diary during the quit phase.*

	Pre-quit (*n*=10)	Week 4 (*n*=10)	Week 8 (*n*=5)	Week 12 (*n*=4)
	M (range)	M (range) PDM	M (range) PDM	M (range) PDM
Micronutrient				
Participant 4				
Time craving	3 (2-3)	2 (1-4) 46%	2 (1-2) 100%	1 (1-2) 100%
Strength craving	3 (3-4)	3 (1-5) 39%	2 (1-2) 100%	1 (1-2) 100%
Participant 5				
Time craving	3 (3)	4 (4) 0%*		
Strength craving	3 (3-4)	4 (4) 0%*		
Participant 7				
Time craving	2 (2)	1 (1-2) 86%	1 (1-2) 71%	
Strength craving	3 (3-4)	2 (2-3) 64%	2 (2) 100%	
Participant 8				
Time craving	1 (1-2)	0 (0-3) 54%	0 (0) 100%	0 (0-1) 57%
Strength craving	1 (1)	0 (0-2) 54%	0 (0) 100%	1 (0-1) 43%
Participant 13				
Time craving	2 (1-3)	1 (1-3) 57%	2 (1-2) 29%	1 (1-2) 57%
Strength craving	2 (1-3)	1 (1-3) 50%	2 (1-2) 29%	1 (102) 71%
Participant 15				
Time craving	0 (0)	3 (1-4) 0%		
Strength craving	0 (0)	3 (1-4) 0%		
Participant 17				
Time craving	3 (3)	4 (0-5) 39%	1 (0-1) 100%	0 (0) 100%
Strength craving	3 (3)	4 (0-5) 39%	0 (0-1) 100%	0 (0) 100%
Participant 19				
Time craving	2 (1-3)	3 (2-3) 0%*		
Strength craving	2 (3-4)	3 (2-4) 0%*		
Participant 21				
Time craving	2 (1-2)	3 (2-4) 0%		
Strength craving	1 (1)	2 (1-3) 0%		
Participant 23				
Time craving	3.5 (3-4)	2.5 (2-4) 50%*		
Strength craving	3 (3-4)	3 (2-4) 33%*		

**relapsed during the phase, incomplete data*

Table 3.6. *Mood and Physical Symptom Scale time spent craving and strength of the cravings subscales median, range, and Percent Deviating from the Median (PDM) scores for participants in the micronutrient group who completed their daily diary during the quit phase.*

	Pre-quit (*n*=4)	Week 4 (*n*=4)	Week 8 (*n*=3)	Week 12 (*n*=3)
	M (range)	M (range) PDM	M (range) PDM	M (range) PDM
Placebo				
Participant 3				
Time craving	3 (3-4)	1 (0-3) 89%	3 (1-3) 33%	3 (1-4) 17%
Strength craving	4 (3-4)	1 (0-4) 86%	3.5 (1-4) 50%	3.5 (1-4) 50%
Participant 11				
Time craving	2 (2)	2 (2) 0%	2 (1-2) 33%	1 (1) 100%
Strength craving	2 (2)	2 (2) 0%	1 (1-2) 83%	1 (1) 100%
Participant 14				
Time craving	2 (2)	2 (2-3) 0%	2 (2-3) 0%	1 (1-2) 71%
Strength craving	2 (2-4)	3 (3-4) 0%	3 (3) 0%	2 (2) 0%
Participant 20				
Time craving	2 (1-2)	3.5 (3-4) 0%*		
Strength craving	2 (1-3)	4 (4) 0%*		

**relapsed during the phase, incomplete data.*

Cigarettes/day

Table 3.7 shows the median, range, and PDM (% below the median) for cigarettes/day at baseline, pre-quit week one, and pre-quit week four for those participants in the micronutrient and placebo groups who completed their daily diary. In the micronutrient group P4, P6, and P7 decreased their median scores at both weeks during pre-quit when compared to baseline. P5 and P8 decreased median cigarettes/day at pre-quit week one followed by an increase in pre-quit week four. Cigarettes/day remained stable for P9 at pre-quit week one compared to baseline and decreased at pre-quit week four. P17 and P19 increased in median cigarettes/day at pre-quit one and decreased at pre-

quit week four. P13, 15, and P21 increased cigarette consumption during pre-quit when compared to baseline.

In the placebo group P1, and P16 increased consumption pre-quit week one and pre-quit week four when compared to baseline. P2 stayed stable at pre-quit week one, then dropped out. Cigarette consumption for P3, P10, P14, P20, and P24 decreased at pre-quit week one and four when compared to baseline. P11 reported stable consumption from baseline to pre-quit week one followed by a decrease each day at pre-quit week four. P18 decreased median cigarettes/day at pre-quit week one and increased consumption at pre-quit week four. The overall composite ES for change in cigarettes/day at pre-quit week four is 57% for the micronutrient group and 71% for the placebo group, indicating no benefit to micronutrients in changing cigarette consumption (Table 3.7).

Table 3.7. *Cigarettes/day median (M), range, and Percent Deviating from the Median (PDM) scores for participants who completed their daily diary during baseline and pre-quit.*

	Baseline (*n*=20)	Pre-quit 1 (*n*=20)	Pre-quit 4 (*n*=19)
	M (range)	M (range) PDM	M (range) PDM
Micronutrient			
Participant 4	17 (10-24)	14 (8-18) 86%	0 (0) 100%
Participant 5	11 (10-13)	9 (3-34) 57%	12.5 (8-16) 46%
Participant 6	9 (6-12)	6 (3-8) 100%	5 (4-6) 100%
Participant 7	20 (9-24)	12 (9-15) 100%	10 (7-13) 71%
Participant 8	12 (8-14)	9 (7-12)14%	16 (16-25) 57%
Participant 9	18 (14-22)	18 (18-25) 43%	5 (3-10) 43%
Participant 13	5 (4-9)	6 (3-14) 29%	11 (8-17) 57%
Participant 15	11.5 (5-16)	13 (12-15) 43%	13 (11-17) 0%
Participant 17	8 (7-14)	9 (4-13) 14%	3 (0-6) 71%
Participant 19	4.5 (1-6)	6 (3-8) 29%	3 (2-3) 29%
Participant 21	2 (2-4)	3 (1-4) 14%	3 (2-3) 0%
Placebo			
Participant 1	25 (24-29)	25.5 (23-27) 17%	26 (23-28) 29%
Participant 2	12 (12-15)	12 (12-14) 0%	
Participant 3	11 (7-15)	9 (9-12) 60%	9 (9-10) 100%
Participant 10	22 (15-26)	5 (4-8) 100%	2 (2-4) 100%
Participant 11	5 (5-9)	5 (4-8) 14%	2 (2-4) 100%
Participant 14	10 (8-17)	9 (7-11) 57%	9 (6-10) 71%
Participant 16	11 (7-15)	20 (18-21) 0%	18 (14-23) 0%
Participant 18	43 (39-59)	41 (38-52) 57%	45 (30-50) 43%
Participant 20	17 (11-24)	15 (9-16) 100%	14 (13-17) 71%
Participant 24	12 (7-15)	11 (4-16) 57%	7 (3-23) 43%

Cigarette consumption as reported in daily dairies during baseline and pre-quit phase weeks one and four is shown in time-series plots (Figure 3.5 shows micronutrient group data and Figure 3.6 placebo data) in order to examine the stability of cigarette consumption prior to the quit intervention. Baseline consumption is shown on the left side of the solid line, and pre-quit week one and four on the right side of the solid line. For both

groups in baseline, while there were differences in overall level of consumption, from typically more than 40/day to typically less than ten per day, consumption was mostly stable; only a few participants (P4, P18) showing an increase and one (P15) a decrease. During the phases prior to quitting, when either micronutrients or placebo were consumed, consumption patterns remained generally stable; only one participant (P4) quit in this phase, and a couple (P7, P10) considerably reduced consumption. In general, then, cigarettes consumption prior to quitting was stable, and not reliably altered by entry into the micronutrient or placebo phase of the study.

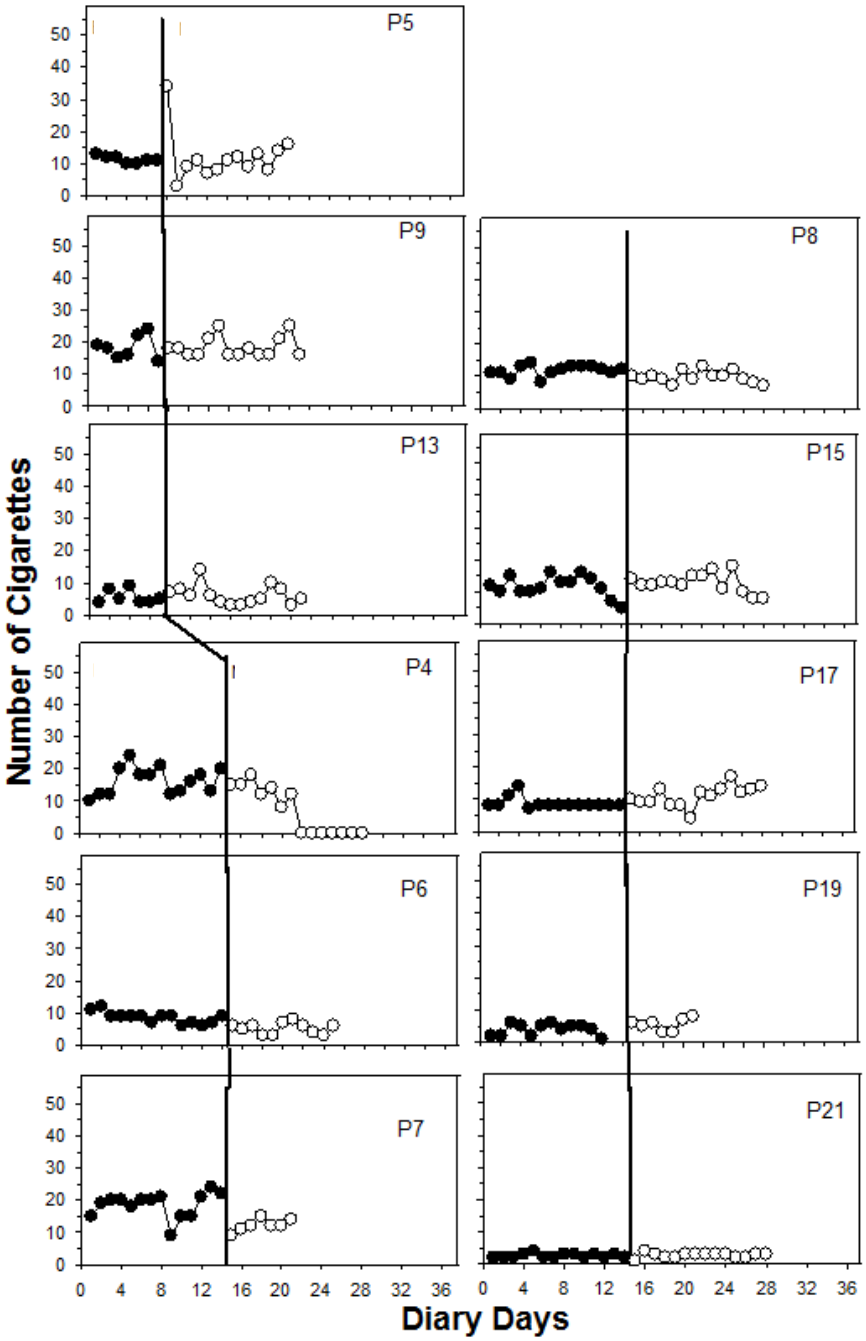

Figure 3.5. *Cigarettes/day for the micronutrient group during baseline (on the left side of the solid line) and pre-quit (for the right side of the solid line) for participants (P) who completed the daily diary.*

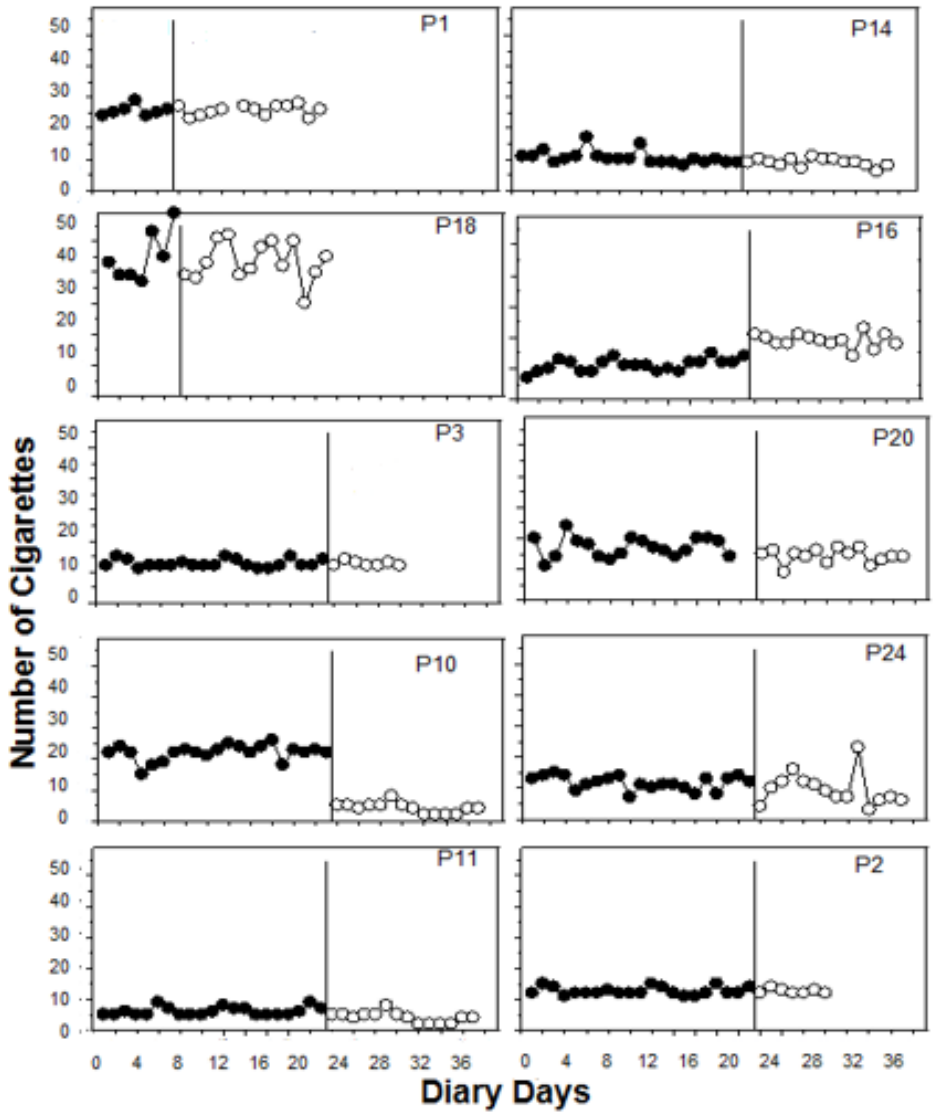

Figure 3.6. *Cigarettes/day for the placebo group during baseline (on the left side of the solid line) and pre-quit (on the right side of the solid line) for participants (P) who completed the daily diary.*

Changes in psychological measures

The median and range of scores and the PDM ES in the therapeutic direction (decrease in median) was calculated for the psychological measures at each study waypoint for both micronutrient and placebo groups (Table 3.8).

Table 3.8. *Psychological questionnaire median scores (M), range, and Percent Deviating from the Median (PDM) effect sizes, with sample sizes (n) at each study way-point.*

	Baseline	Pre-quit	Week 4	Week 8	Week 12
Placebo *(n)*	*12*	*7*	*3*	*3*	*3*
Micronutrient *(n)*	*12*	*11*	*7*	*5*	*4*
DASS-D: Placebo					
M (Range)	3.0 (0-22)	2.0 (1-9)	4.0 (2-14)	16.0 (1-34)	0 (0)
PDM%		75%	0%	67%	100%
Micronutrient					
M (Range)	6.5 (0-38)	3.0 (0-20)	4.0 (0-8)	2.0 (0-16)	0 (0)
PDM%		70%	71%	60%	100%
DASS-A: Placebo					
M (Range)	4.0 (0-24)	6.0 (0-16)	4.0 (0-14)	12.0 (1-14)	2.0 (1)
PDM%		38%	33%	33%	100%
Micronutrient					
M (Range)	8.0 (0-26)	4.0 (0-14)	2.0 (0-12)	4.0 (0-12)	1.0 (0-1)
PDM%		90%	86%	80%	100%
DASS-S: Placebo					
M (Range)	12.0 (0-28)	11.0(0-22)	14.0 (12-16)	8.0 (4-18)	12.0 (10-14)
PDM%		50%	0%	66%	50%
Micronutrient					
M (Range)	16.0 (2-18)	10.0 (0-20)	12.0 (8-18)	8.0 (8-20)	3 (2-10)
PDM%		80%	71%	80%	100%
ASI: Placebo					
M (Range)	10.0 (2-38)	6.5 (3-59)	20.0 (10-47)	19.0 (3-45.0)	23.5 (5-42)
PDM%		63%	33%	33%	50%
Micronutrient					
M (Range)	17.0 (8-33)	15.0 (3-39)	10.0 (1-49)	13.0 (1-53)	7.5 (2-11)
PDM%		50%	71%	80%	100%
DEMF-P: Placebo					
M (Range)	16.8 (7-22)	15.0 (6-20)	15.0 (13-22)	12.0 (1-21)	9.5 (6-13)
PDM%		50%	33%	33%	0%
Micronutrient					
M (Range)	12.8 (4-20)	14.0 (7-20)	12.0 (8-16)	12.0 (5-14)	14.5 (12-24)
PDM%		70%	43%	20%	75%
DEMF-N: Placebo					
M (Range)	5.8 (0-18)	5.5 (0-17)	5.0 (3-9)	5.0 (3-11)	1.5 (0-3)
PDM%		50%	67%	67%	100%
Micronutrient					
M (Range)	4.3 (3-16)	6.0 (0-10)	5.0 (1-9)	9.0 (2-19)	0.5 (0-3)
PDM%		50%	29%	40%	100%

DASS = Depression Anxiety and Stress Scale-21, D (depression), A (anxiety), S (stress) subscales, ASI = Anxiety Sensitivity Index, DEMF = Diener and Emmons Mood Form- P (positive), N (negative) subscales.

DASS-21 scores. The micronutrient group had higher DASS-21 depression (DASS-D), anxiety (DASS-A), and stress (DASS-S) median scores at baseline compared to placebo. At each subsequent study waypoint there was no clear direction of change for depression median scores and PDM effect sizes, however anxiety and stress PDM effect sizes were larger in the micronutrient group compared to placebo, indicating more participants decreased below the baseline median (Table 3.8).

ASI scores. ASI median scores were lower in the placebo group compared to the micronutrient group at baseline and pre-quit. Conversely, post-quit the micronutrient group had consistently lower median ASI scores and larger effect sizes, i.e., more participants decreased ASI scores below the baseline median compared to the placebo group (Table 3.8).

DEMF scores. The placebo group had higher median DEMF-P scores at baseline, pre-quit, and at four-weeks post-quit compared to the micronutrient group, indicating a more positive mood. The median scores did not differ at week eight, and the micronutrient group had higher DEMF-P at 12-weeks. However, at the end of pre-quit and at 4 and 12-weeks post-quit the micronutrient group had larger PDM effect sizes for DEMF-P, i.e. more participants in the micronutrient group increased in positive mood above the baseline median compared to the placebo group (Table 3.8).

The placebo group had higher baseline DEMF-N median scores compared to the micronutrient group, and conversely, the placebo group's median DEMF-N score was lower at pre-quit, four and eight weeks post-quit with larger effect sizes (i.e., more participants in the placebo group decreased negative mood). At 12-weeks post-quit all participants in both groups had decreased in DEMF-N below baseline median scores (PDM = 100%; Table 3.8).

Compliance. All participants who did not drop-out of the 12-week RCT phase were compliant with capsule consumption.

Side effects. Only one participant in the placebo group dropped out of the study directly because of a putative side effect (a rash, see Figure 3.1); otherwise, no common treatment emergent side-effects were reported.

3.4 Discussion

This pilot study investigated the effect of a micronutrient treatment on withdrawal and related symptoms and concurrent success at quitting smoking, in a sample of nicotine-addicted adults. The purpose of the study was to explore a novel approach to helping those who desire to give up smoking to increase two essential aspects of quitting, *viz.,* making a quit attempt and remaining abstinent thereafter. The preliminary results from this pilot study are discussed for the remainder of this chapter.

Withdrawal symptoms were assessed by two measures. Our prediction that the intensity of withdrawal symptoms following quitting would be lower in the micronutrient group was supported, with congruent changes in both relevant measures. First, the median and range of withdrawal scores measured with the MNWS were consistently lower and the composite PDM ES larger in the micronutrient group compared to the placebo group, after metabolic adaptation to the capsules. Second, the micronutrient group had larger composite PDM ES for withdrawal and craving scores measured by the MPSS. This reduction of withdrawal symptoms and craving may have beneficially contributed to the lower relapse rates and higher quit success rates observed in the micronutrient group.

Micronutrient consumption was also associated with significantly more quit attempts and quit success at ≥three days relative to placebo, and participants taking

micronutrients had higher abstinence rates at 4, 8, and 12 weeks post-quit. The micronutrient group had a higher abstinence rate at four weeks than that reported by Quitline (Quitline NZ, 2013), and a higher abstinence rate at three months compared to standard Quitline care (including NRT), although this must be interpreted with caution due to the small sample/replications (Bullen et al., 2010; Walker et al., 2011; Walker et al., 2012), and Quit Victoria care (a programme that does not supply NRT) (Borland et al., 2003). Further, although the three month OR for the current study was lower than that reported in the use of NRT, bupropion, and varenicline (*viz*., 1.98, 2.13 and 3.75 respectively) (Wu et al., 2006), there are advantages of micronutrients relative to pharmacotherapy, including accessibility and lack of adverse side effects, and it is possible that micronutrients combined with pharmacotherapy (or NRT) may be even more effective than each treatment alone. These options should be explored by conducting a RCT with a larger sample that compares micronutrients and placebo alone and in combination with NRT.

Another beneficial effect of taking micronutrients was the lower DASS-21 anxiety and stress scores observed during the quit phase compared to the placebo group. Such lower scores of anxiety and stress in the micronutrient group may have contributed to the lower relapse rates, given that smokers often report that they smoke to ease feelings of anxiety and stress (Taylor et al., 2014). The micronutrient group also had reduced and trending lower ASI scores throughout the quit phase compared to the placebo group. This is consistent with research on the beneficial effects of micronutrient for anxiety and stress (Carroll et al., 2000; Kaplan, Rucklidge, Romijn, & Dolph, 2015; Rucklidge et al., 2012; Rucklidge et al., 2011; Schlebusch et al., 2000). Participants in the micronutrient group also increased levels of positive mood throughout the trial and the placebo group decreased their positive mood, supporting the finding of Kahler et al. (2015) that low positive affect is

associated with poor cessation outcomes and consistent with the beneficial effects of micronutrients to improve mood (Benton et al., 1995; Gariballa & Forster, 2007; Gosney et al., 2008; Harris et al., 2011; Kennedy et al., 2010; Lewis et al., 2013; Mech & Farah, 2016; Sarris et al., 2012).

This pilot study used a single-case research design (See Appendix I), a design that focuses on more heavily on individual differences in data. This allowed for a limited number of participants to undertake this new and exploratory research, an ethical and fair approach. Single-case research designs also require less professionals, resources, and funding. Single-case research designs are useful for developing hypotheses for future studies, and to examine cause and effect relationships (Rassafiani & Sahaf, 2010). Although group comparisons are not the primary goal of single-case research they are often employed in the analysis of single-case trials (Rassafiani & Sahaf, 2010). Therefore, the risk of type I or II error is increased due to the small sample size (or replications) in single-case designs, and between group results should be interpreted with caution. Single-case research may also not generalise to larger groups of participants or populations and lack external validity (as with the majority of clinical trials). This is particularly important in smoking cessation, given the prevalence of smokers.

The current study did not require participants to pay for the interventions, and approximate travel costs were covered with petrol vouchers. This strengthens the current study as participants are not paying for an intervention that has not demonstrated efficacy. This may also have limitations as the participants may not be able to pay for micronutrient treatment (or any smoking cessation treatments) in real-life settings. Furthermore, although the petrol vouchers were given as a way to cover travel costs only, they may have provided

additional incentives for participants in enrol in the study and attempt to quit smoking. This may mean that the reported quit rates are inflated as incentives are a known smoking cessation intervention (Cahill, Hartmann-Boyce, & Perera, 2015). However, it would be expected that this would be comparable between groups due to the randomised design.

A major limitation of this study was that randomization did not achieve comparable study groups with respect to baseline number of cigarettes/day and gender ratio. The unbalanced sex ratio may have had a number of consequences. First, the treatment group smoked fewer cigarettes/day on average in baseline compared to placebo, possibly because there were more males in the placebo group and men are known to smoke at a higher rate than women (Russell, Wilson, Taylor, & Baker, 1980). This may have led to a potential bias favouring the treatment group. Second, the micronutrient group was slightly more nicotine-dependent compared to the placebo group, also consistent with research that women are more addicted to nicotine and quit less easily than men (Bohadana et al., 2003; Collins et al., 2004; Smith et al., 2015; Welsch et al., 1999). It is possible that the higher level of nicotine dependence in the micronutrient group might have balanced the lower rate of smoking. In any event, those taking micronutrients were significantly more likely to make a successful quit attempt, and, compared to prior research, our findings are strengthened by double-blinded random allocation to treatment and the inclusion of placebo control. Another limitation was that randomisation did not achieve comparable baseline length in both groups, with the placebo group having longer baselines. This did not appear to effect the dropout rate with one person in each group dropping out in baseline. However it may have led to bias favouring the treatment group.

Dropout rate was higher than expected in the placebo group during the pre-quitting phase and larger than reported for similar RCTs conducted in NZ (Bullen et al., 2010; Walker et al., 2011; Walker et al., 2012). Despite the high dropout and relapse rate resulting in a smaller sample size, the study still had ≥three replications per study arm satisfying the standard advanced by Horner et al. (2005). Another limitation of the study was that verification of self-reported abstinence was not undertaken, owing to budget constraints. Abstinence rates may have therefore been over or under reported; however, there should not be a difference in the nature of reporting between groups.

Further direct and systematic replication studies (Haig, 2014) with larger samples in double-blind RCT designs are still needed to determine if micronutrients consistently enhance quitting and abstinence for all smokers. As noted above, treatment combinations of micronutrients, NRT and Quitline, with placebo control, should also be investigated to further examine whether micronutrients are efficacious as a smoking cessation treatment on their own or as an adjunct to other treatments.

3.5 Conclusion

This pilot study tentatively supports the use of micronutrients as a treatment to reduce withdrawal symptoms during smoking cessation and to promote quit attempts and quit success. Researchers and, more importantly, consumers, will continue to seek alternative treatments for smoking cessation because of the high prevalence of smoking, the adverse health effects it causes, and the high relapse rates and side effects of current smoking cessation interventions. Treatment options that reduce withdrawal symptoms and increase the likelihood of abstinence, especially those that are relatively inexpensive to

implement and that have few side effects deserve to be explored further. Based on the preliminary results micronutrient treatment is clearly worthy of continuing investigation.

Chapter 4. Study Two: Novel Mineral-Vitamin Treatment for Smoking Cessation: A Fully-Blinded Randomized Placebo-Controlled Trial

This chapter contains a modified version of the following published article: Reihana, P. K., Blampied, N.M, & Rucklidge, J.J. (2018). Novel Mineral-Vitamin Treatment for Reduction in Cigarette Smoking: A Fully-Blinded Randomized Placebo-controlled Trial. Nicotine & Tobacco Research. DOI: 10.1093/ntr/nty168. Published online September 2018.

The pilot study (study one) and Harrison et al. (2013) tentatively supported the use of a broad-spectrum micronutrient treatment to support smoking cessation, and this novel approach deserves further investigation. Study two was, therefore, undertaken as a fully-blind randomised placebo-controlled trial (RCT), with a sample size larger than that used in Study One to further investigate the role of broad-spectrum micronutrients (minerals and vitamins) in supporting quit attempts, reductions in cigarettes/day and withdrawal symptoms.

Aim

The aim of study two was to assess the efficacy and safety of micronutrients combined with a free phone and on-line counselling/support service (Quitline NZ) on quit rates, withdrawal symptoms, cigarettes/day, and associated psychological measures during a smoking cessation attempt.

4.1 Hypotheses

Based upon the results from the pilot study and the limited research evidence that nutritional supplements relieve withdrawal symptoms and assist with quitting smoking, I hypothesised:

1) *Quit attempts and rates will be higher in the micronutrient + Quitline group versus the placebo + Quitline group at each study waypoint after quit date.*
2) *Withdrawal symptoms and craving following a quit attempt will be smaller for the micronutrient + Quitline group versus the placebo + Quitline group.*
3) *Cigarettes/day after metabolic adaptation to the capsules will be less for the micronutrient + Quitline group versus the placebo + Quitline group.*
4) *Self-efficacy of quitting and positive mood will be higher, and negative mood will be lower in the micronutrient + Quitline group versus placebo + Quitline at each study waypoint after quit date.*
5) *Dropout rates will be lower in the micronutrient + Quitline group versus the placebo + Quitline group.*

4.2 Method

Design

In a fully-blinded, randomised, placebo-controlled RCT, participants who met criteria for current smoking and other inclusion criteria were randomly assigned to receive either placebo or micronutrient capsules for four weeks prior to quitting (pre-quit phase) and then attempted to quit smoking on a designated quit day. They were also enrolled with Quitline (pre-quit) and during the subsequent quit phase, they continued to consume their assigned capsules for 12 weeks.

Eligibility criteria

Eligibility for the trial required participants to be ≥18 years old, a current smoker of ≥three cigarettes/day for 12 months prior to baseline, have a desire to quit but not be engaged in other smoking cessation treatments (e.g., NRT), not taking psychiatric medication for at least four-weeks prior to starting the trial (combining the formula with psychiatric medications may result in complex interactions and should be monitored closely (Simpson et al., 2011; Popper, 2001)), not currently pregnant or breast feeding, able to consume up to 12 capsules a day, have no medical conditions that would effect participation in the trial, and able to attend hour long monthly meetings at the University. Non-psychiatric medications (e.g., oral contraceptives, antidiabetic drugs, and statins) were allowed case-by-case. Participants were excluded if they had taken part in study one due to risk of bias.

Recruitment

Participants were recruited between January 2015 and March 2016 via self-referral through advertising on posters around the University of Canterbury (Christchurch, NZ), local businesses, health centres, and a kaupapa Māori service, through advertising on the Mental Health and Nutrition Research Group's Facebook page, and in community newsletters. Advertising referred people to the study website to complete an online questionnaire that assessed eligibility, which 374 people completed. Eligible participants (*n*=118) kept appointments for an initial meeting at the University, others were referred to the Quitline website (www.quit.org.nz). Methods were improved throughout the study aimed at participant retention, including shorter visits at the University, participants did not have to join Quitline at the pre-quit meeting, staying in the study despite relapse, and the opportunity to try the active micronutrient at the end of the study, and

Study Interventions

At the completion of the one-to-two week baseline phase participants were given a four-week supply of placebo or micronutrient capsules, in plain containers with their name, participant number, date received, and date to start taking the capsules on the container. The micronutrient formula was supplied gratis by NutraTek Health Innovation Inc (Raymond, Alberta, Canada). It is a broad-spectrum micronutrient formula for oral administration, containing 17 minerals, 13 vitamins, four amino acids, and four antioxidants/botanicals (see Appendix II). The contents of the pills were independently tested by SupraNaturals in March 2016 and all quality control samples processed yielded acceptable results. All capsules were used within the expiry date, with no compromise in potency. The placebo formula (also supplied gratis by NutraTek Health Innovations Inc) included a small amount of riboflavin to mimic the urine colour associated with taking micronutrients (see Appendix II). The placebo has demonstrated effective masking in a recent study (Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018). Both capsules were identical in appearance. Participants titrated up to the full dose of 12 capsules/day (in routine use, NutraTek Health Innovation Inc recommends consuming between 12-15 capsules/day to enhance mental and physical well-being) over seven days, taking four capsules three times daily, with the last dose at least two hours before bed (as micronutrients can increase energy (Kennedy et al., 2010)), with food and plenty of water for the remainder of the trial. Based on previous clinical experience, expectation was that participants would typically experience a slow and gradual effect from the capsules within four weeks, therefore the pre-quit phase ensured that the metabolic effects of the micronutrients were established before quitting was attempted, and permitted any effects of the micronutrients or placebo alone on smoking and related

symptoms to be detected. This phase then functioned as a second baseline for the quit attempt.

A printed copy of the *Quit Book* was supplied to all participants and read through with the researcher before their quit attempt. The *Quit Book* (see; www.quit.org.nz) explains each step of Quitline's five step program; 1) Set a Quit date, 2) Know your reasons for quitting, 3) Know your triggers, 5) Stay Quit. Step 4, the use of NRT, was removed for this study. The first day of the quit phase was the participant's target quit day, a day where they attempted to stop smoking. Participants continued to consume 12 capsules/day during the quit phase, receiving a four-week supply at each study waypoint meeting (weeks 4, 8, and 12 post-quit day). The participant was instructed to contact Quitline if they had a cigarette (lapse), if they had a relapse they were instructed to contact Quitline and set a new quit date, no other support was provided. The quit phase intervention for this study was micronutrient + Quitline or placebo + Quitline for 12 weeks, however for ease to the reader the two groups are referred to as micronutrient and placebo. At the end of the quit phase participants came to the laboratory to complete study waypoint (baseline, pre-quit week-four, and 4, 8, and 12 weeks post quit) questionnaires, hand in left over capsules, discuss that Quitline can continue to support them, and receive a four-weeks supply of the micronutrient capsules, and advice on how to purchase the capsules commercially should they wish to continue taking them. Participants were informed as to their randomly allocated condition at the end of data analysis and the plain English summary of the results (with further results sent on request).

Randomisation, allocation, and blinding

A research assistant using www.randomization.com (using blocks of four) randomised the first 88 participants in a 1:1 ratio to micronutrient or placebo condition, and the next 19 male participants in were quasi-randomised 3:1 ratio (using blocks of four) to micronutrient or placebo condition. Researchers and participants were blind to the allocation of micronutrient or placebo status until data analysis was complete. There was no difference between the appearances of the capsules; the placebo contained riboflavin to mimic the change in urine colour associated with taking micronutrient capsules. A pharmacist received the randomisation sequence, and all capsules were pre-packaged by the pharmacist in plain containers and labelled with the participant numbers. A separate randomization sheet labelled with A and B groups (micronutrient or placebo) was kept by the research assistant and was given to the statistician for analysis of the primary outcome, and to the researchers for analysis of the secondary outcomes at the end of data collection.

Concomitant medication

Non-psychiatric medications (e.g., oral contraceptives, antidiabetic drugs, and statins) were allowed case-by-case.

Withdrawal criteria

Participants were able to withdraw voluntarily from the study or the primary investigator could discontinue a participant from the study. The primary investigator may discontinue or withdraw a participant from the study for the following reasons: pregnancy, an adverse event associated with the intervention, medical condition(s) or other situation(s) occur such that continued participation in the study would not be in the best interest of the participant, and if the participant meets exclusion criteria (either newly developed or not previously recognised). A participant is considered lost to follow-up if he or she fails to

return for a scheduled visit and is unable to be contacted by researchers (after three attempts on mobile, email, and phone call). If participants wanted to stop their participation they were asked to come in to the University to complete study way-point questionnaires. Any participants that excluded from the study were recommended to contact Quitline NZ for advice.

Baseline assessments

Meetings (approximately 45 minutes) with each individual participant were held at the University of Canterbury Mental Health and Nutrition Research laboratory in the Psychology Department. At the baseline meeting participants were given a full description of the study (Appendix VII), and had an opportunity to ask any questions before giving written consent (Appendix VI). At the end of consent participants used a computer in the laboratory to complete baseline questionnaires through Qualtrics. After the questionnaires were completed participants received instructions to complete the daily diary (Figure 4.1) every day for the next one to two weeks (the duration determined by their schedule of availability for their pre-quit meeting). This phase provided baseline assessments (discussed below) of cigarettes/day, withdrawal symptoms, and cigarette dependence.

Demographic and baseline variables. Demographic variables included sex, age, ethnicity, marital status, and combined household yearly income. Participants provided information on the age they first tried cigarettes, started regular smoking, previous quit attempts, and the quality of their diet. Participants completed a baseline questionnaire on previous and/or current mental illness(s), current medication(s), and any previous psychoactive medication(s).

Fagerstrom Test for Cigarette Dependence (FTCD). The FTCD is a six-item questionnaire that assessed baseline levels of cigarette dependence, with scores ranging from 0 (least dependent) to 10 (most dependent) (Fagerström, 2011). A score of six or higher is recognised as establishing cigarette dependence (Yeomans et al., 2011). Cronbach's alpha = 0.64 (Pomerleau & Rosecrans, 1989).

Daily diary. Participants completed a daily diary (Figure 4.1) during baseline. The daily diary was used to record the number of cigarettes/day (even a puff), consumption of alcohol (standard drinks/day), and MPSS withdrawal and craving scores. The core items of the MPSS consist of five single-item ratings of depressed mood, irritability, restlessness, hunger, and poor concentration (West & Hajek, 2004). All items are rated on a five-point scale from one (not at all) to five (extremely) with total scores ranging from 0 to 25. In addition to these five ratings the MPSS contains two six point sub-scales that rate time spent with the urge to smoke (i.e. craving) (Javitz et al., 2012) and the strength of the urges/craving. The MPSS only uses one item to assess each withdrawal symptom keeping the scale as brief as possible and suitable for a daily self-report diary. Cronbach's alpha = 0.78 (West & Hajek, 2004).

Date:

Please record the amount of cigarettes you inhale (even if it is just a puff it counts as one cigarette).

Please record if you have <u>any alcoholic beverages</u> at any time point (and how many standards you have - e.g. 2 standards can be marked with II)

Please show for each of the items how you have been feeling over the past <u>24 hours</u> (circle one number for each item).

	Not at all	Slightly	Somewhat	Very	Extremely
Depressed	1	2	3	4	5
Irritable	1	2	3	4	5
Restless	1	2	3	4	5
Hungry	1	2	3	4	5
Poor concentration	1	2	3	4	5

How much of the time have you felt the urge to smoke in the past 24 hours? (circle one number).

All the time	Almost all the time	A lot of the time	Some of the time	A little of the time	Not at all
5	4	3	2	1	0

How strong have the urges been? (circle one number).

	Extremely strong Very strong Strong Moderate Slight No urges 5 4 3 2 1 0

Figure 4.1. *Daily diary participants received to complete with cigarettes/day and standard drinks/day on the left-hand side and Mood and Physical Symptoms Scale on the right-hand side.*

Primary Outcome.

The primary outcome for the trial was continuous abstinence 12-weeks after the target quit day (day following the end of the pre-quit phase, ITT analysis), measured by self-report and biochemically confirmed (i.e, ≤ six parts per million (ppm) as recommended by Bedfont (www.bedfont.com) based on data from Jarvis, Belcher, Vesey, & Hutchison, 1986) by exhaled carbon monoxide (CO) using a Bedfont piCO^{+TM} Smokerlyzer$^{®}$, a portable device which measures breath CO levels (Benowitz et al., 2002; Kahler et al., 2015; Macdonald et al., 2004). Continuous abstinence was defined as 12-weeks abstinence with no relapse, and relapse was defined as returning to smoking for ≥ three consecutive days.

Secondary Outcomes

Participants self-reported and biochemically confirmed smoking status at the University meetings. They had the opportunity to complete questions ≤24 hours before their quit attempt, for shorter meeting times, otherwise measures were completed at University meeting.

Quit attempts, success, and rates. A quit attempt was counted if participants tried to quit smoking (≥24 hours) on their target quit day, and was scored as successful if they quit smoking for three or more subsequent days (if participants relapsed and made another quit attempt this was not counted as a quit attempt in the analysis). Continuous quit rates (abstinence with no relapse) versus relapse (defined as above) were counted at 4, 8, and 12 weeks post quit-day (day after end of pre-quit phase) based on self-report and exhaled CO.

Daily diary. Participants completed a daily diary (Figure 4.1) in the first and last week (week-four) of the pre-quit phase, weeks 1-4, 8 and 12 of the quit phase.

Minnesota Nicotine Withdrawal Scale - short form (MNWS). Participants rated eight withdrawal symptoms (i.e., craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite or weight gain, depression, and insomnia) on an ordinal scale from zero (not present) to four (severe) at each study waypoint. The sum of the eight scores gives an overall rating of withdrawal symptoms severity (range 0 to 32). The MNWS has been validated in multiple smoking cessation studies (Zvolensky et al., 2009). Cronbach's alpha >0.8 (Toll et al., 2007).

Wisconsin Smoking Withdrawal Scale (WSWS). The WSWS is a 28-item scale that measured withdrawal symptoms and severity at each study waypoint (Welsch et al., 1999; West et al., 2006). It includes seven reliable subscales of withdrawal symptoms: anger/irritability, anxiety, concentration, craving, hunger, sadness, and sleep/insomnia. The sum of four items rated from zero (strongly disagree) to four (strongly agree), gives an overall withdrawal score for each subscale (range 0-16). Cronbach's = 0.75-0.93 (Welsch et al., 1999).

Self-efficacy of quitting. Self-efficacy of quitting and remaining abstinent was completed at each study waypoint. The two six-item subscales measure confidence in ability to refrain from smoking when facing internal stimuli (e.g., feeling depressed) and external stimuli (e.g., being with smokers) with lower scores indicating more confidence (Etter, Bergman, Humair, & Perneger, 2000). Internal stimuli Cronbach's alpha= 0.95; external stimuli Cronbach's alpha= 0.94.

Depression Anxiety Stress Scale-21 (DASS-21). The DASS-21 is a 21-item questionnaire (a shortened version of the DASS-42) consisting of three self-report scales designed to

measure negative emotional states of depression, anxiety, and stress (Lovibond & Lovibond, 1995). Participants used a four-point severity scale to rate the extent to which they have experienced each state in the week prior to each study waypoint. Each of the three DASS-21 sub-scales contain seven items, and scores for depression, anxiety, and stress subscales were calculated by summing all the scores for relevant items and doubling the outcome to align with the DASS-42 scores (range 0-42). Cronbach's alpha scores = 0.88 for depression, 0.82 for anxiety, and 0.90 for stress (Henry & Crawford, 2005). The DASS-21 has clinical cut offs (greater than "mild") at 10, 8, and 15 for depression, anxiety, and stress respectively (Lovibond & Lovibond, 1995).

Diener and Emmons Mood Form (DEMF). The DEMF consists of nine items used to assess how participants were feeling at each study waypoint on a seven-point scale from zero (not at all) to six (extremely). The sum of four items gives a positive affect score (range 0-24) and the sum of the remaining five gives a negative affect score (range 0-30). Cronbach's alpha = 0.89 for the positive subscale and 0.84 for the negative scale (Diener & Emmons, 1985).

Alcohol Use Disorders Identification Test- Consumption (AUDIT-C). Participants completed the AUDIT-C at each study waypoint, it is a three-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (including abuse or dependence) (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). The AUDIT-C is a modified version of the 10 question AUDIT instrument. Each item has five answer choices with allotted points (range 0 - 4) and scores range from 0 to 12. A score of four or more for men and a score of three or more for women is considered positive and optimal for identifying heavy/hazardous drinking and alcohol use disorders. The higher the score the more likely

the participants drinking is affecting their safety. Sensitivity and specificity scores are presented in Table 4.1.

Table 4.1. *Sensitivity and specificity scores for identifying patients with heavy/hazardous drinking and/or Active-Diagnostic and Statistical Manual alcohol abuse or dependence for Alcohol Use Disorders Identification Test-Consumption.*

Score	Men	Women
≥3	Sens: 0.95 / Spec: 0.60	Sens: 0.66 / Spec: 0.94
≥4	Sens: 0.86 / Spec: 0.72	Sens: 0.48 / Spec: 0.99

Diet quality questionnaire (DQQ). The DQQ completed at baseline and eight weeks, was based on descriptions of a healthy eater by Baker, Little, and Brownell (2003) and adapted by Kuijer and Boyce (2014). A healthy eater eats in a balanced way, consumes three meals a day, doesn't eat too much junk food, eats moderate amounts, and stops eating when full. Total DQQ scores ranged from 9 to 47; a higher score indicates a healthier diet. Cronbach's alpha = 0.67 (Kuijer & Boyce, 2014).

Side effects. Participants were asked about presence/absence of side-effects potentially associated with the consumption of nutrients (e.g., headache, nausea, stomach aches, dry mouth) and to report any other possible effects/concerns. Any reported side effects were followed up and monitored by the researcher (PR). If any adverse effects were reported they would have been discussed with the consultant psychiatrist (Prof. Mulder) to determine whether further investigation was required. Prof. Rucklidge was consulted on all aspects of the project, and was aware of any foreseeable risks. The trial would of been terminated if serious adverse effects known to be caused by the nutrients occurred.

Capsule Compliance, Adherence, and Drop-out. Leftover capsules were counted at the end of each study waypoint. If a participant consumed ≥ 80% of their capsules they were counted as capsule compliant. Participants were classified as *dropped-out* if they advised that they wished to cease participation (withdrawal) or if they ceased responding to emails or texts (lost to follow-up). In the ITT (*n*=107) and full intervention analysis (*n* = 77), drop-outs were counted as still smoking. Adherence was determined at the end of intervention; those classified as adherent had continued to attend meetings and supply data, independent of whether or not they were also capsule compliant. The full intervention sample (*n* = 77) included those who received both the capsule and Quitline intervention, independent of their compliance/adherence. The per-protocol sample (maximum *n* = 65), included only those who completed the intervention and were both compliant and adherent.

Sample size

A sample size of 80 participants (40 in placebo and 40 in micronutrient) conferred more than 80% power, with two tailed α=0.05, to detect an abstinence rate at 12 weeks similar to that of study one's four week abstinence rate (53% versus 25%, micronutrient and placebo group respectively) with a large effect size. The four-week quit rate was used to calculate sample size, as it was predicted that this study would have lower rates of dropout because of planned improvements in methods directed at participant retention. The final sample size of participants who received either kind of capsule intervention and were included in the ITT analysis was 107 (Figure 4.2).

Statistical analysis

At completion of data collection for the first 88 participants (the first year of collection) an interim analysis of demographic data only was conducted by a research

assistant to investigate if the baseline characteristics were comparable across the two groups (in particular sex). This was conducted due to the significant differences in baseline data in Study one and to avoid the need for multiple subgroup analyses which can increase the chance false-positive and false-negative results due to chance or lack of power (Schulz & Grimes, 2005). An independent statistician blind to treatment conditions conducted the analysis of the primary outcome data. Three samples were separately analysed. These were (1) the ITT sample, which included all participants who received capsules at any point (*n*=107); (2) the full-intervention sample, which included those who received the micronutrient/placebo + Quitline (*n*=77) regardless of their degree of capsule compliance and adherence with study protocol following the quit date; and (3) the per-protocol sample (maximum *n* = 65), which included all those who were fully capsule compliant/adherent at each waypoint. Frequencies of the categorical variables of quit/not quit, dropped-out/continuing, and side-effects/no side effects at specified study waypoints were analysed using *chi*-squared ($\chi 2$) tests with odds ratios (OR) and 95% Confidence Intervals (95% CI) using IBM Statistics version 20. OR determines whether the probability of an event (or disease), for example quitting, is the same of differs across two groups. The range of OR is from O to infinity: A value of 1= no association with the specified event (that is, the event is equally likely in both groups); as the value of the OR increases or decreases away from 1, the association grows increasingly stronger. As proposed by Chen, Cohen, and Chen (2010) we interpreted OR ≤1.68 as small, OR ≤ 3.47 as medium, and ≤6.71 as a large treatment effect. All tests of statistical significance were two-tailed; exact *p*-values are reported, and no adjustments were made for multiple comparisons, consistent with recent best-practice recommendations (Armstrong, 2014; Nakagawa, 2004; Perneger, 1998). Further, as recommended by the American Statistical Association (Wasserstein & Lazar, 2016), and

Wilkinson and Task Force on Statistical Inference (Wilkinson, 1999) (and many others (Cumming, 2013; Gigerenzer, 2018; Gigerenzer & Marewski, 2015; Hubbard, 2004; Hubbard & Lindsay, 2008; Sedlmeier, 2009)) we report effect sizes (ES; Cohen's *d* and the Common Language ES, calculated using software by Lakens (2013)) and 95% CIs (calculated using Exploratory Software for Confidence Intervals; (Cumming, 2013)). Cohen's *d* was calculated using the pooled SD for between-subjects comparison and the average SD for within-subjects comparisons (Lakens, 2013). When the 95% CI on *d* does not cross zero this is interpreted as indicating that there is a reliable (significant) treatment effect, i.e., an effect that is not zero, with the minimum likely effect being at the lower (if *d* is positive) or upper (if negative) CI. Further, we interpreted *d* ≤0.3 as small and values ≥0.8 as large to very large effects (Sullivan & Feinn, 2012). The between-group CLES expresses the probability (as a %) that for any two individuals from the placebo group or treatment group, the treatment participant has a therapeutically better score than the control/placebo participant (Lakens, 2013), while the within-group CLES reports the probability that any randomly chosen participant has a therapeutically better score in the treatment phase relative to baseline and adjusted for the direction of the therapeutic effect on the particular measure. CLES % scores range from 0 (for between-group designs, no treatment participant has a better score than the placebo participants, and for within-group designs, no participants have a better score compared to t_1) to 100 (between-group: all treatment participants have a better score than the control participants; within-group: all participants have a better score than at t_1).

Primary outcome. The primary outcome measure defined *a priori* was continuous abstinence at 12 weeks post quit-day (day after pre-quit) for the ITT sample, with participants categorized as quit/not quit and quit rate compared between groups using $\chi 2$. Participants lost to follow-up (i.e., did not reply to texts, emails, and calls) were counted as

not quit and included in the analysis. The number needed to treat (NNT) for 1 person to achieve smoking abstinence above the placebo effect at 12 weeks with 95% CI was also calculated (Biswas, 2017). Consistencies of effects of subgroups (gender [men vs women], ethnicity [Māori vs non-Māori]) for the primary outcome were assessed using Cochran-Mantel-Haenszel tests.

Other outcomes. Means (*n*), standard deviations (*SD*), ranges and percentages (where appropriate) were calculated for baseline demographic characteristics, smoking history, and diet quality, history of mental illness, and psychoactive medication use, differences between groups were calculated using $\chi 2$ and *t*-tests.

Drop-out. Lost to follow up and withdrawal (drop-out) during each phase was compared using categorical outcome for participants who started the phase, and total drop-out was compared for those who received the capsule intervention (*n*=107). A Post hoc analysis was conducted to compare baseline measures of those dropped out and completers.

Quit success and quit rates. Frequency of quit attempts (≥24 hours continuous abstinence), and quit rates at 3 days (quit success), at weeks 4, 8, and 12 post quit-day were compared between groups by $\chi 2$. Participants were counted as still smoking if they were lost to follow-up (i.e., did not reply to texts, emails, and calls).

Withdrawal and mood symptoms. Visual analyses of individual change in withdrawal, self-efficacy of quitting, and mood scores was undertaken using modified Brinley plots (Blampied, 2017), as described for Study one.

For all measures the first plot compares baseline (t_1) to pre-quit (t_2), to observe any change in withdrawal or mood during the capsule only intervention. Thereafter, for the withdrawal scales (MNWS and WSWS) pre-quit scores are used as t_1 because participants

had attempted to cut-down on their cigarette smoking at this point and withdrawal symptoms may have been evident, subsequent study way-points are used as t_2. For all other psychological scales (quitting self-efficacy, DASS-21, and DEMF) baseline is used as t_1 for each of the plots and study way-points as t_2 to observe changes in these measures across study way-points. For each measure, the reliable change index (RCI) (Jacobson & Truax, 1991) as calculated in Study one, is displayed as two lines on each side of the 45-degree angle line. Only when a data point lies outside the RCI boundaries is it deemed reliable (i.e., larger than likely due to measurement error alone). The percentage of participants demonstrating positive reliable change (RC+) was calculated and is displayed on each plot. This effect size (ES) is a conservative outcome measure because it requires a shift in both the clinical direction and reliable change (Blampied, 2017). The mean of the data at t_1 and t_2 are displayed as a pair of lines at right angles, such that the cross-point indicates the co-ordinates of the respective means and the length of the lines display the 95% CI's of the means. As mentioned, if there is no change in mean scores between t_1 and t_2 the cross-point will lie on the 45 degree line; alternatively the mean therapy effect is shown by vertical displacement of the mean cross-point above or below the line (Blampied, 2017). The magnitude of this displacement is proportional to Cohen's *d.* For measures with clinical cut offs, these are displayed on the plots as horizontal and vertical lines; an arrow on the vertical line indicates the direction of therapeutic change. For plots where there is no clinical cut off, an arrow at the side of the plot indicates the direction of clinically beneficial change.

Cigarettes/day and MPSS symptoms. Within group changes in cigarettes/day and MPSS withdrawal scores were averaged for each week of data collection (baseline, pre-quit week 1, pre-quit week 4, quit week 1, 2, 3, 4, 8 and 12) and displayed on a spaghetti plot. A spaghetti plot graphs an individual's value for a repeated measure (Y axis) versus time (X

axis) and connects the dots chronologically. Within group Cohen's *d* ES with 95% CIs and the CLES were calculated for t_1 versus t_2 comparisons. Baseline was used as t_1 for cigarettes/day plots, but quit week 1 was used as t_1 for MPSS plots as participants were at their highest withdrawal at this point. Between group effect sizes (Cohen's *d* ES and CLES) were also calculated for each time point. Linear regression was used to predict the direction of change of cigarettes/day and MPSS scores, for both before and after quit day.

DQQ and AUDIT-C. One-way ANCOVAs were conducted to compare the effectiveness of the placebo or micronutrient treatments on change in diet quality (DQQ) and AUDIT-C scores whilst controlling for baseline scores. Unpaired *t*-tests were conducted to compare baseline and eight week post-quit scores within groups.

Data management

All study data was entered by the writer and contained in locked storage systems; either a password protected computer system at the University of Canterbury or on a web-based data collection system (www.canterbury.qualtrics.com) for electronic documents, while hard copies were kept in secure filing cabinets at the university.

Ethical Considerations.

The study was approved by the University of Canterbury Ethics Committee (HEC 2015/11) and prospectively registered with the Australian and New Zealand Clinical Trial Registry (Trial ID: ACTRN12615000201572).

4.3 Results

Recruitment went from the 08/03/2015 until the 29/02/2016. The last face-to-face interview with a participant was on the 30/7/2016 and data were locked as of 20/08/2016. An interim analysis showed that the micronutrient group had significantly fewer men than the placebo group (18 versus 9, χ^2 (1, n=88) = 4.02, p=0.04), therefore, the sample size was increased by 19 men randomized in a 3:1 (micronutrient: placebo) ratio. As shown in Figure 4.2, from 374 self-referrals, 118 adults were deemed eligible, gave informed consent and started baseline. Of these, 107 were randomized to either the active treatment (micronutrients; n=57) or the placebo (n=50) for the pre-quit phase (ITT sample) and 77 (full-intervention sample) participants received the micronutrient/placebo + Quitline intervention. Participant blinding was successful with only 48% correctly identifying their condition.

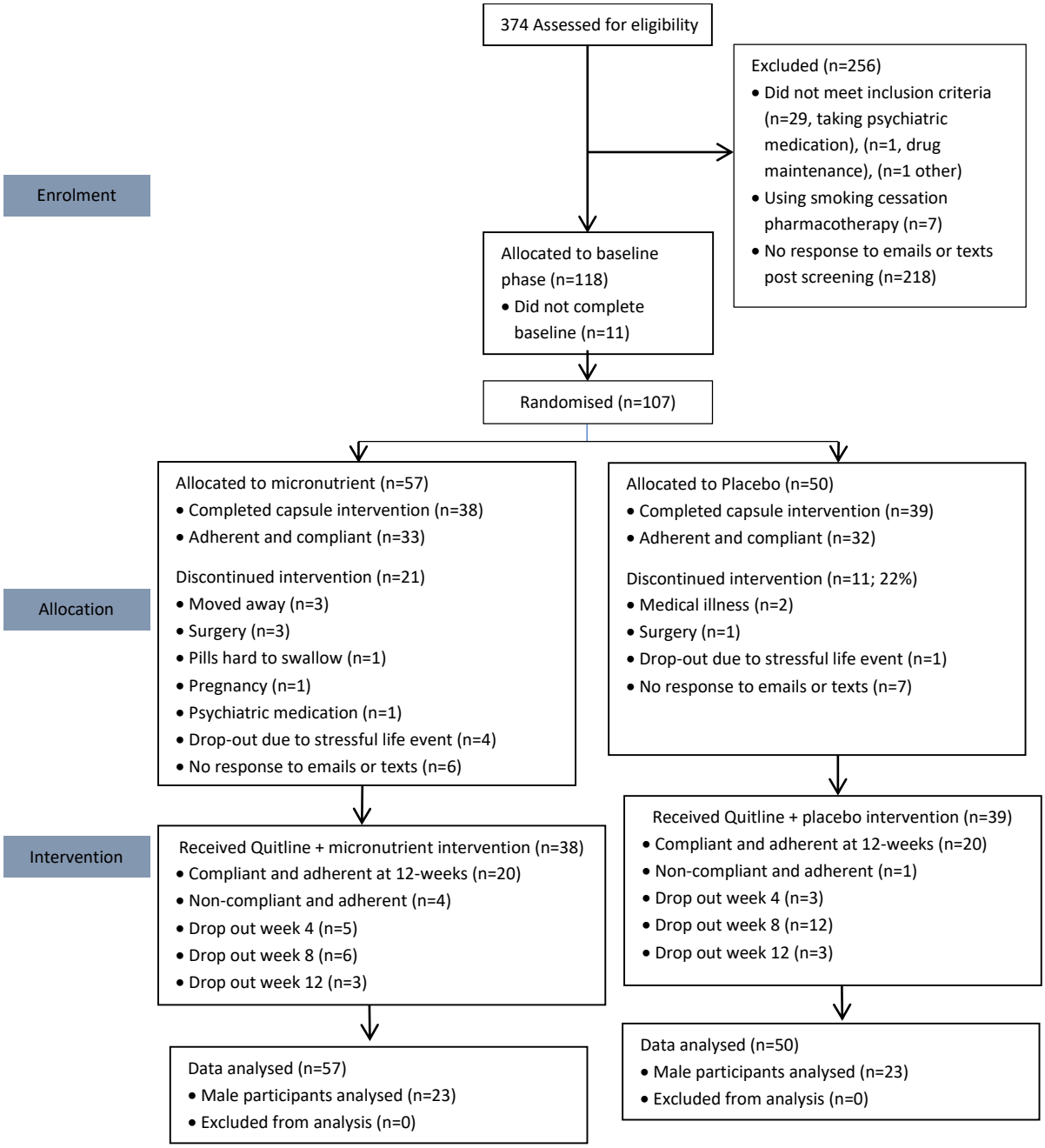

Figure 4.2. *Consolidated Standards of Reporting Trials (CONSORT) diagram.*

Demographic and baseline Information

Ages ranged from 18.8 to 62.2 years and the majority of the sample were NZ European (65%), followed by NZ Māori (22%). In the event that participants reported two ethnicities, ethnicity was randomised according to NZ Statistics Guidelines, under this system, Māori had priority coding, followed by Pacific, then Asian, then other ethnic

groups, with people of only European ethnicities last. Randomization achieved comparable study groups, with no substantive differences between the groups on demographic variables (Table 4.2).

Table 4.2. *Demographic characteristics at baseline for the Intention-to-treat sample (n=107).*

	Micronutrient (*n*=57)	Placebo (*n*=50)	Total (*n*=107)
Gender			
Male, n (%)	23 (40%)	23 (46%)	46 (43%)
Average age (years) (SD)	35.7 (10.9)	36.6 (10.1)	36.1 (10.5)
Range	18.8-62.2	20.8-59.0	18.8-62.2
Ethnic origin			
NZ European, *n* (%)	38 (67%)	31 (62%)	69 (65%)
NZ Māori *n* (%)	13 (23%)	12 (24%)	24 (22%)
Samoan *n* (%)	1 (2%)	2 (4%)	3 (3%)
Chinese *n* (%)	0 (0%)	2 (4%)	2 (2%)
Other, *n* (%)	5 (9%)	4 (8%)	9 (8%)
Marital Status			
Married	14 (25%)	14 (28%)	28 (26%)
De-Facto	16 (28%)	9 (18%)	25 (23%)
Single	24 (42%)	20 (40%)	44 (41%)
Divorced	3 (5%)	6 (12%)	9 (8%)
Separated	0 (0%)	1 (20%)	1 (1%)
Household Income[a]			
<$20,000	10 (18%)	9 (18%)	14 (13%)
$20,000-$40,000	9 (16%)	6 (12%)	15 (14%)
$40,000-$60,000	16 (28%)	14 (28%)	30 (28%)
$60,000-$80,000	7 (12%)	8 (16%)	15 (14%)
$80,000 - $100,000	5 (9%)	5 (10%)	10 (9%)
>$100,000	9 (16%)	9 (18%)	18 (17%)
Unknown	4 (7%)	1 (2%)	5 (5%)

[a]NZ dollars; the poverty line would roughly be <NZ$40,000.

Average baseline consumption (cigarettes/day) was 12.4 (range 3.9-42.8) and 14.0 (range 3.4-25.9) in the micronutrient and placebo groups respectively. The average FTCD score was 4.5 (range 0-9) indicating low to moderate dependence on nicotine. On average, participants started regular smoking at 16.8 years (range 11.0-48.0 years), had attempted to quit 3.3 times (range 0-10). More participants in the micronutrient group had ever used NRT

in the past compared to the placebo group (35.1% vs 12.0%, *p*=0.005). Overall, 21.5% had ever used varenicline tartrate and 12.1% had used bupropion hydrochloride (Table 1). Participants reported average consumption of 1.2 standard (std) alcoholic drinks/day and negligible use of illicit substances (<once/day) during baseline. Dietary patterns were comparable across both groups. More participants in the micronutrient group (39%) had previously taken psychoactive medication for the treatment of mental illness compared to the placebo group (18%; *p*=0.02; Table 4.3).

Table 4.3. *Baseline smoking information, substance use, diet quality, previous/current mental illness and history of psychoactive medication use for Intent-to-treat sample (n=107)*.

	Micronutrient (*n*=57)	Placebo (*n*=50)	Total (*n*=107)
Smoking Information			
Cigarettes/day in baseline, mean (SD)	12.4 (6.9)	14.0 (5.6)	13.2 (6.33)
Range	3.9-42.8	3.4-25.9	3.4-42.8
Age (years) first puffed cigarette, mean (SD)	14.7 (3.8)	14.6 (2.4)	14.6 (3.2)
Range	7.0-27.0	9.0-22.0	7.0-27.0
Age (years) started regular smoking, mean (SD)	16.9 (3.6)	16.6 (5.2)	16.8 (4.4)
Range	11.0-27.0	12.0-48.0	11.0-48.0
Previous quit attempts, mean (SD)	3.6 (2.3)	3.0 (1.9)	3.3 (2.2)
Range	0-10	0-10	0-10
FTCD Score, mean (SD)	4.4 (2.2)	4.6 (2.0)	4.5 (2.1)
Range	0-9	0-9	0-9
Previous use of:			
NRT, n (%)	20 (35%)*	6 (12%)*	26 (24%)
Champix, n (%)	9 (16%)	14 (28%)	23 (22%)
Zyban, n (%)	7 (12%)	6 (12%)	13 (12%)
Std drinks/day baseline, mean (SD)	1.2 (1.2)	1.3 (1.5)	1.2 (1.3)
Range	0-5	0-5	0-5
Days/week illicit substance use baseline, mean (SD)	0.3 (1.1)	0.5 (1.6)	0.4 (1.3)
Range	0-7	0-6	0-7
Diet Questionnaire, mean (SD)	29.5 (6.1)	28.4 (5.2)	29.0 (5.7)
Range	16-47	15-40	15-47
Previous and/or current mental illness, n (%)	21 (37%)	13 (26%)	34 (32%)
Psychoactive medication history, n (%)	22 (39%)*	9 (18%)*	31 (30%)

*FTCD =Fagerstrom Test for Cigarette Dependence; score range 0-10, ≥6 = dependence, ≥7 high dependence, NRT=Nicotine Replacement Therapy, *significant difference between groups (p≤0.05)*

Drop-out

Drop-out rates (withdrawal and lost to follow-up) are shown in Table 4.4; despite methodological improvements relative to Study one, these were somewhat high for both withdrawal and lost to follow-up. During the pre-quit phase significantly (p<0.05) more participants in the micronutrient withdrew from the study compared to the placebo group (26% versus 10%). However at all other study way-points drop-out was much the same for

the micronutrient and placebo groups. Post hoc comparisons showed that at baseline, those who dropped out or smoked more cigarettes (14.5 versus 11.5 cigarettes/day; *p*=0.01), started regular smoking at a younger age (16.0 versus 17.9; *p*=0.02), had higher FTCD scores (5.0 versus 3.6; *p*=0.01), and lower diet quality scores (27.8 versus 30.4; *p*=0.01) relative to completers (Table 4.5).

Table 4.4. *Number (n) and percentage (%) of participants who withdraw or were lost to follow-up at each study waypoint, with sample size at the start of each phase for micronutrient (mn) and placebo (pl) groups.*

Study waypoint *(sample size at start of phase)*	Micronutrient	Placebo	Odds Ratio	95% CI	Chi squared
	n (%)	*n* (%)			
Pre-quit					
Withdrawal	15	5	3.21	1.07-9.61	χ^2 (1, *n*= 107) = 4.65, *p*=0.03
Lost to follow-up *(mn=57, pl=50)*	6	7	0.70	0.23-2.31	χ^2 (1, *n*= 107) = 0.30, *p*=0.58
Week 4					
Withdrawal	1	1			
Lost to follow-up *(mn=36, pl = 39)*	4	2			
Week 8					
Withdrawal	2	5			
Lost to follow-up *(mn=31, pl=36)*	4	7			
12 week					
Withdrawal	2	2			
Lost to follow-up *(mn=25, pl=24)*	1	1			
Total Withdrawal	20 (35%)	13 (26%)	1.54	0.69-3.54	χ^2 (1, *n*= 107) = 1.03, *p*=0.30
Total Lost to follow-up	15 (26%)	17 (34%)	0.69	0.30-1.59	χ^2 (1, *n*= 107) = 0.75, *p*=0.39
Total Drop-out *(mn=57, pl=50)*	35 (61%)	29 (58%)	1.15	0.53-2.50	χ^2 (1, *n*= 107) = 0.72, *p*=0.84

Table 4.5. *Differences in baseline characteristics for participants who dropped out or were lost to follow-up at any study waypoint (DO) compared to those who completed the study.*

	DO (*n*=64)	Completer (*n*=43)
Gender		
Male, *n* (%)	29 (45.3%)	17 (39.5%)
Age (years), mean (SD)	35.4 (10.0)	37.2 (11.3)
Range	20.0-62.2	18.8-59.3
Ethnic origin		
NZ European, n (%)	40 (46.9%)	29 (67.4%)
NZ Māori, *n* (%)	16 (25.0%)	8 (18.6%)
Samoan, *n* (%)	2 (3.1%)	1 (2.3%)
Chinese n (%)	0 (0%)	2 (4.7%)
Other, n (%)	6 (9.4%)	3 (7.0%)
Marital Status		
With Partner	34 (53.1%)	19 (44.2%)
Without Partner	30 (46.9%)	24 (55.8%)
Income		
<$20,000	8 (12.5%)	6 (14.0%)
$20,000-$40,000	9 (14.1%)	6 (14.0%)
$40,000-$60,000	18 (28.1%)	12 (18.8%)
$60,000-$80,000	9 (14.1%)	6 (14.0%)
$60,000 - $80,000	7 (11.0%)	3 (7.0%)
>$100,000	8 (12.5%)	10 (23.3%)
Cigarettes/day baseline, mean (SD)	14.5 (7.0)**	11.5 (4.9)**
Range	5.0-42.8	3.4-25.2
Age (years) first puffed cigarette, mean (SD)	14.2 (3.0)	15.1 (3.4)
Range	7.0-23.0	10.0-27.0
Age (years) started regular smoking, mean (SD)	16.0 (3.0)*	17.9 (5.8)*
Range	11.0-27.0	12.0-48.0
Previous quit attempts mean (SD)	3.3 (2.1)	3.3 (2.3)
Range	1.0-10.0	0.0-10.0
Previous use of smoking cessation pharmacotherapy	33 (51.6%)	29 (67.4%)
FTCD Score, mean (SD)	5.0 (2.1)**	3.6 (1.8)**
Range	1.0-9.0	0.0-7.0
Std drinks/day in baseline, mean (SD)	1.2 (1.3)	1.3 (1.4)
Range	0.0-4.8	0.0-5.2
Days/week used illicit substance in baseline, mean (SD)	0.2 (0.9)	0.7 (1.7)
Range	0.0-6.0	0.0-7.0
Diet Questionnaire, mean (SD)	27.8 (6.3)**	30.4 (4.5)**
Range	15.0-47.0	22.0-43.0
Previous and/or current mental illness, *n* (%)	18 (28.1%)	16 (37.2%)
Previous psychoactive medication, *n* (%)	22 (34.4%)	9 (20.9%)

*FTCD = Fagerstrom Test of Cigarette Dependence, * Significant difference between groups (p≤0.05), **(p≤0.01)*

Primary outcome

All self-reported quitters biochemically confirmed abstinence with ≤5 ppm. At 12 weeks (Table 4.6) the ITT quit status was 28% (micronutrient group) versus 18% (placebo group), a small positive effect in favour of micronutrients (OR=1.78, 95% CI [0.71, 4.48]), but estimated with low precision/high uncertainty. NNT = 10 (95% CI [-5.72, 25.86]), consistent with a small, additional treatment effect in the presence of a large placebo effect.

Table 4.6. *Comparison of quit attempts and quit successes at each follow-up between micronutrient and placebo groups for the Intent-to-treat sample (n=107).*

	Micronutrient (*n*=57)	Placebo (*n*=50)	Odds Ratio	95% CI	Chi squared
Quit Attempt	36 (63%)	35 (70%)	0.73	0.33-1.65	χ^2 (1, *n*= 107) = 0.56, *p*=0.46
Quit Success (≥3 days)	31 (54%)	28 (56%)	0.94	0.44-2.01	χ^2 (1, *n*= 107) = 0.03, *p*=0.87
4 Week Quit Rate	25 (44%)	16 (32%)	1.66	0.75-3.66	χ^2 (1, *n*= 107) = 1.59, *p*=0.20
8 Week Quit Rate	18 (32%)	11 (22%)	1.64	0.68-3.91	χ^2 (1, *n*= 107) = 1.24, *p*=0.27
Primary Outcome					
12 Week Quit Rate	16 (28%)	9 (18%)	1.78	0.71-4.48	χ^2 (1, *n*= 107) = 1.51, *p*=0.22

Full Intervention analysis

With drop-outs during the pre-quit phase excluded, this analysis (Table 4.7) showed that almost all participants successfully made a quit attempt. The micronutrient group showed higher quit rates at all subsequent waypoints, especially at week 4 (66% vs 41%; OR = 2.76, 95% CI [1.10, 6.97]).

Table 4.7. *Comparison of quit attempts, quit success, and continuous quit rates at follow-up between micronutrient and placebo groups for the full-intervention sample (n=77).*

Study waypoint	Micronutrient (*n*=38) *n* (%)	Placebo (*n*=39) *n* (%)	Odds Ratio	95% CI	Chi squared
Quit Attempt	36 (95%)	35 (90%)	2.06	0.35-11.96	χ^2 (1, *n*= 77) = 0.69, *p*=0.42
Quit Success	31 (82%)	28 (72%)	1.74	0.59-5.11	χ^2 (1, *n*= 77) = 1.03, *p*=0.31
4 Week Quit Rate	25 (66%)	16 (41%)	2.76	1.10-6.97	χ^2 (1, *n*= 77) = 4.74, *p*=0.03
8 Week Quit Rate	18 (47%)	11(28%)	2.29	0.89-5.89	χ^2 (1, *n*= 77) = 3.01, *p*=0.08
12 Week Quit Rate	16 (42%)	9 (23%)	2.44	0.91-6.49	χ^2 (1, *n*= 77) = 3.18, *p*=0.08

mn= micronutrient group sample size, pl= placebo sample size.

Per-protocol analysis

This analysis excluded both drop-outs and the non-compliant/non-adherent at each waypoint. Again, the majority made a quit attempt, and those taking micronutrients were somewhat more successful (Table 4.8). Those taking micronutrients had a higher quit rate at each waypoint, especially weeks 4 (83% vs 57%; OR = 3.60, 95% CI [1.06, 12.20]) and 8 (81% vs 50%; OR= 4.25, 95% CI [1.08-16.77]), with OR indicative of a medium treatment effect.

Table 4.8. *Per-protocol sample analyses for quit attempts, success, and continuous abstinence at each study waypoint with sample size at the start of the study waypoint.*

Study waypoint *(sample size)*	Micronutrient	Placebo	Odds Ratio	95% CI	Chi squared
	n (%)	n (%)			
Quit Attempt *(mn=33, pl=32)*	32 (97%)	30 (94%)	1.03	0.52-2.07	χ^2 (1, *n=65)* = 0.38, *p*=0.54
Quit Success *(mn=33, pl = 32)*	29 (88%)	25 (78%)	2.13	0.18-24.76	χ^2 (1, *n=66)* = 1.10, *p*=0.21
4 Week Quit Rate *(mn=29, pl=28)*	24 (83%)	16 (57%)	3.60	1.06-12.20	χ^2 (1, *n*= 57) = 4.47, *p*=0.04
8 Week Quit Rate *(mn=21, pl=22)*	17 (81%)	11 (50%)	4.25	1.08-16.77	χ^2 (1, *n*= 43) = 4.53, *p*=0.03
12 Week Quit Rate *(mn=20, pl=20)*	14 (70%)	9 (45%)	2.59	0.70-9.64	χ^2 (1, *n= 40*) = 2.06, *p*=0.11

mn=micronutrient group sample size, pl= placebo group sample size.

Subgroup analysis.

The Cochran-Mantel-Haenszel test was used to analyse any difference in the primary outcome for subgroups (gender [male versus female], ethnicity [Māori versus Non-Māori]). The results showed no significant differences (p>0.05) in the primary outcome (continuous abstinence at 12-weeks) for male versus female (Cochran Q(1)=1.7, p=0.12) , or Māori versus Non-Māori (Cochran Q(1)=1.5, p=0.23).

Other outcomes

Quit attempts, success, and rates

ITT analyses showed similar quit attempts and success for micronutrient and placebo groups. The placebo group made more quit attempts and was more successful at ≥three days. ITT analyses also showed small differences in quit rates in favour of micronutrients, with OR >1. The differences in quit attempts, success, and rates were again estimated with low precision (Table 4.6).

Quit vs not-quit at 12-weeks

Baseline measures were compared for each group for those participants with and without 12-week continuous abstinence (the primary outcome) using $\chi 2$ and t-test analyses (Table 4.9). There was a significant difference (p=0.04) between quitters and non-quitters for age they first started regular smoking in the micronutrient group. All other comparisons between quitters and non-quitters were not significantly different.

Table 4.9. *Baseline measures, smoking information, of the participants who achieved continuous abstinence at 12-weeks in each group compared to those who did not achieve continuous abstinence.*

	Micronutrient Group Quit (*n*=16)	Micronutrient Non-Quit (*n*=41)	Placebo Quit (*n*=9)	Placebo Non-Quit (*n*=41)
Gender				
Male, *n* (%)	7 (44.0%)	16 (39.0%)	6 (67.0%)	17 (41.5%)
Age (years), mean (SD)	34.8 (11.1)	36.0 (11.0)	38.8 (11.4)	36.1 (9.9)
Range	18.8-59.3	20.0-62.2	22.4 - 54.3	20.8-59.0
Ethnic origin,				
NZ European, n (%)	12 (75%)	26 (63.4%)	5 (56%)	26 (63.4%)
NZ Māori, *n* (%)	3 (19%)	10 (24.4%)	1(11%)	11 (26.8%)
Samoan, *n* (%)	0 (0%)	1 (2.4%)	0 (0%)	2 (4.9%)
Chinese n (%)	0 (0%)	0 (0.0%)	1 (11%)	1 (2.4%)
Other, n (%)	1 (6%)	4 (9.8%)	2 (22%)	1 (2.4%)
Marital Status				
With Partner*	6 (38%)	24 (58.5%)	6 (67%)	17 (41.5%)
Without Partner**	10 (63%)	17 (41.5%)	3 (33%)	24 (58.5%)
Income				
<$20,000	1 (6%)	10 (24.4%)	2 (22%)	6 (14.6%)
$20,000-$40,000	1 (6%)	8 (19.5%)	0 (0%)	6 (14.6%)
$40,000-$60,000	8 (50%)	8 (19.5%)	0 (0%)	14 (34.1%)
$60,000-$80,000	2 (13%)	5 (12.2%)	2 (22%)	6 (14.6%)
$60,000 - $80,000	1 (6%)	4 (9.8%)	1 (11%)	4 (9.8%)
>$100,000	3 (19%)	6 (14.6%)	4 (44%)	5 (12.2%)
Cigarettes/day baseline, mean (SD)	9.6 (4.4)	13.7 (4.4)	11.9 (4.8)	14.5 (5.7)
Range	3.9-19.5	5.2-42.8	6.5-20.9	3.4-25.9
Age (years) first puffed cigarette, mean (SD)	16.1 (3.6)	14.1 (3.7)	14.4 (1.8)	14.6 (2.5)
Range	11.0-25.0	7.0-27.0	11.0-16.0	9.0-22.0
Age (years) started regular smoking, mean (SD)	18.5 (3.2)***	16.3 (3.6)***	16.0 (2.1)	16.7 (5.6)
Range	13.0-26.0	11.0-27.0	13.0-20.0	12.0-48.0
Previous quit attempts, mean (SD)	2.8 (1.8)	3.9 (2.5)	2.6 (1.9)	3.0 (1.9)
Range	0.0-7.0	1.0-10.0	0.0-5.0	1.0-10.0
Previous use of smoking cessation pharmacotherapy	5 (31%)	18 (43.9%)	5 (56%)	15 (36.6%)
FTCD Score, mean (SD)	3.0 (2.0)	4.9 (2.1)	3.8 (1.3)	4.7 (2.1)
Range	0.0-6.0	1.0-9.0	2.0-6.0	0.5-9.0
Std drinks/day in baseline, mean (SD)	0.9 (0.7)	1.2 (1.2)	2.0 (1.7)	1.0 (1.3)
Range	0.0-1.8	0.0-4.8	0.3-5.2	0.0-4.8
Days/week used illicit substance in baseline, mean (SD)	0.9 (2.2)	0.1 (0.2)	0.9 (2.3)	0.3 (1.1)
Range	0.0-7.0	0.0-1.0	0.0-6.0	0.0-6.0
Diet Questionnaire, mean (SD)	31.0 (5.1)	28.7 (6.5)	30.9 (3.6)	27.8 (5.4)
Range	19.5-23.5	16.0-47.0	24.0-35.0	15.0-40.0
Previous and/or current mental illness, *n* (%)	8 (50.0%)	13 (31.7%)	2 (22.2%)	11 (26.8%)
Previous psychoactive medication, *n* (%)	6 (37.5%)	16 (39.0%)	1 (11.1%)	8 (19.5%)

*FTCD =Fagerstrom Test for Cigarette Dependence; score range 0-10, ≥6 = dependence, ≥7 high dependence *with partner includes married, de facto relationship **without single, divorced, or widow, *** p<0.05*

Withdrawal Measures

Modified Brinley plots

Modified Brinley plots were used to examine individual change over study phases in MNWS, WSWS, self-efficacy of quitting, DASS-21, and DEMF scores (Figure 4.3-4.17). The bottom three plots for the withdrawal measures (MNWS and WSWS) compare pre-quit week four (t_1) scores to post-quit follow-up score (t_2; 4, 8, and 12-weeks post-quit). Pre-quit week-four scores are used as baseline as Quitline suggests participants cut down on cigarettes/day before their quit attempt, therefore if participants followed this suggestion some withdrawal symptoms would be evident. For the mood measures (quitting self-efficacy, DASS-21 and DEMF) each figure compares baseline (t_1) to post-quit follow-up scores (t_2). Cohen's *d* ES, with 95% CI and CLES are displayed on each plot for t_1 versus t_2.

Withdrawal measures

Changes in individual MNWS scores are displayed in Figure 4.3 for the micronutrient and placebo groups. Both groups decreased their mean withdrawal scores (as shown by the horizontal line on the cross) as the quit phase progressed. The micronutrient group had more participants decrease in MNWS scores pre-quit, with the mean MNWS score decreasing when compared to baseline. Cohen's *d* ES was large and significant, *d*=0.80; 95% *CI* [-1.2, -0.3]. Conversely the placebo had more participants decrease post-quit; however Cohen's *d* ES was not significant.

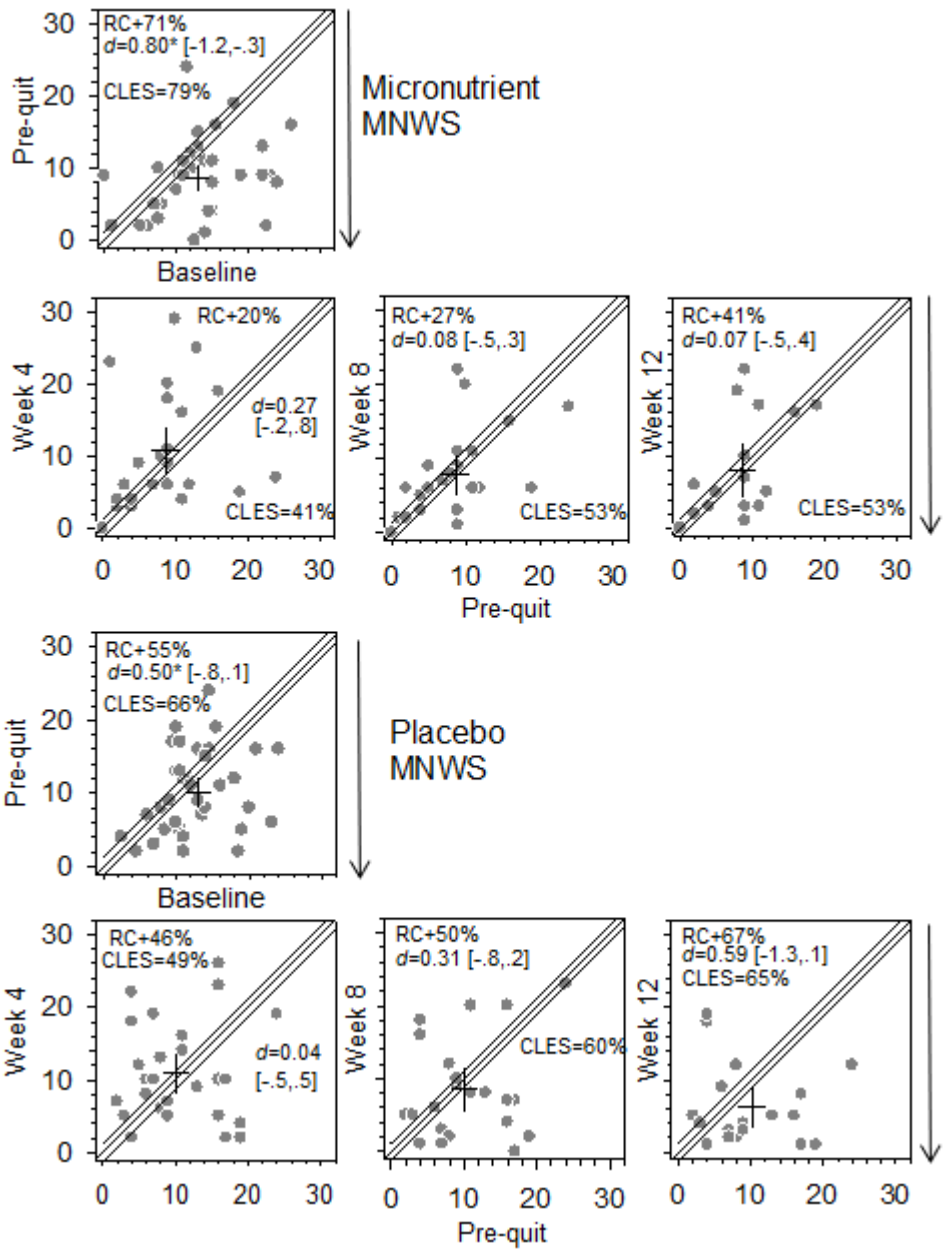

Figure 4.3. *Modified Brinley plots displaying change in participant rated Minnesota Nicotine Withdrawal Scale scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Figure 4.4 shows individual changes in WSWS irritability at each study waypoint. More participants in the micronutrient group showed decreases in irritability scores at each follow-up when compared to the placebo group, as shown by larger RC+ percentages and CLES. At 12 weeks post-quit, irritability scores significantly decreased in the micronutrient

group when compared to pre-quit, Cohen's *d* ES is large and significant, *d*=0.93 95% CI [-1.7,-0.2].

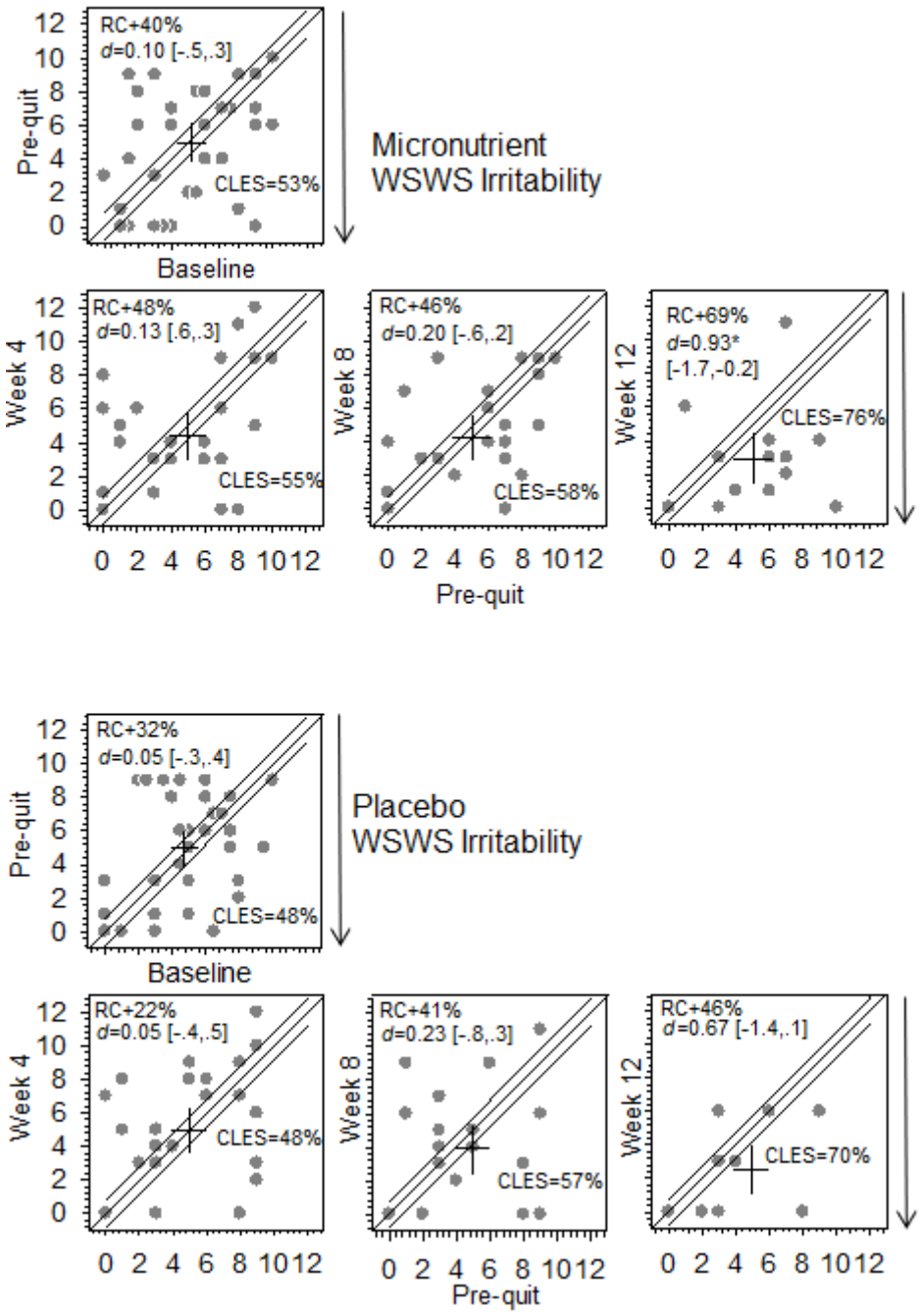

Figure 4.4. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS)- irritability scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentage, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Figure 4.5 shows that the micronutrient group had more participants decrease in WSWS anxiety scores pre-quit, as supported by larger RC+ and CLES. Post-quit the micronutrient and placebo groups showed a decreasing trend in anxiety at each study waypoint (Figure 4.5). The placebo group had more participants decrease in anxiety scores post-quit, as shown by larger RC+ percentages and CLES (Figure 4.5).

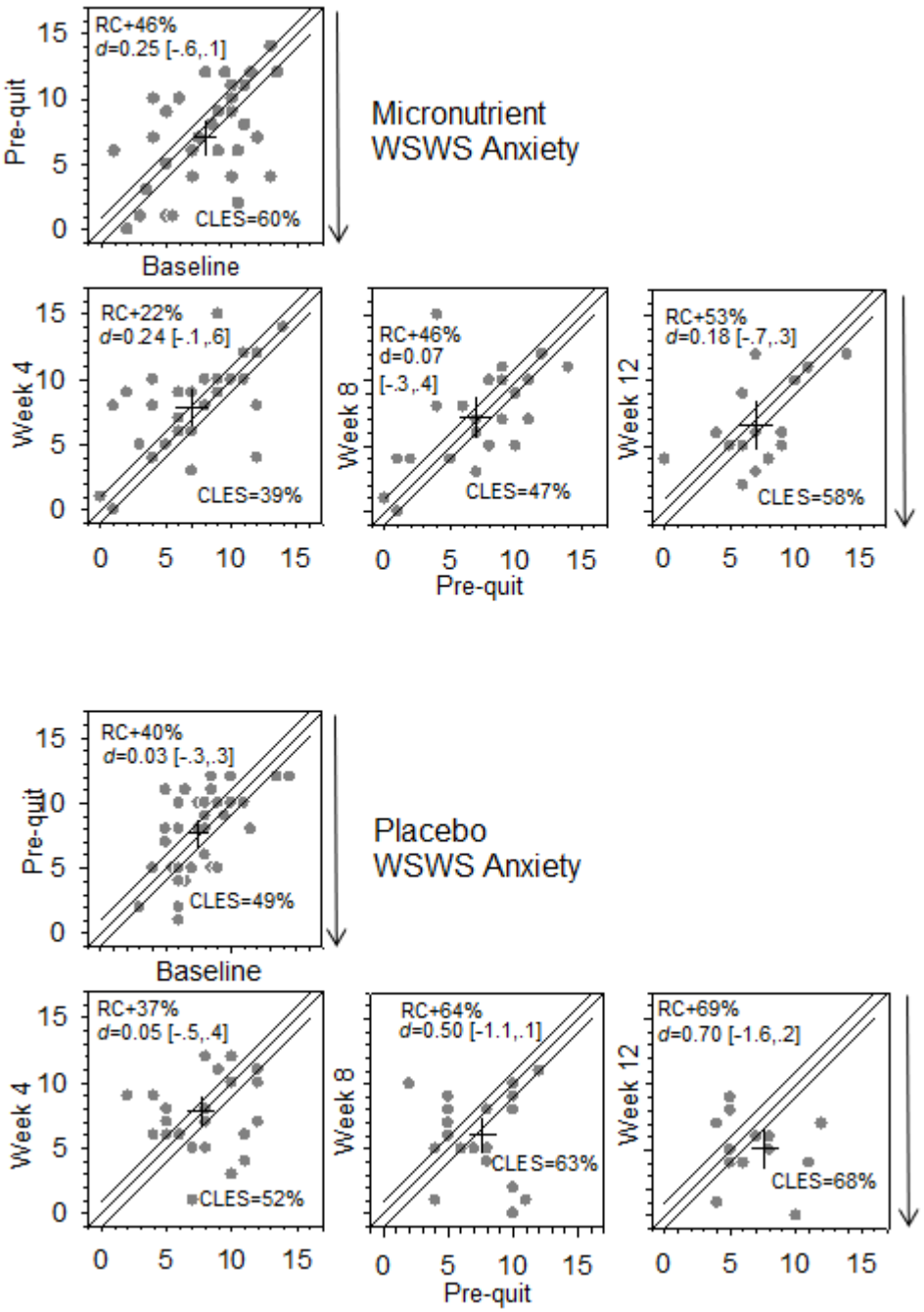

Figure 4.5. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) anxiety scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Figure 4.6 shows individual scores for WSWS concentration, with scores above the diagonal line of no change indicating decreases in concentration and scores below the line indicating improvements in concentration. Cohen's *d* values are mostly small for both

groups but the micronutrient group had more participants show improvements in concentration at each follow-up, as shown by larger CLES, and had more participants show reliable improvement at each follow-up excluding week-12 post-quit where the placebo group had more participants reliably improve (>RC+ percentages; Figure 4.6).

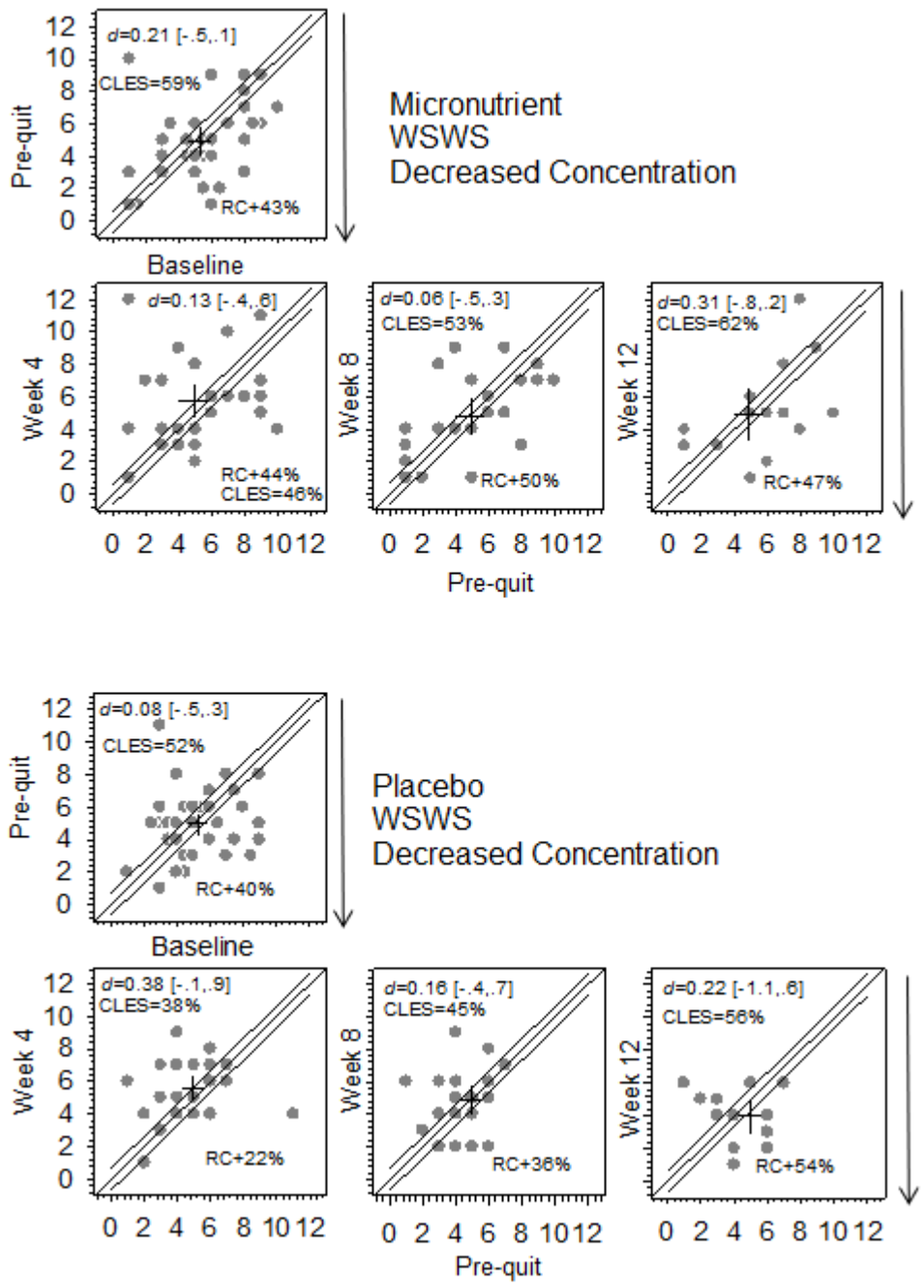

Figure 4.6. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) decreased concentration scores with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) and 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

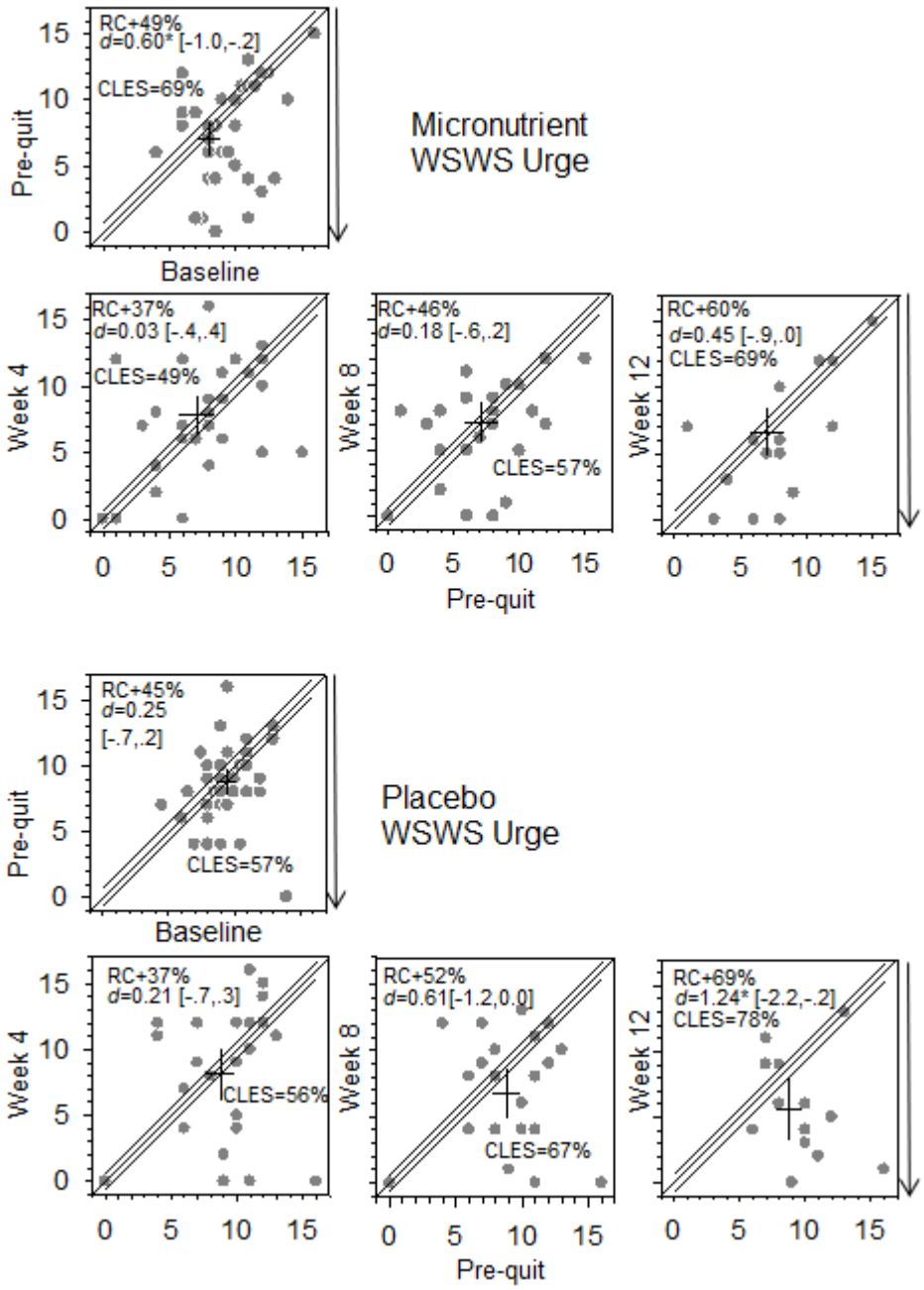

Figure 4.7. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) craving or urge to smoke scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) and 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

At pre-quit the micronutrient group had somewhat more participants report decreases in the WSWS urge to smoke (>RC+ percentage and CLES) compared to the placebo group, and the micronutrient group had a decrease in mean urge to smoke scores with a medium and significant effect size (*d*=0.60, 95% CI [-1.0,-0.2]). Conversely, the

placebo group had more participants decrease in urge to smoke at each follow-up post-quit, and significantly decreased their urge to smoke mean score at 12 weeks. Cohen's *d* was large and significant (*d*=1.24. 95% CI [-2.2, -0.2]). Furthermore, the majority of participants in both groups had larger decreases in urge to smoke as time in the quit phase progressed (Figure 4.7).

Figure 4.8 shows individual scores for WSWS increased appetite scores, scores below the line show participants who moved in the therapeutic direction (no increased appetite; as shown by the arrow). The majority of participants in both groups had an increase in appetite at each follow-up, indicated by RC+ and CLES of >50%; however, no significant differences were observed (Figure 4.8).

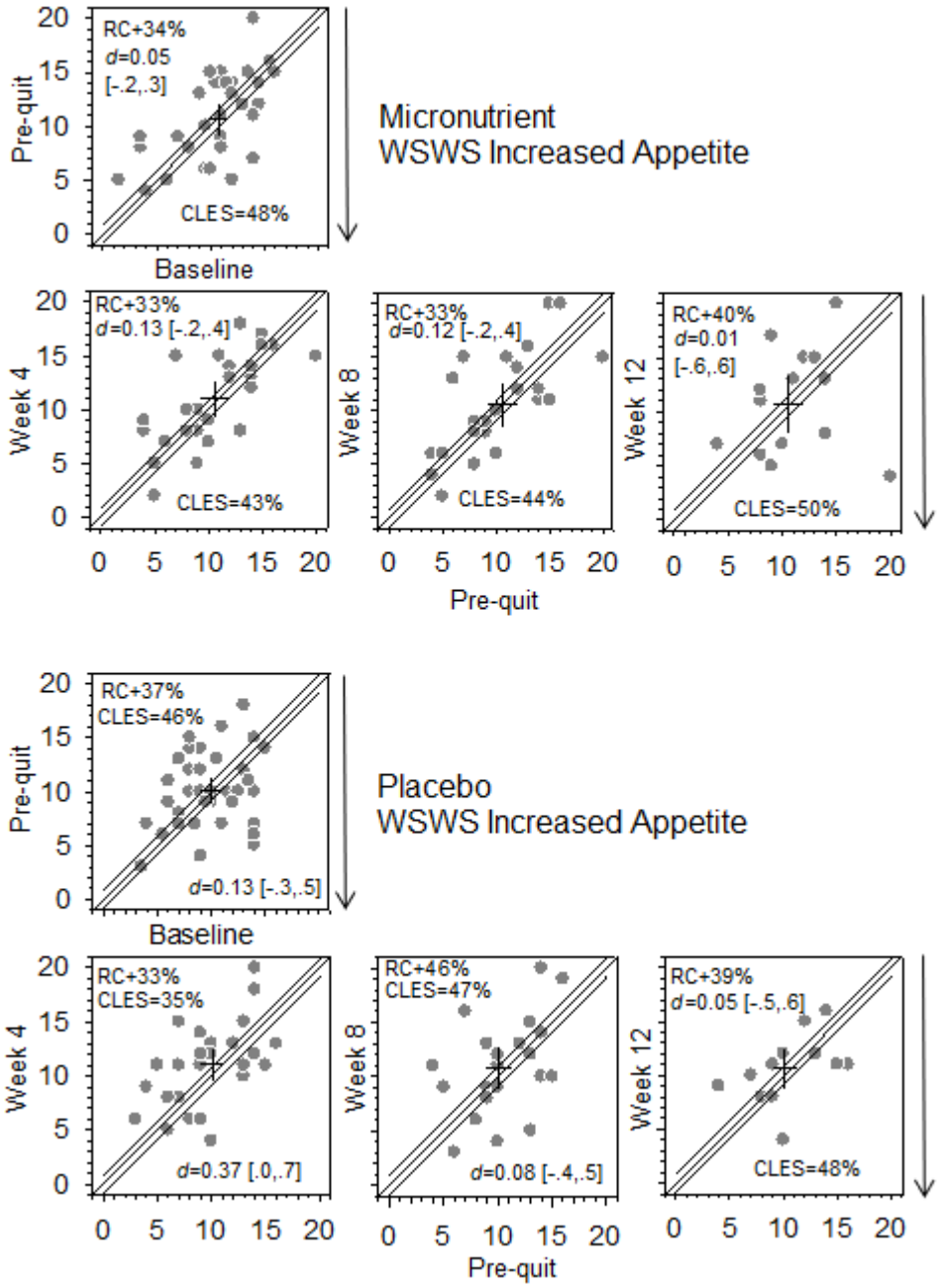

Figure 4.8. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) increased appetite scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) and 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

During the pre-quit phase more participants in the placebo group showed reliable decrease in WSWS insomnia scores when compared to the micronutrient group (>RC+ percentage), and the same percentage of participants showed a decrease in their scores as shown by the CLES's. At four weeks post-quit more participants decreased in insomnia

scores in the micronutrient group compared to the placebo group, with the opposite trend shown at 8 and 12-weeks post-quit, i.e., more participants decreased in the placebo group (Table 4.9).

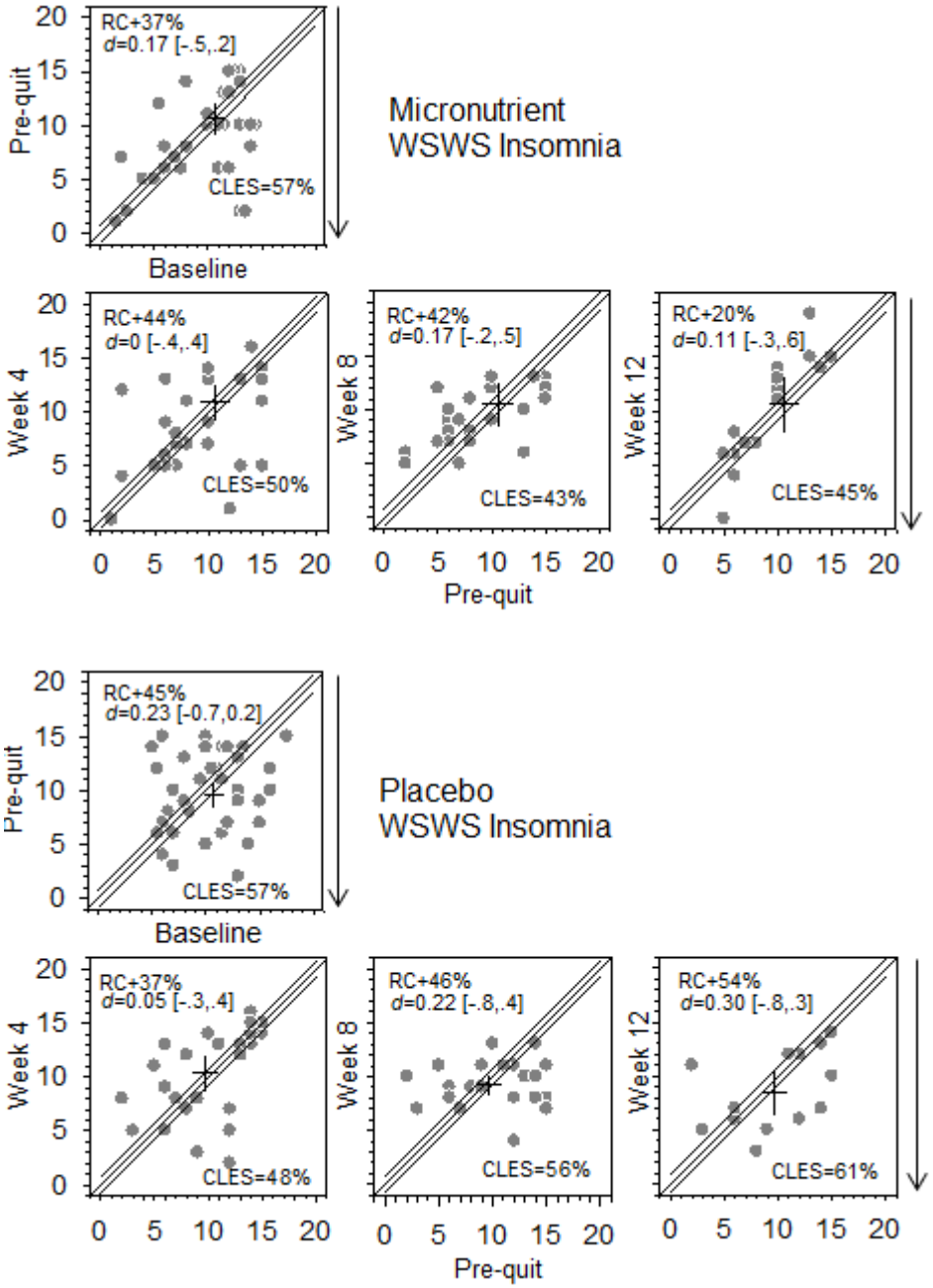

Figure 4.9. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) insomnia scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change percentages (RC+), Cohen's d effect size (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Figure 4.10 shows that mean WSWS low mood scores decreased as the study progressed. At the pre-quit follow-up, and four weeks post-quit the micronutrient group had more participants report decreases in WSWS low mood compared to the placebo group, as indicated by larger RC+ percentages and CLES's. At 8 and 12 weeks post-quit the micronutrient group had more reliable decreases in the therapeutic direction, but the placebo group had larger CLES showing more of an overall group decrease. The majority of participants who remained abstinent for the 12 weeks decreased in low mood when compared to pre-quit (Figure 4.10).

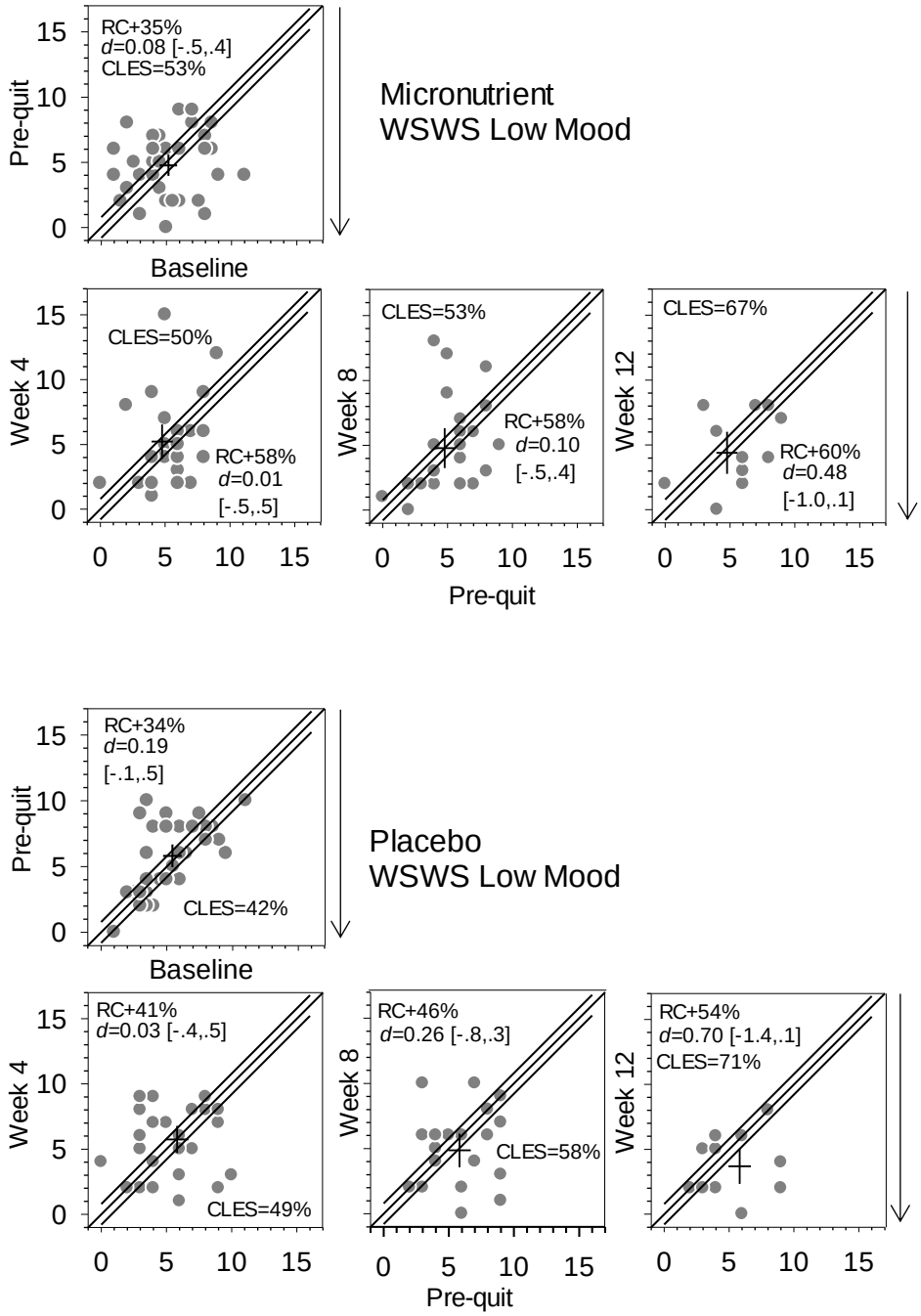

Figure 4.10. *Modified Brinley plots displaying change in participant rated Wisconsin Smoking Withdrawal Scale (WSWS) low mood scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Self-efficacy of quitting

Figures 4.11 and 4.12 show modified Brinley plots for internal and external self-efficacy of quitting (SE) scores at each study waypoint (t_2) compared to baseline (t_1), with lower scores indicating more self-efficacy of quitting. The micronutrient and placebo groups showed significant decreases in mean self-efficacy internal scores at each study waypoint, with Cohen's *d* effect sizes ranging from 0.64-1.30 in the micronutrient group and 0.58-2.14 for the placebo group. At the pre-quit, the micronutrient group had more participants move in the therapeutic direction compared to the placebo group (>CLES), but the placebo group had more participants show reliable change (>RC+ percentages). At four weeks post-quit more participants in the micronutrient group showed improvement in self-efficacy internal scores, and at 8 and 12-weeks the placebo group had more participants show improvement compared to the placebo group (Figure 4.11).

Both the micronutrient and placebo groups showed significant decreases in mean self-efficacy external scores at each study waypoint, with Cohen's *d* effect sizes ranging from 0.52-1.46 in the micronutrient group and 0.48-2.20 for the placebo group. At pre-quit and week four post-quit the micronutrient group had more participants move in the therapeutic direction for self-efficacy external scores (>CLES). At eight weeks post-quit, the micronutrient group had more participants show reliable decrease in self-efficacy external scores (>RC+ percentage), but the placebo group had more participants show any decrease (>CLES). At 12 weeks post quit, the placebo group had more participants decrease in self-efficacy external scores, as shown by larger RC+ percentage and CLES (Figure 4.12).

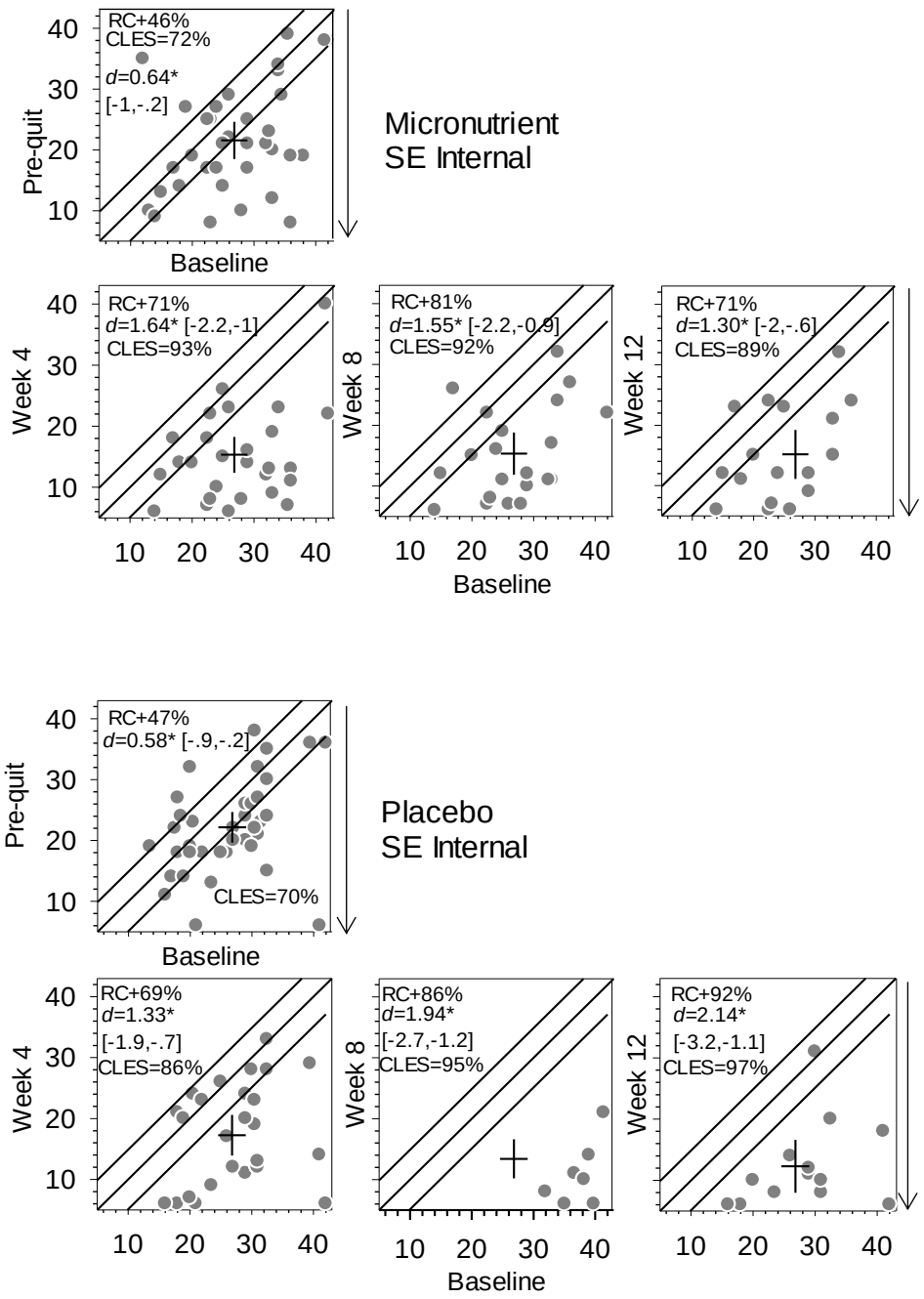

Figure 4.11. *Modified Brinley plots displaying change in participant rated smoking self-efficacy (SE) questionnaire internal stimuli scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change percentages (RC+), Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

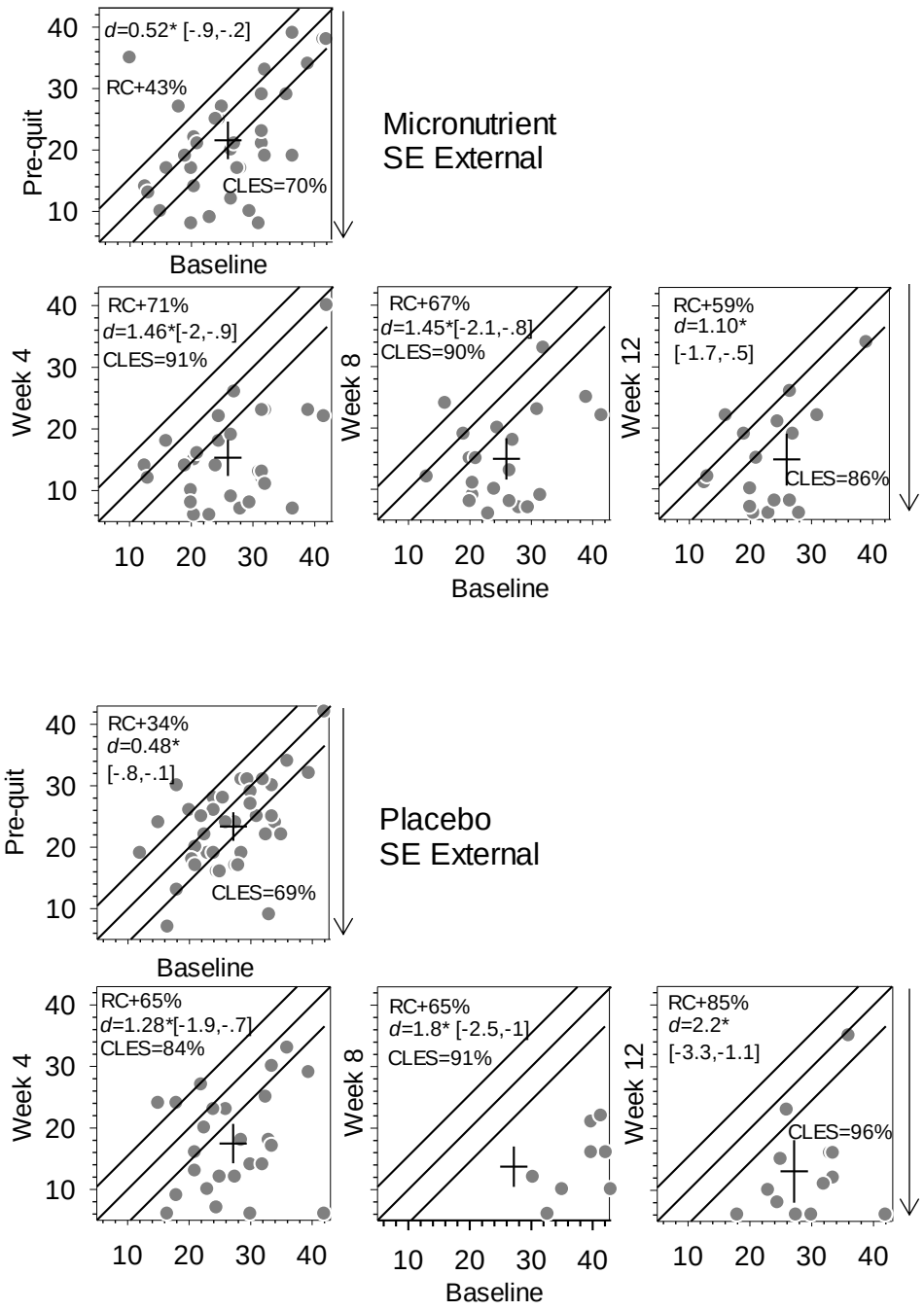

Figure 4.12. *Modified Brinley plots displaying change in participant rated smoking self-efficacy questionnaire (SE) external stimuli scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change percentages (RC+), Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Mood measures

Figure 4.13 to 4.17 presents modified Brinley plots for mental health/ psychological measures of depression, anxiety, and stress (DASS-21) and mood (DEMF) at each study waypoint (t_2) compared to baseline (t_1). Very few participants had scores above the clinical cut-off in baseline or at the end of pre-quit, so interpretation of any change by way of reduction in scores is affected by a strong floor effect for both groups. Nevertheless, the micronutrient group had a significant decrease in mean DASS-21 depression (DASS-D) scores at pre-quit (Cohen's *d*=0.60, 95% CI -1, -0.1) when compared to baseline and more participants showed a decrease in depression scores compared to the placebo group as shown by larger RC+ percentages and CLES. Post-quit, the placebo group showed more reliable change (>RC+ percentages) compared to the micronutrient group, and at 12-weeks post-quit, the placebo group had a significant decrease in mean depression scores (*d*=1.04, 95% CI -1.8, -0.2). At 12 weeks post-quit, only one participant in each group was above the clinical cut-off for DASS-21 depression scores (Figure 4.13).

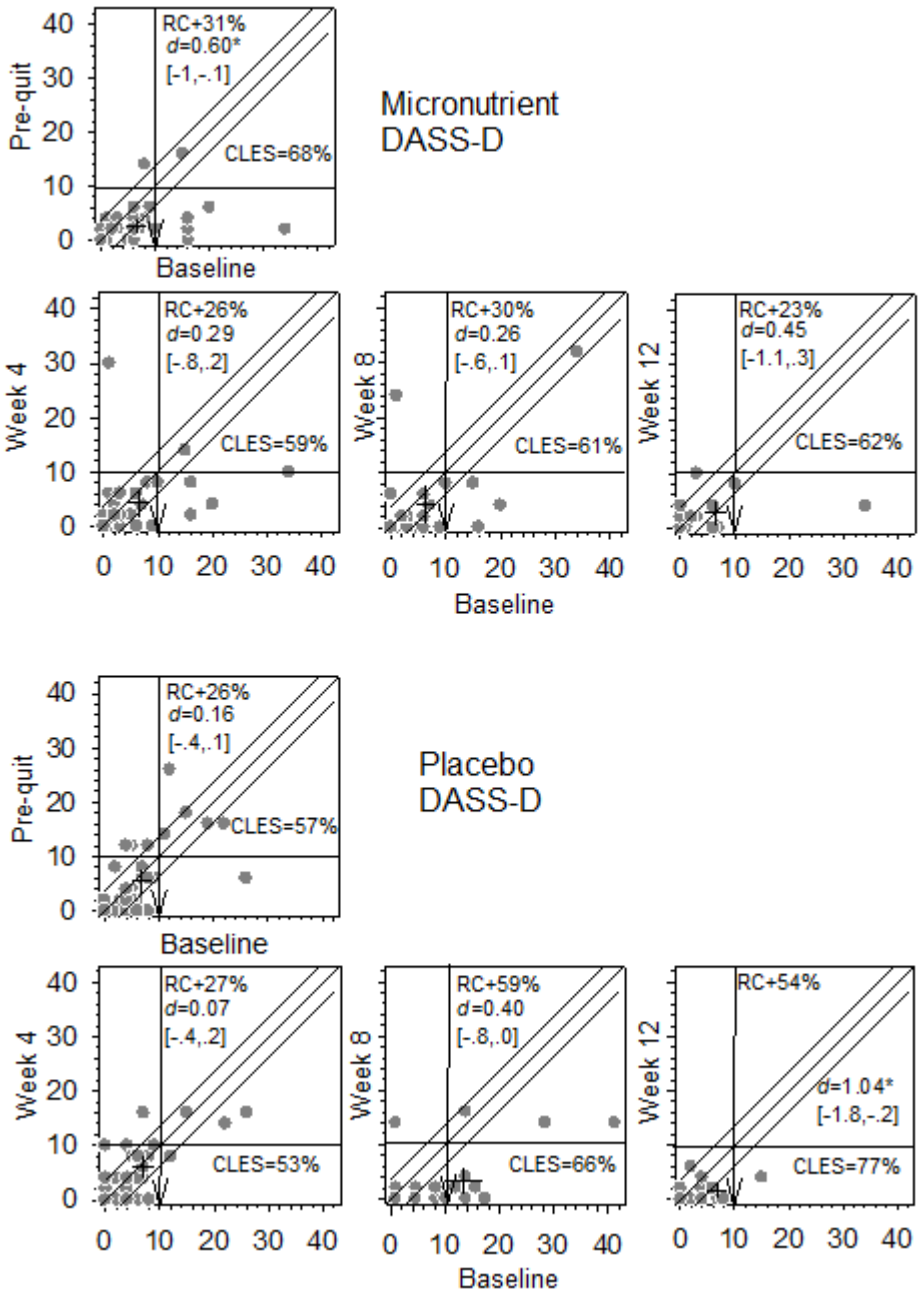

Figure 4.13. *Modified Brinley plots displaying change in participant rated Depression Anxiety and Stress Scale-21 depression scores (DASS-D), with clinical cut off scores and arrows indicating the direction of desired change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect size (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

The DASS-21 anxiety scores (DASS-A) are somewhat less constrained by a floor effect than are the depression scores. DASS-21 anxiety group mean scores remained relatively stable in both groups post-quit. The micronutrient group had a significant decrease in mean

anxiety scores at pre-quit and week four and eight post-quit when compared to baseline, with Cohen's *d* ES's ranging from 0.30-0.57. The placebo group significantly decreased in mean scores at 8 and 12 weeks post-quit when compared to baseline, with Cohen's *d* effect sizes of 0.78 and 0.80 respectively. At pre-quit and four-weeks post-quit, the micronutrient group had more participants decrease in anxiety scores (>CLES), but more participants showed a reliable decrease in the placebo group (>RC+ percentages). At 8 and 12-weeks post-quit the placebo group had more participants decrease in DASS-21 anxiety scores, as shown by the larger RC+% and CLES. The majority of participants from both groups were below clinical cut-offs for anxiety scores post-quit (Figure 4.14).

Compared to DASS depression scores, DASS-21 stress (DASS-S) scores were more widely distributed at baseline and at pre-quit for both groups, with numbers of participants scoring above the clinical cut-off. Group mean scores decreased as time went on in the quit phase for both groups. The micronutrient group had a significant decrease in mean stress scores at the end of pre-quit, Cohen's *d* ES= 0.37. At each follow-up the micronutrient group had more participants decrease in stress scores, as shown by the larger CLES, and had more participants reliably decrease in DASS stress scores, excluding week eight when both groups had RC+ percentages=66% (Figure 4.15).

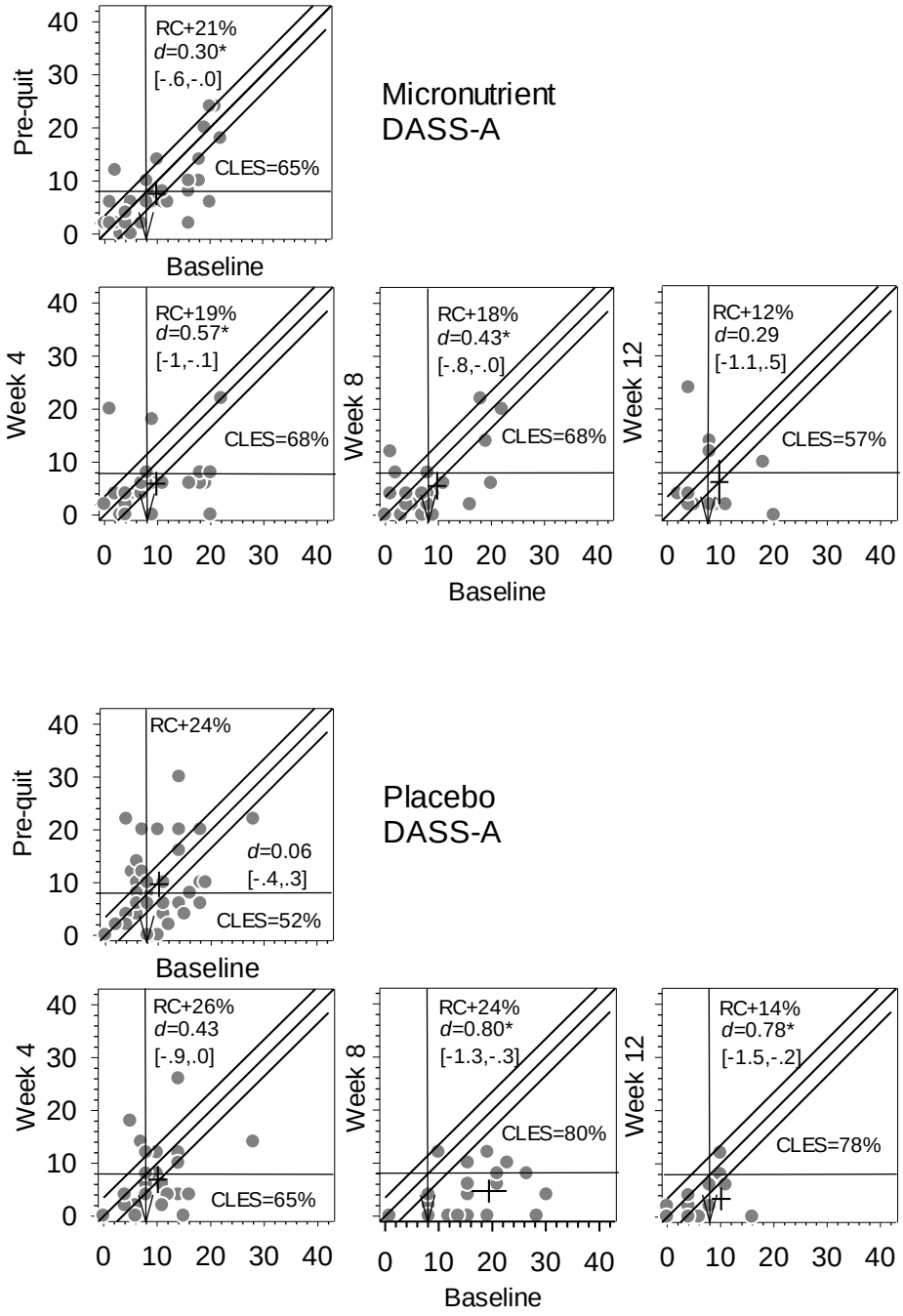

Figure 4.14. *Modified Brinley plots displaying change in participant rated Depression Anxiety and Stress Scales-21 anxiety (DASS-A) scores, with clinical cut off scores and arrows indicating the direction of desired change, crosses to show mean scores with 95% Confidence Intervals and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

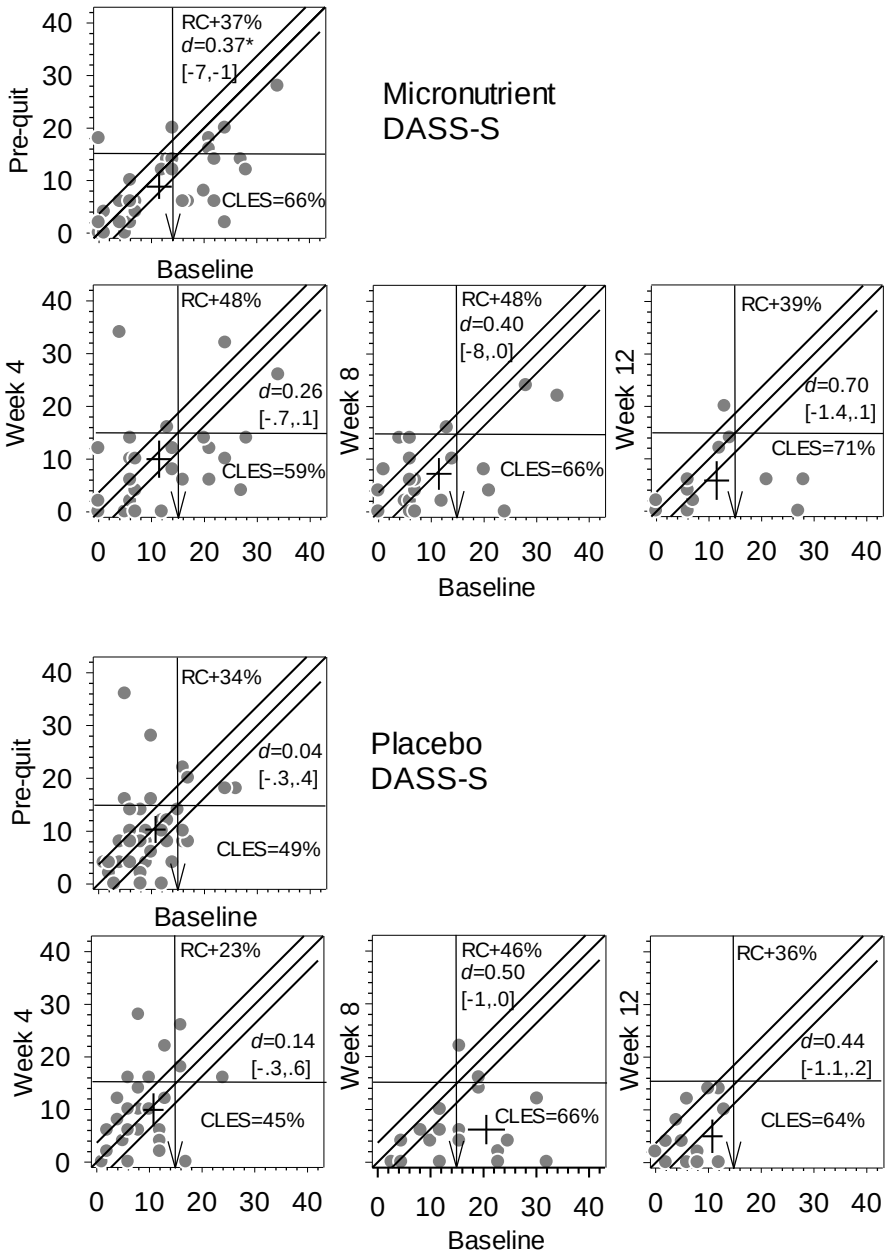

Figure 4.15 *Modified Brinley plots displaying change in participant rated Depression Anxiety and Stress Scale-21 stress scores (DASS-S), with clinical cut off scores and arrows indicating the direction of desired change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Both groups increased in mean DEMF positive mood as the quit phase progressed. However, the majority of participants did not reliably increase in positive mood at each follow-up post-quit when compared to baseline, as indicated by RC+ percentages less than 50% (Figure 4.16). The micronutrient group had higher CLES scores at each follow-up

compared to the placebo group, indicating higher scores of positive mood and more overall group movement in the therapeutic direction. At four weeks post-quit, participants in the placebo group showed significant decreases in positive mood (deterioration), Cohen's *d ES*=0.47 [-0.9,-0.1].

Figure 4.17 shows that the majority of participants did not reliably decrease in DEMF negative mood scores at each follow-up (RC+<50%); however, the horizontal line shows that the mean group negative affect score decreased (in the therapeutic direction) at each study waypoint post-quit when compared to baseline. At each post-quit follow-up, the micronutrient group had higher RC+ percentages than the placebo group, however, the placebo group had higher CLES scores at each follow-up compared to the micronutrient group, indicating more participants moved in the therapeutic direction and at four-weeks post-quit the placebo group significantly increased in negative affect scores (therapeutic direction; Cohen's *d* ES=0.47, 95% CI -0.9, -0.1).

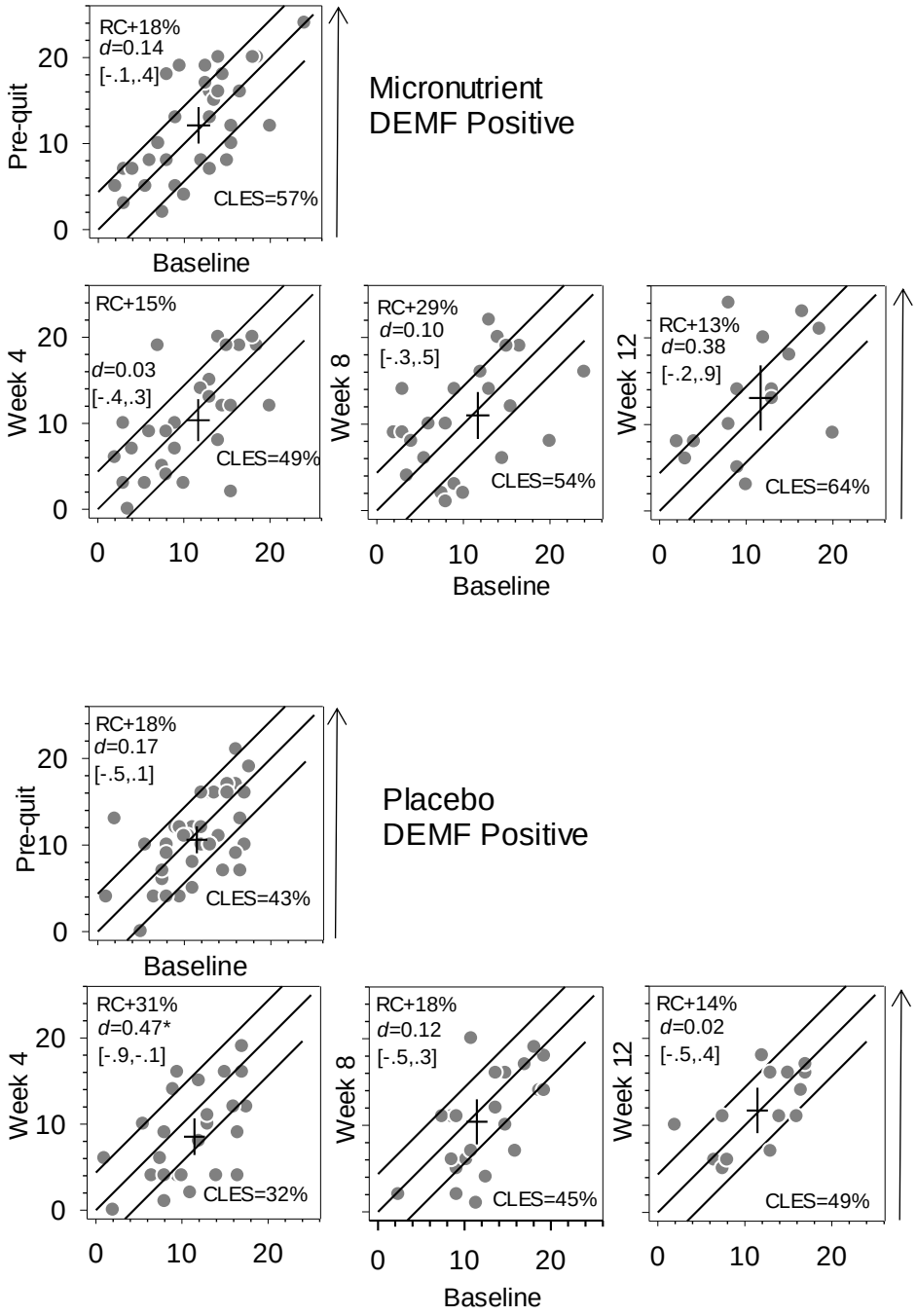

Figure 4.16. *Modified Brinley plots displaying change in participant rated Diener and Emmons Mood Form (DEMF) positive affect scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

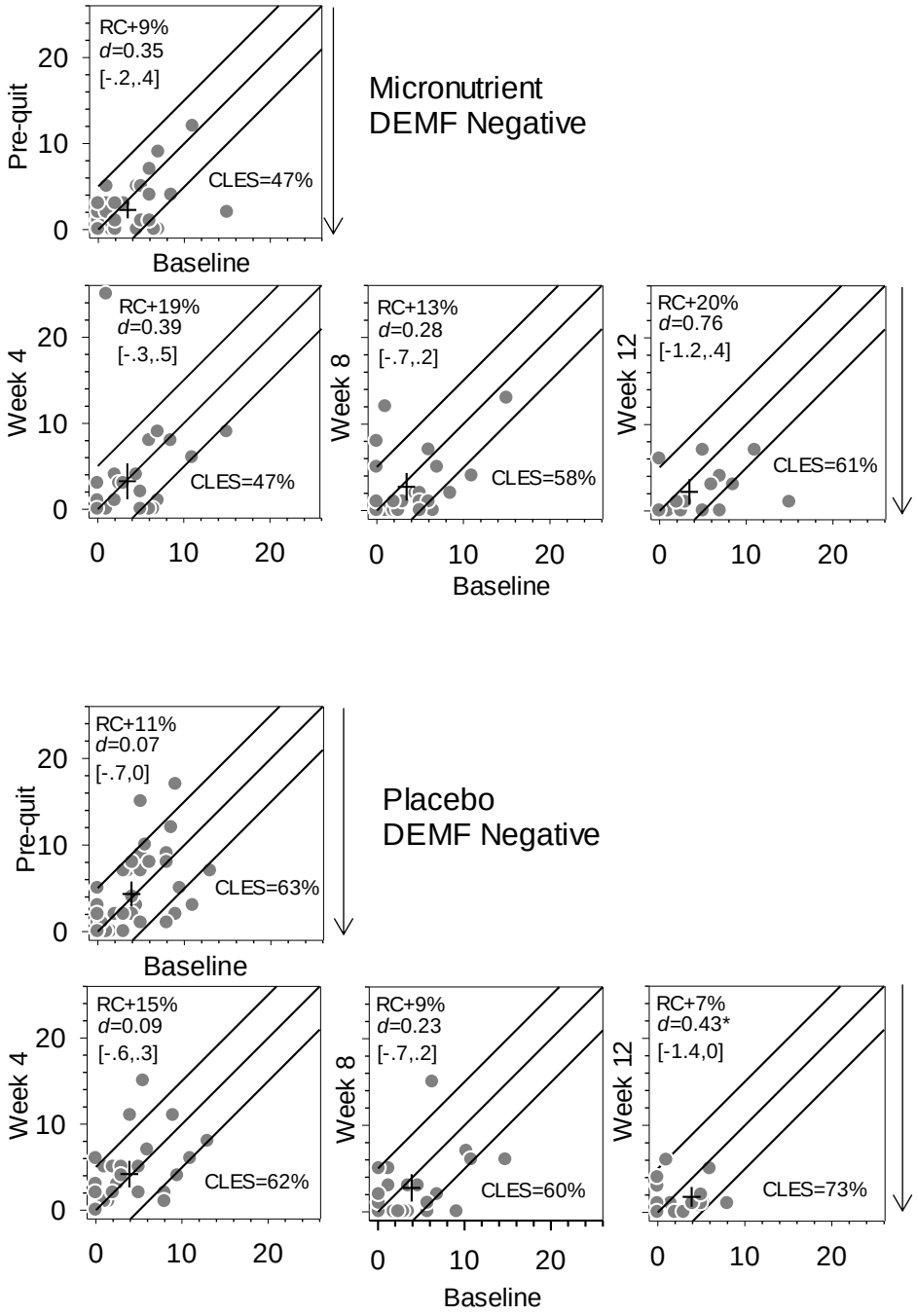

Figure 4.17. *Modified Brinley plots displaying change in participant rated Diener and Emmons Mood Form (DEMF) negative affect scores, with arrows indicating the direction of desired therapeutic change, crosses to show mean scores with 95% Confidence Intervals, and Reliable Change (RC+) percentages, Cohen's d effect sizes (d) with 95% Confidence Intervals, and Common Language Effect Sizes (CLES) shown.*

Daily Diary Measures

Cigarettes/day

Cigarettes/day were averaged for each week for participants who completed their daily diary and results revealed that there were no substantive differences between micronutrient and placebo groups in cigarette consumption (average cigarettes/day) at baseline. The micronutrient group reported smoking fewer cigarettes/day compared to the placebo group during pre-quit week one (Cohen's *d*=0.6, 95% CI [0.1,1.1], CLES=70%) and pre-quit week four (Cohen's *d*=0.7, 95% CI [0.2,1.2], CLES=70%). For the first four weeks of the quit phase the micronutrient group continued to smoke less compared to the placebo group (Cohen's *d*=0.6, 95% CI [0.0, 1.1], CLES=66%), but at quit weeks 8 and 12 there was no longer a meaningful difference in consumption between the two groups, although the micronutrient group continued to smoke fewer cigarettes (Table 4.10).

Table 4.10. *Mean and standard deviation (SD) of cigarettes/day at each week of daily diary data collection for micronutrient and placebo groups, with between groups Cohen's d and Common Language (CLES) effect sizes.*

	Micronutrient (*n*=57)	Placebo Mean (*n*=50)	Cohen's *d* [95% Confidence Interval]	CLES
	Mean (SD)	Mean (SD)		
Baseline	12.4 (7.0)	14.0 (5.6)	0.3 [-0.1,0.7]	60%
Pre-quit week 1	9.3 (4.7)	12.5 (5.6)	0.6 [0.1,1.1]	70%
Pre-quit week 2	6.9 (4.3)	10.2 (5.2)	0.7 [0.2,1.2]	70%
Quit week 1	0.4 (0.8)	1.9 (3.6)	0.5 [0.0,1.0]	65%
Quit week 2	0.5 (1.3)	3.1 (4.6)	0.8 [0.2,1.3]	70%
Quit week 3	0.7 (1.3)	3.5 (4.8)	0.8 [0.3,1.3]	71%
Quit week 4	1.1 (2.3)	3.1 (4.3)	0.6 [0.0,1.1]	66%
Quit week 8	1.2 (2.2)	2.1 (3.0)	0.4 [-0.7,0.7]	60%
Quit week 12	1.1 (2.5)	1.2 (4.0)	0.0 [-0.7,0.7]	51%

Figure 4.18 shows the average number of cigarettes consumed per participant/day for participants who completed daily diary measures at each study way-point. While trajectories of change in smoking were similar in the micronutrient and placebo groups during the pre-quit phase, in that individuals in both groups reduced consumption to a relatively similar degree, substantial differences are evident between groups in the quit phase. In particular, many more individuals in the placebo group maintained relatively high levels of daily consumption, and the variability in consumption was also notably higher in the placebo group than in the micronutrient group. As indicated by the relevant ESs, the micronutrient group substantially decreased the number of cigarettes/day at each quit

phase way-point when compared to baseline, with Cohen's *d* ES ranging from 0.3 to 2.6 (i.e., from borderline small-medium to large). The CLESs were all >70%, in favour of the micronutrient group. The largest decrease in cigarettes/day for the micronutrient group was during quit week 1 with a large ES (Cohen's *d*=4.0, 95% CI [4.3, 2.3], CLES=99%). The placebo group also reported decreases in cigarettes per day at each study way-point excluding pre-quit 1, with Cohen's *d* ranging from 0.2-2.7 (small to large) and CLES >63%. The largest decrease in cigarettes/day for the placebo group was during week eight (Cohen's *d*=2.9, 95% CI [3.8, 1.8], CLES=98%). These findings indicate that both groups experienced a treatment effect that at times could be rated as large, but the ESs were larger for the micronutrient group – implying a larger treatment effect - and the largest ES in that group happened much earlier in the treatment phase than for the placebo group.

Overall trends displayed in Figure 4.18 were analysed by simple linear regressions conducted between each study way-point pre-and post-quit separately for each group. Both groups reduced consumption in the pre-quit phase [micronutrient ($F(1,56)= 17.8$, $p=0.01$); placebo ($F(1,49)=9.8$, $p=0.01$)] with a steeper trend in the micronutrient group ($R^2 = 0.14$ vs $R^2 = 0.02$), equivalent overall to a mean reduction of 2.8 cigarettes/day in the micronutrient group but only 1.9 in the placebo group. These trends in consumption levelled off in the quit phase and no substantive difference is evident between groups (both R^2 negligible).

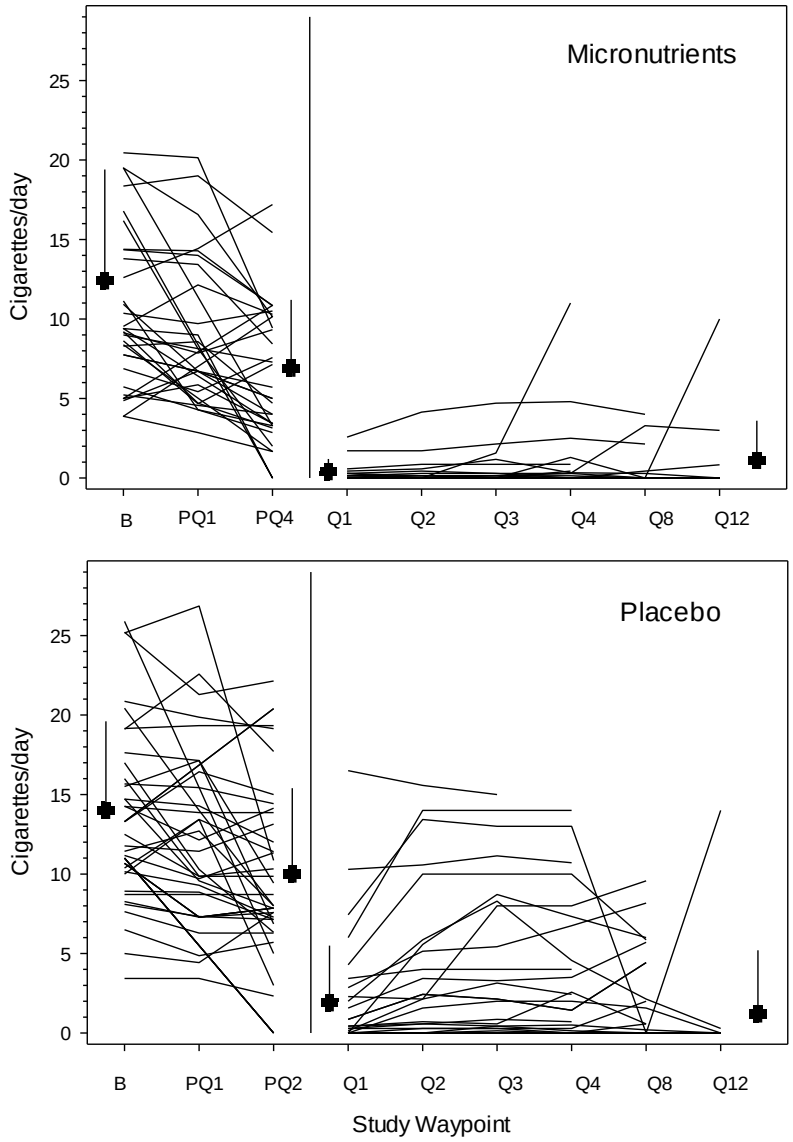

Figure 4.18. *A spaghetti plot showing the average number of cigarettes per day for each participant at each study waypoint, plotted separately for the micronutrient and placebo groups. Also shown are the means for each group at baseline (B), pre-quit week 4 (PQ4), quit week 1 (Q1), and quit week 12 (Q12). Other waypoints are pre-quit week 1 (PQ1) and quite weeks 2–8 (Q2–Q8). The line above the mean shows +1 SD.*

MPSS daily withdrawal scores

MPSS scores were averaged for each week for participants who completed their daily diary and results revealed that both groups had the highest MPSS scores during quit week one then decreasing at each subsequent study waypoint post-quit. The placebo group had significantly lower MPSS scores when compared to the micronutrient group at 12-weeks post-quit (Cohen's *d*=1.2, 95% CI 2.2, 0.2), with no other significant differences observed (Table 4.11).

Table 4.11. *Mean and standard deviation (SD) for Mood and Physical Symptoms Scale total scores at each week of daily diary data collection for micronutrient and placebo groups, with between groups Cohen's d with 95% Confidence Interval (CI) and Common Language (CLES) effect sizes.*

	Micronutrient (*n*=57)	Placebo (*n*=50)	Cohen's *d* [95% CI]	CLES
	Mean (SD)	Mean (SD)		
Baseline	8.8 (2.4)	8.4 (2.1)	0.2 [-0.6,0.2]	55%
Pre-quit week 1	8.2 (2.4)	7.7 (2.5)	0.2 [-0.8,0.3]	56%
Pre-quit week 2	8.6 (2.9)	8.6 (3.0)	0.0 [-0.5,0.6]	51%
Quit week 1	11.1 (4.9)	11.9 (3.7)	0.2 [-0.5,0.8]	55%
Quit week 2	10.8 (4.9)	9.6 (3.7)	0.3 [-0.9,0.4]	57%
Quit week 3	10.4 (4.7)	8.3 (3.4)	0.4 [-1.1,0.2]	64%
Quit week 4	9.9 (5.2)	8.1 (3.3)	0.4 [-1.1,0.3]	61%
Quit week 8	8.6 (3.7)	7.8 (3.0)	0.2 [-1.0,0.5]	56%
Quit week 12	9.0 (3.0)	6.0 (1.0)	1.2 [2.2,0.2]	82%

There were no between group differences in mean daily MPSS time spent craving and strength of the craving scores. However, both groups showed decreases in craving scores at 12-weeks post-quit when compared to baseline, pre-quit, and quit week one (Table 4.12).

Table 4.12. *Mean and standard deviation (SD) for Mood and Physical Symptoms Scale – time spent craving and strength of craving scores at each week of daily diary data collection for micronutrient and placebo per-protocol sample, with between groups Cohen's d with 95% Confidence Interval (CI) and Common Language (CLES) effect sizes.*

	Micronutrient (n=57)	Placebo (n=50)	Cohen's *d* [95% CI]	CLES
	Mean (SD)	Mean (SD)		
Time spent craving				
Baseline	2.3 (0.7)	2.3 (0.8)	0.0 [-0.4, 0.4]	51%
Pre-quit week 1	2.1 (0.7)	2.4 (0.8)	0.4 [-0.1, 0.9]	62%
Pre-quit week 2	2.0 (0.8)	2.3 (0.8)	0.3 [-0.2, 0.9]	60%
Quit week 1	2.3 (0.9)	2.6 (1.0)	0.3 [-0.4, 0.9]	57%
Quit week 2	2.1 (0.9)	1.9 (1.2)	0.1 [-0.8, 0.5]	54%
Quit week 3	1.8 (1.0)	1.6 (1.2)	0.1 [-0.8, 0.5]	54%
Quit week 4	1.7 (1.0)	1.5 (1.1)	0.2 [-0.8, 0.5]	54%
Quit week 8	1.4 (0.9)	1.8 (1.1)	0.4 [-0.4, 1.1]	59%
Quit week 12	1.1 (1.0)	0.9 (0.7)	0.3 [-1.2, 0.7]	57%
Strength of the craving				
Baseline	2.5 (0.8)	2.4 (1.0)	0.0 [-0.4, 0.4]	51%
Pre-quit week 1	2.1 (0.8)	2.4 (0.9)	0.3 [-0.2, 0.9]	59%
Pre-quit week 2	2.2 (0.9)	2.3 (1.1)	0.1 [-0.4, 0.6]	52%
Quit week 1	2.4 (1.0)	3.0 (1.1)	0.5 (-0.1, 1.2)	65%
Quit week 2	2.2 (1.1)	2.2 (1.3)	0.0 [-0.6, 0.6]	51%
Quit week 3	1.9 (1.2)	1.8 (1.2)	0.1 [-0.7, 0.6]	52%
Quit week 4	1.9 (1.2)	1.7 (1.2)	0.1 [-0.8, 0.5]	54%
Quit week 8	1.6 (0.9)	1.7 (1.2)	0.1 [0, 0.8]	53%
Quit week 12	1.4 (1.1)	1.1 (0.8)	0.3 [-1.3, 0.7]	59%

Diet Quality Questionnaire

Participants completed the DQQ at baseline and eight weeks post-quit. A one-way ANCOVA was conducted to compare the effectiveness of the placebo or micronutrient on change in diet quality scores whilst controlling for baseline scores. Participants completed

the DQQ at baseline and eight weeks post-quit. The ANCOVA showed no significant difference between the micronutrient and placebo groups in eight-week scores of diet quality when controlling for baseline scores (p=0.57). An unpaired t-test showed no differences between pre and post scores for the micronutrient group (p=0.64) and the placebo group (p=0.77).

Alcohol Use Disorders Identification Test- Consumption

Participants completed the AUDIT-C at baseline and eight weeks post-quit. A one-way ANCOVA was conducted to compare the effectiveness of the placebo or micronutrients on change in AUDIT-C scores whilst controlling for baseline scores. The ANCOVA showed no significant difference between the micronutrient and placebo groups in eight-week scores of AUDIT-C when controlling for baseline scores (p=0.70). An unpaired t-test showed no differences between pre and post scores for the micronutrient group (p=0.22) and the placebo group (p=0.45).

Capsule compliance

There was no difference between groups for the ITT sample in capsule compliance (consuming ≥80% of their capsules; p=0.27), with 35% (n=20) of the micronutrient group and 40% (n=20) of the placebo group fully capsule compliant for the full study (12-weeks). Analysis of participants who did not drop-out at 12-weeks post-quit (n=43) revealed no differences between groups (p=0.20) in capsule compliance, with 83% (n=20) of the micronutrient group and 90% (n=20) of the placebo group compliant for the full intervention.

Side-effects

The frequency of the most common treatment emergent side-effects did not significantly differ between micronutrient and placebo group*s* (*p*>0.05). Although, more participants in the micronutrient group reported blurred vision and constipation, with this difference nearing significance. However, no participants dropped out of the study due to side effects, reporting them to be no worse than 'mild'. The most common side effects reported for both groups were change in appetite (*n*=28, 26%) and weight gain (*n*=25, 23%; Table 4.13).

Table 4.13. *Treatment-emergent adverse side effects reported by at least 5% of participants in the micronutrient group during the trial.*

	Micronutrient (*n*=57)	Placebo (*n*=50)	*p*
Dry mouth	4 (7.0%)	10 (20.0%)	0.40
Urinary retention	4 (7.0%)	4 (8.0%)	1
Blurred vision	7 (12.3%)	1 (2.0%)	0.08
Constipation	8 (14.0%)	3 (6.0%)	0.08
Sedation	7 (12.3%)	9 (18.0%)	0.60
Sleep disruption	6 (10.5%)	9 (18.0%)	0.63
Nightmares	6 (10.5%)	8 (16.0%)	0.77
Change in appetite	13 (22.8%)	15 (30.0%)	0.70
Weight gain	13 (22.8%)	12 (24.0%)	0.86
Headache	8 (14.0%)	9 (18.0%)	0.58
Nausea	8 (14.0%)	10 (20.0%)	0.61
Gastrointestinal disturbance	8 (14.0%)	7 (14.0%)	0.13
Abdominal pain	7 (12.3%)	12 (24.0%)	0.73
Loss of libido	8 (14.0%)	6 (12.0%)	0.11
Agitation	8 (14.0%)	9 (18.0%)	0.66
Anxiety	5 (8.8%)	11 (22.0%)	0.20

The following chapter contains the discussion and conclusions from study two. A summary of the overall thesis is also provided in Chapter 5.

Chapter 5. Discussion Study Two

Study two extended the serendipitous findings of Harrison et al. (2013) and the single-case research of study one as a fully-blinded RCT to investigate the use of a broad-spectrum micronutrient combined with a free phone and on-line counselling/support service (Quitline NZ) for smoking cessation, reduction of cigarettes/day and withdrawal symptoms, and improvement of psychological symptoms associated with withdrawal. This discussion will highlight the hypotheses of study two, summarise the key findings and whether these support the hypotheses, and if they are consistent with previous research including study one. Strengths and limitations of study two will be addressed along with future research recommendations. The chapter will end with a summary of the current thesis.

5.1 Hypotheses of study two

Based on the tentative theory that broad-spectrum micronutrient treatment may improve brain function, and the limited research supporting nutrient supplementation to relieve stress, withdrawal symptoms, and quitting addictive drugs, the following hypotheses were formed for study two (as outlined in section 4.1).

1) *Quit attempts and rates will be higher in the micronutrient + Quitline group versus the placebo + Quitline group at each study waypoint after quit date.*
2) *Withdrawal symptoms and craving following a quit attempt will be smaller for the micronutrient + Quitline group versus the placebo + Quitline group.*
3) *Cigarettes/day after metabolic adaptation to the capsules will be less for the micronutrient + Quitline group versus the placebo + Quitline group.*

4) *Self-efficacy of quitting and positive mood will be higher, and negative mood will be lower in the micronutrient + Quitline group versus placebo + Quitline at each study waypoint after quit date.*
5) *Dropout rates will be lower in the micronutrient + Quitline group versus the placebo + Quitline group.*

5.2 Summary of key findings

Hypothesis 1: Quit success

Our primary prediction that taking micronutrients daily before and after a quit attempt would assist with continuous abstinence at 12-weeks post-quit for the ITT group, was not unequivocally supported, although the direction of the difference in quit rates at 12 weeks between the groups (micronutrients = 28% versus placebo = 18%; OR=1.78) is consistent with beneficial effects of micronutrient treatment and with study one's 12 week quit rates (viz, micronutrients = 33% versus placebo = 25%, OR=1.50). The NNT of 10 and quit rate for the micronutrient treatment at 12 weeks was comparable to varenicline (NNT=11 and quit rate at 12 weeks 28%) (Cahill et al., 2016; Cahill et al., 2014) and better than NRT (NNT=15 and quit rate at 12 weeks 17%) (Cahill et al., 2014; Ministry of Health, 2007).

The hypothesis that the micronutrient group would make more quit attempts (≥24 hours abstinence) and be more successful (≥three days) was not supported in the ITT sample. Although there was no statistically significant difference in the number of quit attempts made and their success between groups, the placebo group made more quit attempts and had more success at day three when compared to the micronutrient group. Conversely, the micronutrient group had higher rates of continuous abstinence at four and

eight-weeks post-quit in the ITT sample, although the difference was not statistically significant.

Study two demonstrated in a sub-sample consisting of those who did not drop-out before their quit meeting but had varying degrees of compliance/adherence (the full intervention sample), that the micronutrient group had higher rates of quit attempts and success at each follow-up compared to the placebo group. The micronutrient group also had a significantly higher four week quit rate compared to the placebo group (66% versus 41%, OR = 2.76) in the full intervention sub-sample, which is comparable to the four week quit rate of bupropion hydrochloride (OR=2.13) and varenicline (OR=2.88) reported in a meta-analyses (Cahill et al., 2014; Wu et al., 2006).

Participants who followed study protocol and were compliant with taking their capsules were counted as being fully compliant, and their quit rates were analysed as a sub-sample (the per-protocol sample). Analysis of the per-protocol sample showed that the micronutrient group had significantly higher quit rates compared to the placebo group at four (83% versus 57%; OR=3.60) and eight weeks post-quit (81% versus 50%; OR=4.25). The micronutrient group also had higher number of quit attempts, and success at three days and 12-weeks, but this difference was not statistically significant. The higher quit rates observed in the full intervention and per-protocol sub-samples for both groups is consistent with empirical evidence that suggests participants who adhere to study protocols and treatment tend to do better than those who do not adhere, irrespective of assignment to treatment or placebo (Montori & Guyatt, 2001).

In summary, all significant quit rate results are in the same direction for the sub-sample analyses, (i.e., participants who reported they took the capsules and attended the

quit meeting) and tentatively support that the micronutrient treatment increases the chance of abstinence of quitting. Furthermore, significant differences between the micronutrient and placebo groups were reported during the first eight weeks of quitting. Given what we know of the trajectory of tobacco withdrawal symptoms (American Psychiatric Association, 2013; Piasecki, 2006), the micronutrients were most successful in supporting quitting and abstinence during the acute withdrawal period, a highly desirable finding.

Hypothesis 2: Withdrawal symptoms

Modified Brinley plots with effect sizes were used to analyse changes in withdrawal symptoms before and after quitting. There was variability in withdrawal scores, both within and between groups, with significant results in different directions, consistent with the multi-dimensional nature of withdrawal symptoms observed in other research (Javitz et al., 2012; Piasecki, 2006). However, the results still warrant discussion. Both the micronutrient and placebo groups showed the characteristic rise and fall pattern consistent with withdrawal symptoms (Piper et al., 2011), i.e., withdrawal symptoms peaked in the acute phase and then as time in the quit phase increased, mean withdrawal symptoms decreased. The results further support the need for adequate smoking cessation interventions in the first four weeks post-cessation when withdrawal symptoms are at their highest (American Psychiatric Association, 2013; Piasecki, 2006).

The MNWS was used to give an overall rating of withdrawal symptom severity. The micronutrient and placebo groups significantly decreased in MNWS withdrawal scores at the pre-quit meeting, with the micronutrient groups having larger effect sizes. Post-quit, the placebo group had more participants decrease in MNWS withdrawal scores at each follow-

up post-quit when compared to pre-quit scores, with a lower mean MNWS score at 12-weeks post-quit. The steeper reduction of withdrawal observed in the placebo group post-quit compared to the micronutrient group is not consistent with study one's MNWS results and does not support our hypothesis that the micronutrient group would experience lower withdrawal symptoms measured using the MNWS post-quit compared to the placebo group.

The WSWS allowed for the analysis of individual withdrawal symptoms using seven sub-scales. This is particularly useful given that the tobacco withdrawal syndrome consists of several different types of symptoms (Javitz et al., 2012). The results revealed considerable intra- and inter-individual variability observed across the different withdrawal symptoms comparable with other cigarette withdrawal research (Piasecki, 2006).

The micronutrient group had lower scores of WSWS irritability at each study way-point when compared to the placebo group, with a significant decrease in irritability scores at 12 weeks post-quit. This may tentatively support the use of a broad-spectrum micronutrient formula to reduce irritability, particularly when an individual is experiencing withdrawal, and may have contributed to more participants achieving abstinence in this group.

The micronutrient group had more participants decrease in WSWS anxiety scores compared to the placebo group at the pre-quit follow-up; however, at each follow-up post-quit, the placebo group had more participants decrease in anxiety scores when compared to pre-quit scores, and lower mean scores when compared to the micronutrient group. The decrease in anxiety for the majority of participants in the micronutrient group at pre-quit is consistent with the observed beneficial effects of micronutrient formulas to support anxiety and stress (Carroll et al., 2000; Kaplan, Rucklidge, Romijn, & Dolph, 2015; Rucklidge et al.,

2012; Rucklidge et al., 2011; Schlebusch et al., 2000). However, the smaller mean anxiety scores observed in the placebo group post-quit may does support the use of micronutrients to decrease anxiety during withdrawal.

More participants in the micronutrient group did not report increases in problems with concentration at each study way-point when compared to the placebo group, i.e., the placebo group reported higher scores of concentration difficulties associated with withdrawal, supporting the use of micronutrient treatment to protect against the concentration problems that are often observed during cigarette withdrawal. The results are consistent with the body of research supporting the use of micronutrient treatment to improve Attention-Deficit Hyperactivity Disorder symptoms (Gordon, Rucklidge, Blampied, & Johnstone, 2015; Rucklidge et al., 2018; Rucklidge, Frampton, Gorman, & Boggis, 2017; Rucklidge & Kaplan, 2014; Vesco, Young, Arnold, & Fristad, 2018). ADHD is diagnosed when a person has difficulty with inattention and/or hyperactivity and impulsivity (American Psychiatric Association, 2013), and although there are differences between inattention and decreased concentration the two are often referred to interchangeably, as concentration is sustained attention (Anderson, 2005).

Both the micronutrient and placebo groups had a similar pattern of WSWS increased appetite scores, with the majority of participants in both groups increasing appetite at each study way-point. High levels of increased appetite (as a withdrawal symptom) after smoking cessation often lasts longer (more than 10 weeks) when compared to other withdrawal symptoms (Gross & Stitzer, 1989), therefore, this withdrawal symptom may require a longer treatment. Smoking and nicotine directly affect glucose metabolism and body weight as a result of changes in metabolism. Post-cessation weight gain has been reported to be one of

the main reason why smokers, especially women, fail to initiate smoking cessation or relapse after a quit attempt (Siahpush et al., 2014). There are no substantial data showing that any smoking cessation approach is effective at limiting post-cessation weight gain and increase in appetite (Siahpush et al., 2014). Smoking cessation approaches that account for increased appetite and weight gain during the first six months of cessation must be considered in order to increase the chance of long-term abstinence (Harris, Zopey, & Friedman, 2016).

The placebo group had more participants reliably improve in insomnia at the pre-quit follow-up when compared to the micronutrient group. At four-weeks post-quit the micronutrient group had more participants improve in insomnia; however, at eight and 12-weeks the placebo group showed more improvement when compared to pre-quit. There was no direction of change that consistently favoured either group across each study way-point, and further research into smoking cessation interventions that support insomnia post-quitting is needed. Furthermore, although we asked participants to take the last dose of the capsules before bed, we did not monitor this. Micronutrient formulas have been reported to improve mood and negatively effect sleep if taken late at night (Kennedy et al., 2010; Sarris et al., 2012), it is possible that this has occurred.

The micronutrient group had more participants reliably improve in low mood scores at each study way-point compared to the placebo group. This supports the substantial body of literature supporting the use of micronutrient supplements to improve mood symptoms (Benton et al., 1995; Gariballa & Forster, 2007; Gosney et al., 2008; Harris et al., 2011; Kennedy et al., 2010; Lewis et al., 2013; Mech & Farah, 2016; Sarris et al., 2012). Given that smokers often report a desire for relief from negative affect as a primary reason for smoking

and often attribute relapses to acute negative affect (Kahler et al., 2015; Piasecki, 2006), this finding is particularly important. Furthermore, the improvement in low mood may have supported the higher abstinence rates in the sub-samples (full intervention and per-protocol) micronutrient group.

The micronutrient group had more participants decrease in WSWS urge to smoke compared to the placebo group at the pre-quit follow-up. At each follow-up post-quit, the placebo group had larger decreases in urge to smoke, with a significant decrease observed at 12 weeks post-quit. This does not support the hypothesis that those taking the micronutrient formula would have lower cravings (urge to smoke) due to withdrawal post-quit compared to the placebo group. It is suggested that craving may be one of the most sensitive predictors for continued smoking and relapse (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012), but the results do not support this as the micronutrient group had larger decreases in craving but lower quit rates. However, the majority of the research suggests that craving should continue to be an important target for smoking cessation treatment (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012), and therapies that assist by decreasing craving for cigarettes during a quit attempt need to be explored.

The MPSS consists of five single-item ratings for depressed mood, irritability, restlessness, hunger, and poor concentration. This brief scale was used for the self-report daily diary. The placebo group had lower mean MPSS scores at each study-waypoint excluding quit week one. This does not support the hypothesis that the micronutrient group would have lower daily withdrawal scores. The MPSS includes two six-point sub-scales to measure time spent craving cigarettes and strength of the cravings. There were no between- group differences in daily MPSS time spent craving and strength of craving

cigarettes. Both groups showed a significant increase at quit week one followed by decreases at each study way-point thereafter, consistent with the typical strong increase in the first week after quitting and decreases after a lengthy period of abstinence (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012). Notably, the decreases in MPSS scores at each study way-point could also reflect the drop-out of those who were experiencing more withdrawal symptoms.

As mentioned, effective smoking cessation treatments show an advantage over control treatments very soon after the quit date, within the 5–10 day window in which the relapse risk is highest. After this time, relapse curves from treatments and control groups tend to be parallel. This may suggest that the determinants of early and late relapse are qualitatively different (Piasecki, 2006). For the majority of the withdrawal measures used, the micronutrient treatment had lower daily withdrawal scores in the pre-quit phase and the first week of quitting. Given that a majority of participants in the micronutrient group (81%) and placebo group (74%) had cut down on cigarettes/day during the pre-quit phase, it is likely that they were experiencing withdrawal symptoms prior to the quit phase (Piasecki, 2006). It is possible, therefore, that the micronutrient treatment may have been protective against the acute withdrawal symptoms and contributed to the larger quit rates observed in the micronutrient group in the full-intervention and per-protocol samples.

Hypothesis 3: Cigarettes/day

The micronutrient group reported smoking fewer cigarettes/day compared to the placebo group at each study way-point. Within group analysis showed that both groups reduced consumption to a similar degree; however, there were substantial differences during the quit phase with the micronutrient group reporting a larger treatment effect and

reduction in overall cigarettes/day, supporting the hypothesis. This finding is particularly important, given research that shows reductions in cigarette consumption can increase self-efficacy about controlling one's smoking and promote cessation attempts resulting in higher chances of abstinence (Begh, Lindson-Hawley, & Aveyard, 2015; Broms et al., 2008; Falba, Jofre-Bonet, Busch, Duchovny, & Sindelar, 2004; Farkas, 1999; Lindson-Hawley et al., 2012; Polosa & Benowitz, 2011). A recent review of intervention trials found that for every 1% decrease in cigarettes per day (NRT assisted) there was a 3% to 4% increase in cessation success, and in the naturalistic studies quartile decreases in cigarettes per day were associated with 50% to 290% increased odds of quitting (Klemperer & Hughes, 2016). Furthermore, many smokers are able to maintain smoking reductions after a relapse predicting subsequent quit attempts and success (Piasecki, 2006). Additionally it should be noted that a systematic review analysed 10 studies, with a total of 3760 participants, comparing quitting abruptly versus reducing cigarettes before a quit date, and found comparable quit success rates in both conditions (Lindson-Hawley et al., 2012).

Several factors may contribute to smoking reduction promoting rather than deterring cessation. Reduction in cigarettes/day may be a more attainable and realistic goal compared to complete abstinence, and is more desirable than continued smoking at the current rate. Once achieved this may encourage efforts to achieve complete abstinence (Begh et al., 2015). Attempts to cut down in smoking are also viewed by smokers as steps towards quitting (Piasecki, 2006). Further, smoking reduction may reduce the severity of withdrawal and cravings when complete abstinence is achieved (Balfour, 2009), these being the main barriers to achieving abstinence and contributing to relapse (West et al., 2006). Furthermore, the neural processes produced by continued smoking lead to the

development of conditioned relationships between environmental stimuli and smoking (e.g., stress and smoking) and a reduction in smoking may interrupt these relationships so that the desire to smoke is less triggered by the previously conditioned cues (Balfour, 2009). Shaping uses differential reinforcement of successive approximation to change behaviour, thus gradually strengthening a desired behaviour. In the context of smoking, gradual reduction of cigarettes/day may induce intermittent reinforcement, encouraging and increasing the likelihood of complete abstinence (Begh et al., 2015).

One of the primary reasons that smokers want to quit is to mitigate the health harms it causes (Bottorff et al., 2014; West, McEwen, Bolling, & Owen, 2001). A reduction in cigarettes/day reduces an individual's risk of adverse health effects and mortality (Banks et al., 2015; US Department of Health Human Services, 2004). However, it is important to note that the risk of mortality in those who continue to smoke at a reduced rate is still much higher than for a non-smoker (Banks et al., 2015), and complete abstinence should still be the goal of any smoking reduction/cessation campaign. It is also possible that reductions in cigarette consumption are compensated for by changes in cigarette brands and/or smoking behaviour that maintain or increase nicotine (and other toxin) consumption (Benowitz, Jacob, Kozlowski, & Yu, 1986; Godtfredsen, Prescott, Vestbo, & Osler, 2006; Hurt et al., 2000), limiting any conclusions about harm reduction and supporting the goal to achieve abstinence.

Hypothesis 4: Psychological symptoms

Modified Brinley plots demonstrated changes in psychological symptoms pre- and post-quit. There was considerable intra and inter-variation in the psychological measures assessed for both groups. The micronutrient group did not consistently have reduced levels

of measures of psychological state at each study way-point when compared to baseline, and therefore the results do not support our hypothesis. However, discussion of psychological symptoms may provide direction for future research and/or smoking cessation interventions.

The majority of the participants increased in internal and external self-efficacy, i.e., one's confidence to abstain from smoking at each follow-up when compared to baseline, with large (significant) effect sizes. Comparison between groups shows that the micronutrient group had larger effect sizes at four weeks post-quit, and the placebo group had larger effect sizes at 8 and 12 weeks post-quit. Given that increases in early self-efficacy in one's ability to quit smoking predicts abstinence (Gwaltney, Metrik, Kahler, & Shiffman, 2009), the large increases in self-efficacy may have contributed to the greater odds of quitting observed in the micronutrient group.

The micronutrient group had a significant decrease in mean DASS-21 depression and anxiety scores at the pre-quit follow-up, with no significant reduction observed in the placebo group. The majority of participants in both groups did not reliably improve in DASS-21 depression and anxiety scores at four-weeks post-quit. At 8 and 12 weeks post-quit the placebo group had more participants decrease in DASS-21 depression and anxiety scores when compared to baseline. This is not consistent with the WSWS low mood scores; however, the majority of participants scored below the clinical cut-offs and it is likely that there was a floor effect making the detection of change difficult, therefore the measure may have not been sensitive enough to detect change in participants state below the clinical cut-off.

Both the micronutrient and placebo groups decreased in DASS-21 stress scores at each study way-point, with micronutrient treatment associated with larger decreases in stress scores at each follow-up post-quit when compared to baseline. These results are consistent with study one's DASS-21 stress results and the beneficial effects of micronutrient treatment reducing stress (Carroll et al., 2000; Kaplan, Rucklidge, Romijn, & Dolph, 2015; Rucklidge et al., 2012; Rucklidge et al., 2011; Schlebusch et al., 2000), and may support the use of micronutrient treatment to reduce stress after a quit attempt.

The majority of participants did not show a reliable improvement in DEMF positive and negative affect scores. More participants increased in positive affect in the micronutrient group when compared to the placebo group, consistent with study one's results. Conversely, more participants decreased in negative affect in the placebo group when compared to the micronutrient group. Both groups moved in the direction of therapeutic change at each follow-up post-quit (increased positive affect and decreased negative affect), consistent with the trajectory of withdrawal symptoms that they are worst in the early stages of withdrawal (Piasecki, 2006; Van Zundert, Ferguson, et al., 2012).

Hypothesis 5: Drop-out

More participants withdrew from the study during the pre-quit phase in the micronutrient group. This was not due to reported side effects, rather, a variety of different reasons likely occurring due to chance. Drop-out rates were equivalent for the micronutrient and placebo groups after the capsule + Quitline intervention, and, despite explicit attempts to reduce drop-out (continued support after a relapse and the offer of a four-weeks supply of the micronutrient at the end of the study), nearly 60% of participants dropped out during the study. This is considerably more than other smoking cessation RCT

conducted in NZ, who report drop-out rates of 22-27% at six-months (Bullen et al., 2010, Walker et al., 2011, Walker et al., 2012). Propensity to drop-out was associated with smoking more at baseline, taking up regular smoking at a younger age, being more nicotine dependent, and having a lower quality diet. Targeting such individuals with more support during cessation attempts, such as by combining micronutrients with NRT and or general nutritional advice, should be among the issues investigated in future research.

5.3 Research Strengths

The main strength of study two was the rigorous study design, which was placebo-controlled, fully-blind, and randomised. The study was conducted in line with the CONSORT guidelines. The method of the study was prospectively registered on the Australia New Zealand Clinical Trials Registry, ensuring that the pre-specified primary outcome measure and other key design features of the study were not changed after registration. The efficacy analysis of the primary outcome and quit rates were completed by an independent statistician, and the secondary measures were analysed while the researcher was blind to treatment allocation. These measures were put in place with the aim to remove any potential bias.

The trial had broad eligibility criteria and recruited a diverse sample of smokers, helping to ensure to generalizability of findings and adding to the external validity of the results. Particularly important in the NZ context was the participation of Māori (22%) at a rate higher than in the local (8%) and national (15%) population (New Zealand Statistics, 2013), given that Māori have high rates of smoking (Ministry of Health, 2014) and suffer high rates of smoking-related illnesses (Bramley et al., 2005). The selection criteria may also

limit interpretation, given that the results may not generalise to populations such as teenage smokers, medically compromised smokers, or smokers on psychiatric medications.

There were several strengths in the implementation of the current study. Firstly, the use of bio-chemical (CO) validation of self-reported abstinence provided additional assurance that the participants' self-reports were accurate and is recommended by the Society For Research on Nicotine and Tobacco Subcommittee on Biochemical Verification (Benowitz et al., 2002). Analysis of the primary outcome was an intent-to-treat analysis where all participants lost to follow-up were considered to be smoking, thus making it a highly conservative analysis. Withdrawal symptoms, craving, and associated psychological symptoms were measured both at baseline, with treatment alone, and during quitting, and the modified Brinley plots allowed analyses of these scores both within and between groups. Assessment of pre- and post-quit change helps to determine both the withdrawal profile and whether a score reflects nicotine withdrawal symptoms, versus pre-existing traits and response styles (Piper 2011). Reported side effects were mild and might well have been associated with reductions in smoking (American Psychiatric Association, 2013; Hatsukami et al., 1984), and not systematically associated with group membership. This suggests that micronutrient treatment is a safe and readily available alternative for those who have experienced common side effects associated with smoking pharmacotherapy (Cahill et al., 2014; McRobbie et al., 2008; Polosa & Benowitz, 2011; Singh et al., 2011; Thomas et al., 2015; Wu et al., 2006). Participants were not successful at detecting their allocated treatment condition, which increases confidence that the results are not biased by participants detecting that they were not receiving the active treatment.

As with study one, the current study did not require participants to pay for the interventions, and approximate travel costs were covered with petrol vouchers, strengthening the current study as participants were not paying for an intervention that has not demonstrated efficacy in a large RCT study. This may also have limitations as the participants may not be able to pay for micronutrient treatment (or any smoking cessation treatments) in real-life settings. Furthermore, although the petrol vouchers were given as a way to cover travel costs only, they may have provided additional incentives for participants in enrol in the study and attempt to quit smoking. This may mean that the reported quit rates are inflated as incentives are a known smoking cessation intervention (Cahill, Hartmann-Boyce, & Perera, 2015). However, it would be expected that this would be comparable between groups due to the randomised design.

5.4 Research Limitations and Directions for Future Research

Although this research employed a rigorous design, with numerous measures taken to reduce bias and ensure reliable results, some limitations are inevitable in research, particularly when the research is exploratory and the aim is behaviour change. Some of the limitations of study two are discussed below, along with how these limitations of the study could be addressed in future research.

A major limitation of the current research was that it didn't follow all of the criteria proposed by the 'Russell Standard'. The Russell standard are six standard criteria applied to trials of cessation aids where participants have a target quit date and there is face-to-face contact with researchers or clinic staff as proposed by West, Hajek, Stead, & Stapleton, 2005. The six criteria are: (1) Follow-up for 6 or 12 months from the target quit date or the end of a predefined 'grace period', for example, a 2 week period at the start of the quit

attempt, after which the cessation period begins; (2) self-report of smoking abstinence over the whole follow-up period allowing up to five cigarettes in total; (3) biochemical verification of abstinence at least at the 6 or 12-month follow-up period; (4) use of an intention-to-treat approach, where data from all randomized smokers are included in the analysis, unless they are deceased or moved from an untraceable address; (5) following up protocol violators and using their true smoking status in the analysis; and (6) collecting follow-up data blind to smokers' allocation to trial group (West et al., 2005). The current trials only followed up participants for three months post-quit attempt and did not allow for a grace period; however, biochemical validation was used. Participants were counted as not quit if they self-reported smoking cigarettes for ≥three days in a row, instead of the Russell standard of ≤five cigarettes in total. Intention-to-treat analysis was used for the primary outcome, and protocol violators (that were not lost to follow-up) true smoking status was used. Follow-up data (up to three months) were collected while researchers and participants remained blind to smokers' allocation; however, there was no follow-up once participants completed the randomized phase. Furthermore, the current study had a biochemical validation of abstinence cut off set at ≤6ppm, as recommended by Bedfont (see www.bedfont.com). However, the Society for Research on Nicotine and Tobacco suggests a cut off of 8ppm (Benowitz et al., 2002). Although no participants who self-reported abstinence were between the 6-to-8ppm cut off, this could have contributed to a major limitation in the current study.

The current study used 0.8 (80%) power to calculate sample size. The reason for selecting 0.8 and not 0.9 power was due to this research being exploratory (i.e., the first RCT using micronutrients in smoking cessation). A high power, and therefore larger sample size, can be unethical in exploratory research as it may waste participants' time and subject them

to a non-efficacious intervention. Also, with larger sample sizes more resources are needed, and these may also be wasted. However, using a smaller power may have subjected the current research to be more prone to Type I or II error.

A serious limitation of this study was the result of the higher than expected drop-out rate (60%), which reduced the sample size for full (12-week) participation, increased the width of the CIs, and reduced power to detect within and between-group differences. In addition to dropping out, participants might also not be compliant with the requirements to consume 12 capsules/day (a considerable challenge), and might also fail to comply with other study requirements such as keeping appointments and maintaining diary records. As Figure 4.2 shows, those who failed to consume their capsules also tended to drop-out. The three analyses reported – ITT, full intervention, and per-protocol – were thus differentially affected by drop-out, non-compliance, and non-adherence, with the ITT analysis the most and the per-protocol analysis the least affected. As Tables 4.6-4.8 shows, there is a fairly systematic trend for the OR for each comparison to increase from the ITT analysis to the per-protocol analysis, reflecting the systematic reduction in the influence of these factors on the outcomes reported.

In addition to frank dropping out, compliance with the requirements to consume 12 capsules/day was low for both the micronutrient (35%) and placebo (40%) groups, and compared with previous smoking cessation RCTs, which have reported adherence with instructions of approximately 80% (Anthenelli et al., 2016; Koegelenberg et al., 2014; Rose & Behm, 2016). Analysis of those participants who did not drop-out at 12-weeks post-quit revealed comparable rates of compliance with 83% of the micronutrient group and 90% of the placebo group capsule consumption compliant for the full intervention. Unfortunately,

due to the majority of participants who dropped out not replying to contact attempts, it is impossible to ascertain the reasons for drop-out. The consumption of 12 capsules a day, keeping up with study requirements such as keeping appointments and completion of the daily diary may have become tedious for some participants and only those with a high level of commitment to the micronutrient treatment may have been able to follow the full treatment regime.

Since the study completion, the bioavailability of the formula has been improved, reducing the dose down to eight capsules per day which could be taken as two doses. This change could address adherence in future studies, as adherence is inversely proportional to frequency of the dose, and simpler dosing helps to maximise adherence to drug therapy (Osterberg & Blaschke, 2005). Furthermore, complex capsule taking regimens and failing to explain benefits and side effects of a treatment adequately contributes to poor adherence (Osterberg & Blaschke, 2005) and this was present in the current study due to the experimental nature of the trial and its fully-blinded nature. Future research should investigate the reasons for drop-out and efforts to reduce the drop-out should be taken. Future research should also aim to support participants to be compliant and adherent to study protocols.

Having multiple dependent variables and measuring them at multiple study way-points increased the chance of making a Type 1 error; however, all the significant efficacy results in the sub-sample analyses were in the same direction, namely, favouring micronutrient treatment over placebo, indicating that it is unlikely our findings were compromised by false positives (Bender & Lange, 2001). The presentation of effect sizes, confidence intervals, and clinical and practical significance (e.g., how many responded to

treatment) provides additional assurance regarding the clinical interpretation of our findings and follows an approach that is increasingly being encouraged (Cumming, 2013; Haig, 2014; Mark, Lee, & Harrell, 2016). Given that many of the observed efficacy effect sizes were small to medium, results should be considered encouraging, but preliminary, as is consistent with findings from exploratory studies. Further direct and systematic replication studies (Haig, 2014) with larger samples (>600 participants), consistent with other recent smoking cessation RCTs conducted in NZ (Bullen et al., 2013; Walker et al., 2011; Walker et al., 2012), in double-blind randomised controlled designs are needed to determine if micronutrients consistently enhance quitting and abstinence for all smokers and to explore their full potential as a smoking cessation intervention.

Some individuals who are trying to achieve abstinence may also benefit from combination therapy, e.g., the simultaneous use of different micronutrient and nicotine replacement therapies (NRT). Combination therapy can capitalize on the synergy obtained from two different mechanisms of actions (Ramon, Morchon, Baena, & Masuet-Aumatell, 2014). Researchers also need to establish the optimal duration of treatment. Perhaps an intervention that is longer than 12 weeks would be of greater benefit for long-term abstinence. Both study one and two would have been strengthened by the analysis of Quitline use information. Although this analysis was outside of the scope of the current thesis it cannot be ruled out that the micronutrient and placebo groups had different amounts of Quitline use (an active intervention) and this may have skewed the outcome of the results.

The approach used in the current study was to analyse withdrawal symptoms of the randomised sample, regardless of their smoking status. This has the advantage of increasing

the generalizability of the findings; however, the results may become contaminated because participants who smoke/lapse during withdrawal possibly have a decrease in their symptoms (Jorenby et al., 2006). Given that the placebo group smoked significantly more cigarettes than the micronutrient group during the first six weeks of treatment, this contamination may have varied across groups. Fiore, Smith, Jorenby, and Baker (1994) found that those who lapsed during a quit attempt reported weaker withdrawal symptoms than those who did not relapse. Future research could be supported by only assessing tobacco withdrawal in those who are completely abstinent after quit date, thereby eliminating the possibility of confounding effects from contamination due to smoking. However, this will also decrease the sample size and generalizability of the results, and the participants' receiving placebo may be more likely to smoke and therefore excluded from the analyses, and this might result in the treatment condition being confounded with participant type.

5.5 Conclusion

The current thesis presents two studies that are the first randomised controlled trials to investigate a broad-spectrum micronutrient formula to support smoking cessation, reduction of cigarettes/day, and decrease withdrawal symptoms. Over the two studies reported and the research by Harrison et al. (2013), the results tentatively support the use of micronutrients as a treatment to assist smoking cessation and reduce cigarette consumption. Researchers will continue to seek treatments for smoking cessation because of the high prevalence of smoking, its adverse health effects, side effects, and high relapse rates experienced by those using current quit-smoking methods. Treatment options that increase quitting rates, reduce cigarette consumption, and decrease withdrawal symptoms,

especially those treatments that are relatively inexpensive to implement and that have few side effects clearly deserve further exploration and research.

Thesis Summary

Over the two studies completed and the research by Harrison et al. (2013) into the effects of micronutrients on smoking, the results support a tentative conclusion that there is a replicated, small, positive treatment effect, favouring micronutrient treatment over baseline or placebo. The use of several effect sizes measures, and the agreement between them for quit rates and cigarette/day reduction, provides meaningful information regarding the clinical interpretation of our findings and follows an approach that is now strongly recommended (Biswas, 2017; Cumming, 2013; Gigerenzer, 2018; Gigerenzer & Marewski, 2015; Hubbard, 2004; Hubbard & Lindsay, 2008; Kline, 2013; Lakens, 2013; Sedlmeier, 2009; Sullivan & Feinn, 2012; Wasserstein & Lazar, 2016). Given that many of the observed effect sizes were small to medium, the results should be considered encouraging, but preliminary, as is consistent with findings from an exploratory research such as this. Although there was considerable intra- and inter-variability in withdrawal symptoms, the results consistently show that the micronutrient supplement supported larger reductions in the majority of withdrawal and psychological symptoms during the pre-quit phase, when participants were attempting to reduce cigarettes/day. Further direct and systematic independent replication studies (Haig, 2014) with larger samples in fully-blind RCTs are needed to determine if micronutrients consistently enhance quitting and abstinence, and support withdrawal for all smokers.

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Appendices

Appendix I. ***An Introduction to Single-case Research Design***

Single-case research designs (SCRD) are a family of research designs that specify the design, conduct, and analysis of true experiments (i.e., experiments that permit the drawing of causal inferences) where the focus is on single cases not group aggregates. Broadly speaking, SCRD can be characterised as *quantitative ideographic* designs, in contrast to the *quantitative nomothetic* designs used within the group-based Null Hypothesis Statistical Test (NHST) tradition or the *qualitative ideographic* designs used in qualitative social science research. In this context, nomothetic refers to research that is focussed on group average results obtained from samples for the purpose of making inferences at the population level in order to support some highly general statement or law. Ideographic research is directed at understanding individuals in context (Lamiell, 1998). Formal SCRD emerged in the middle of the 20th C, based on principles articulated by late 19th and early 20th C physiologists, notably Claude Bernard and Ivan Pavlov. Bernard's *Introduction `a l'étude de la medicine expérimentale* (Bernard, 1985; translated into English as *An Introduction to the study of experimental medicine* in 1927; Dover edition 1957) is often taken as the first systematic exposition of the principles of SCRD. Pavlov's *Conditioned Reflexes* (Pavlov, 1927) is in the same tradition.

Although single-case methods were widely used in psychology prior to World War II (Smith, Best, Cylke, & Stubbs, 2000), group research and group statistical inference became dominant in the course of what has been called the inference revolution of the 1950's (Rucci & Tweney, 1980). This saw the wholesale adoption in psychology research of the factorial designs and inferential NHST analyses developed by R.A. Fisher, all of which required group

aggregate data (Blampied, 2013). Only recently has the hegemony of this tradition been challenged (Balluerka, Gomez, & Hidalgo, 2005; Nickerson, 2000; Wilkinson & Task Force on Statistical Inference, 1999) along with allegations of it being associated with many questionable research practices (see https://replicationindex.wordpress.com/2015/01/24/questionable-research-practices-definition-detect-and-recommendations-for-better-practices/) and a replication crisis adversely affecting research in psychology and the health sciences (Gigerenzer, 2018).

Despite the dominance of NHST following the inference revolution of the 1950's, SCRD continued to be developed and used, but only by a small minority of researchers. Skinner (1938), in founding the area known as the experimental analysis of behaviour (also known as the study of operant behaviour), espoused SCRD, and these were formalized for use in laboratory research by Sidman (1960). In time, applied researchers began to extend the principles of SCRD for use in applied settings, particularly in the assessment of therapy outcomes. The first systematic statement of applied SCRD was by Hersen and Barlow (1976; 3rd Ed 2009), with other important contributions by Barlow, Hayes, and Nelson (1984) and (for health research) by Morgan and Morgan (2009).

The core element of SCRD is a single case. This is very frequently a single individual, but may be a unit composed of individuals sharing some common attribute, such as a family, class, team, or work group, etc (Valsiner, 1986). Once a target response/behaviour has been identified repeated measurement of the target as performed by the case can begin. Measures (ideally, many measures) are made under constant conditions to form a data time series in an experimental phase called *baseline*. The baseline phase serves to establish, for the particular case, the level of the response, any trends (increasing,

decreasing, cyclical), and the variability typical of the case. It is important for the integrity of SCRD that the baseline be stable (within limits), since the baseline time series serves as the comparison phase against which any change occurring in the subsequent treatment phase (the phase where the independent variable, IV, is experienced by the case) is assessed. Differences in the data paths between baseline and treatment phases permits the detection of any change occurring coincident with the application of the IV. All SCRD are composed of baseline-treatment phase pairs (cf the basic element of any group design, which is the control and the treatment group). For information about the full range of SCRD the reader is referred to Cooper, Heron, and Heward (2007) and/or to Barlow, Nock, and Hersen (2009). What follows is a brief statement of key features of two common SCRD.

The detection of change (if any) is the first essential step in any SCRD, but it is not sufficient to justify a conclusion that the IV caused the observed change; this requires *replication*. Replication may be achieved in different ways; these give rise to different forms of SCRD (Cooper, et al, 2009). Some replications may be accomplished within-case. For instance, in reversal (also known as withdrawal) designs, the IV is withdrawn after the initial baseline phase (said to be a reversal to baseline conditions) and then after a time (a second baseline phase) reintroduced in a second treatment phase. If the change observed initially then disappears, with the data returning to baseline levels coincident with the removal of the IV and then re-appears with the reintroduction of the IV, a causal inference that the IV caused the change is tentatively drawn. This conclusion may be made less tentative by way of additional direct replications with the same or other cases. Only when there is evidence of consistent replication of treatment effects is there some confidence established in the reliability of the IV as a cause of the observed behavioural changes. Reversal designs require that any desirable changes observed in the initial treatment phase be permitted to reverse

in the reversal phase, which may be impractical or even unethical. For that reason such SCRD are not commonly used to assess treatments of damaging behaviour, such as smoking or illicit drug consumption.

Between-case replications are illustrated by one form of multiple-baseline design, namely the multiple-baseline across participants/cases design. This design is now the workhorse design for applied behaviour analysis and is suitable for investigating treatments for smoking and drug addiction because no treatment withdrawal occurs. In the design, several cases participate in the research, either recruited concurrently or sequentially (non-concurrently). All cases enter the study in the baseline phase. When baseline stability is achieved for one case, the IV (treatment) is introduced for that case and a further time-series of data in the treatment phase is recorded; all other cases remain in baseline. After some further baseline data has been recorded for the other cases, one further case is exposed to the IV, and so forth until all cases have experienced treatment. There are as many opportunities to observe change coincident with the introduction of the IV as there are case in the design (a minimum of three is required); consistent replication of change when and only when the IV is introduced is the basis for drawing the tentative inference that the IV caused the change, with the additional proviso that the different baseline phase lengths rule out some potential confounding variables, such as the change being due to regression to the mean, or to non-specific effects of participation in the study and/or exposure to measurement. Again, further direct replication with additional cases helps strengthen the conclusion that the treatment reliably caused the change.

The logic of SCRD is thus profoundly different from that of group designs with NHST. Participants are not simply regarded as samples from some putative population, serving

only to supply sample statistics for the estimation of population parameters. SCRD researchers are not interested in inferences about abstract population parameters, but about the extent, reliability and consistency of treatment-induced changes in target responses by individual cases. Replication, via direct, systematic, and clinical replication (Barlow, et al., 1984), is the key for drawing inferences. There is no equivalent of the computation of a *p*-value or its comparison to some criterion for statistical "significance". There is, therefore, no equivalent in SCRD to the common confusion in group NHST research of statistical with clinical significance Wasserstein & Lazar, 2016), nor is there any direct equivalent to power calculations in SCRD, although the number and consistency of replications somewhat serves as a measure of power in SCRD.

SCRD are rarely taught as part of the curriculum of research methods in psychology or the health sciences (Aiken, West, & Millsap, 2008; Friedrich, Childress, & Cheng, 2018). Nevertheless, they have received increasing recognition as valid ways to identify evidence-based treatments in psychology and the health sciences. Twenty years ago Chambless and Hollon (1998) stated that properly conducted SCRD with sufficient independent replications were the equivalent of randomised-controlled trials (RCT) for determining the efficacy of psychological treatments. Very recently, the American Psychological Association Publications and Communications Board Taskforce reported on standards for reporting qualitative research (Appelbaum, Cooper, Kline, Mayo-Wilson, Nezu, & Rao, 2018) and specified standards for SCRD along with those for other qualitative approaches such as RCTs and other clinical trials, and meta-analyses, supplementing work by Smith (2012) and the CONSORT statement of N=1 designs (Shamseer, et al., 2015). These several statements can be taken as evidence that, although generally poorly understood and seriously underutilised in clinical research, SCRD are fully valid ways of doing clinical science.

Appendix II. Ingredients of Daily Essential Nutrients™ and Placebo with recommended daily allowances (RDA) for adults given in the same unit

Ingredients:	**1 capsule**	**12 capsules**	**Male RDA**	**Female RDA**
Vitamin A (as retinyl palmitate)	384 IU	4,608 IU	3000	2333
Vitamin C (as ascorbic acid)	40 mg	480 mg	90	75
Vitamin D (as cholecalciferol)	200 IU	2,400 IU	600	600†
Vitamin E (as d-alpha tocopheryl succinate)	24 IU	288 IU	22.5	22.5
Vitamin K (as phylloquinone)	6 mcg	72 mcg	120	90
Vitamin K (as menaquinone-7)	2 mcg	24 mcg	120	90
Thiamin (as thiamin mononitrate)	4 mg	48 mg	1.2	1.1
Riboflavin	1.2 mg	14.4 mg	1.3	1.1
Niacin (as niacinamide)	6 mg	72 mg	16	14
Vitamin B6 (as pyridoxine hydrochloride)	4.7 mg	56.4mg	1.3	1.3†
Folate (as L-methylfolate calcium)*	53.3 mcg	639.6 mcg	400	400
Vitamin B12 (as methylcobalamin)	60 mcg	720 mcg	2.4	2.4
Biotin	72 mcg	864 mcg	30	30*
Pantothenic acid (as d-calcium pantothenate)	2 mg	24 mg	5	5*
Calcium (as chelate)	88 mg	1,056 mg	1000	1000†
Iron (as chelate)	0.9 mg	10.8 mg	8	18†
Phosphorus (as chelate)	56 mg	672 mg	700	700
Iodine (as chelate)	14 mcg	163.2 mcg	150	150
Magnesium (as chelate)	40 mg	480 mg	400	310†
Zinc (as chelate)	3.2 mg	38.4 mg	11	8
Selenium (as chelate)	13.6 mcg	168 mcg	55	55
Copper (as chelate)	0.5 mg	5.8 mg	0.9	0.9
Manganese (as chelate)	0.6 mg	7.7 mg	2.3	1.8*
Chromium (as chelate)	42 mcg	504 mcg	35	25*†
Molybdenum (as chelate)	10 mcg	120 mcg	45	45
Potassium (as chelate)	16 mg	192 mg	4700	4700
Choline bitartrate	36 mg	432 mg	550	425*
Alpha-lipoic acid	33.3 mg	399.6 mg	-	-
Mineral wax	12.5 mg	150 mg	-	-
Inositol	12 mg	144 mg	-	-
Acetylcarnitine (as acetyl-L-carnitine hydrochloride)	4 mg	48 mg	-	-

Grape seed extract	3 mg	36 mg	-	-
Ginkgo biloba leaf extract	2.4 mg	28.8 mg	-	-
Methionine (as L-methionine hydrochloride)	2 mg	24 mg	-	-
Cysteine (as N-acetyl-L-cysteine)	2 mg	24 mg	-	-
Germanium sesquioxide (as chelate)	1.4 mg	16.6 mg	-	-
Boron (as chelate)	0.2 mg	1.9 mg	-	-
Vanadium (as chelate)	0.1 mg	1.0 mg	-	-
Lithium orotate (as chelate)	0.07 mg	0.8 mg	-	-
Nickel (as chelate)	0.002 mg	0.024 mg	-	-

*reference values are given as Adequate Intake not RDA as RDA not available, †RDA varies with age

Placebo Ingredients	15 capsules(mg)
Fiber Acacia Gum	4500.00
Maltodextrin	5938.50
Cocoa Powder	60.0
Riboflavin Powder	1.5

Appendix III. Information sheet Study one

Nutritional supplements and withdrawal symptoms in smoking cessation

Information Sheet for Participants

Principal Investigator: Phillipa Newton (phillipa.newton@pg.canterbury.ac.nz)

Other investigators: Assoc Prof Neville Blampied (Neville.blampied@canterbury.ac.nz), Assoc Prof Julia Rucklidge (Julia.Rucklidge@canterbury.ac.nz),

What is the purpose of the study?

This study is interested in investigating the impact of a micronutrient formula on symptoms of withdrawal and negative affect related to the withdrawal from nicotine dependence because of cigarette smoking. The supplement we are studying is called Daily Essential Nutrients (revised version of EMPowerplus). You are invited to participate in this study as you are a current smoker with no acute or chronic illness and are not currently on psychoactive medication.

What would I have to do?

If you agree to take part you will be asked to do the following:

Over an eight month period you will be required to come in to the laboratory at the University of Canterbury 6 times, during these meetings you will fill out questionnaires to measure mood, withdrawal, anxiety sensitivity, and nicotine dependence.

Monitor number of cigarettes smoked, and withdrawal and mood symptoms for 1, 2, or 3 weeks while continuing with a normal smoking pattern.

After the 1, 2, or 3 weeks take four capsules three times a day of a micronutrient or a placebo for four weeks. On specific days during these four weeks you will monitor for cigarette smoking, withdrawal and mood.

After the four weeks of taking the capsules you will attempt to quit smoking.

For a six month period you will abstain from smoking while continuing to take four capsules three times a day. During the first month you will be required to monitor cigarette smoking, withdrawal and mood measures, after this you will only monitor the measures on the last week of each month.

If you relapse in to a normal smoking routine before the end of the six months it will signal the end of your involvement in the study.

What are the risks?

You may experience some physical effects of withdrawal and/or become stressed during smoking cessation. You may also experience some emotional distress of increased stress and negative affect during smoking cessation. Quitline has many resources to minimize this risk.

Although we have no reason to suspect that this supplement can harm a physically healthy individual in any way, we will monitor you throughout the trial by asking you whether you are experiencing side effects or other changes to your physical or mental health.

This type of supplement has been used by many people for many years without any unpleasant results reported. More recently, investigators in Canada have published a research paper outlining the safety of the micronutrients being studied. Data were assembled from all the known published and unpublished studies for the complex formula with the largest amount of published research in mental health. Biological safety data from 144 children and adults were available from six sources: there were no occurrences of clinically meaningful negative outcomes/effects or abnormal blood tests that could be attributed to toxicity. In our trials conducted here at Canterbury, we have assessed to date over 100 participants taking micronutrients for up to 4 months. There were no abnormal blood results that concluded that these micronutrients were having an adverse effect on liver and kidney function. Further, any side effects reported by this sample were temporary and mild.

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. Other side effects that are reported by people taking micronutrients are headaches and stomach aches, although they are typically mild and transitory. These difficulties can be avoided by taking capsules on a full stomach, and so we suggest you *always take your capsules with food and plenty of water.* We will review side effects fortnightly 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+.

Micronutrients have the potential to interact with other medicines or drugs so you should avoid taking 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 to take other medications, such as over-the-counter medications to treat colds, flu, stomach upset and sleep problems, because they may interact with the micronutrients, 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 the micronutrients 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 DSD. 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 DSD.

For safety reasons if you are, or become pregnant, *you will have to withdraw from the study.* Pregnancy should be avoided while taking the supplements. Further, we advise that during the trial, if relevant, you use appropriate contraception.

Will I benefit if I take part?

There may or may not be a direct medical benefit to you. Your withdrawal symptoms may be improved during the study, and negative affect levels may decrease, but there is no guarantee that this research will help you. The information we obtain from this study may help us to provide better interventions in the future for patients suffering from nicotine dependence.

Do I have to participate?

If you decide not to participate in this study, or if you decide part-way through that you want to stop, you are certainly free to do so. This decision will not influence your ongoing health care in any way. Similarly, the study's investigators might choose to end your participation in the study at any time for any reason. If new information becomes available that might affect your willingness to participate in the study, you will be informed as soon as possible.

Will I be paid for participating, or do I have to pay for anything?

Arrangements will be made with each individual participant to ensure that your transportation costs to the university (to meet with the investigator) and parking are covered. The capsules that you will take during the study will be provided at no cost.

Will my records be kept private?

I will take particular care to ensure the confidentiality of all data gathered for the study. I will also take care to ensure anonymity in publications of the findings. Neville Blampied and Julia Rucklidge will also have access to the data obtained during the study. Data will be stored on password protected computer files on the UC system with paper records held in locked storage in the Psychology Department for 10 years. It will then be destroyed.

What happens after the study?

If you feel you have benefited at the end of the trial, and want 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. Quitline will also be available after the end of the study.

The results of this research will be reported in a thesis held digitally in the UC library, reported at professional and scientific conferences, submitted for publication in peer reviewed scientific articles, and may be publicized in the media. You may request the reports from this study.

Who can I contact during the study if I have a question?

If you have any questions throughout the study you can contact me (details above) or the supervisors of this research by email Neville.blampied@canterbury.ac.nz and Julia.rucklidge@canterbury.ac.nz. This project has received ethical approval from the University of Canterbury Educational Research Human Ethics Committee, and you should address any complaints to The Chair, Educational Research Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz)

If you understand and agree to take part in the study please complete the attached consent form.

I am looking forward to working with you and thank you in advance for your contributions.

Phillipa Newton

Appendix IV. Consent form Study one

Using Micronutrients in smoking cessation

Consent form for participants

Principle Investigator: Phillipa Newton

Other Investigators: Profs Neville Blampied & Julia Rucklidge

I have read and I understand the information sheet dated 10/06/2013 for volunteers taking part in the study designed to assess the impact of a micronutrient formula on quit success and the associated withdrawal symptoms and psychological measures during a smoking cessation intervention. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my continuing health care. I also understand that I may withdraw any information already provided.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study. I understand that the treatment, or investigation, will be stopped if it should appear harmful to me. I understand the compensation provisions for this study. I have had time to consider whether to take part. I know who to contact if I have any side effects to the study, or if anything occurs which I would consider a reason to withdraw from the study. I know who to contact if I have any questions about the study.

I wish to receive a copy of the results YES/NO

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

I consent to being contacted 3 months after completion of the study regardless of whether I chose to continue to take the micronutrients and at that point I can choose whether to complete questionnaires. YES/NO

I consent to my name being placed in a separate database so that I can be contacted in the future should there be other studies for me to participate in with the understanding that I can choose whether to participate in such studies or not.

YES/NO

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

I hereby consent to participate.

Signed:		Date:	
Printed name:			
Signature of person who gained consent:			
Address for results:			

The person who may be contacted about the research is:

Principle Investigator: Phillipa Newton, phillipa.newton@pg.canterbury.ac.nz

Or: Julia Rucklidge & Neville Blampied

A signed copy of this consent form has been given to you to keep for your records and reference. Ingredients of Daily Essential Nutrients are on the following page.

Appendix V. Study One Ethics Approval

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

HUMAN ETHICS COMMITTEE

Secretary, Lynda Griffioen
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2013/55

10 June 2013

Phillipa Newton
Department of Psychology
UNIVERSITY OF CANTERBURY

Dear Phillipa

The Human Ethics Committee advises that your research proposal "Nutrients and withdrawal from smoking cessation" has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your emails of 4 and 10 June 2013.

Best wishes for your project.

Yours sincerely

Lindsey MacDonald
Chair
University of Canterbury Human Ethics Committee

Appendix VI. Consent form Study two.

CONSENT FORM

Title of the research project: Using micronutrients in smoking cessation: A randomised controlled trial.

Principal Investigator: Phillipa Newton

Other Investigators: Profs Neville Blampied & Julia Rucklidge

I have read and I understand the information sheet dated 5 February 2015 for volunteers taking part in the study designed to assess the impact of a micronutrient formula on quit success and symptoms of withdrawal from nicotine dependence. I have had the opportunity to discuss all four phases of the study and any questions I had have been answered. I am happy with the answers I have been given. I understand that taking part in this study is voluntary (my choice) and that I may stop taking part in the study at any time and this will in no way affect my continuing health care. I also understand that I may remove any information already provided.

I understand that my participation in this study is private and confidential and that no material that could identify me will be used in any reports on this study. I understand that the treatment, or investigation, will be stopped if it should appear harmful to me. I understand the payment for this study and that all costs to me are covered. I have had time to consider whether to take part. I know who to contact if I have any side effects to the study, or if anything occurs which I would consider a reason to withdraw from the study. I know who to contact if I have any questions about the study.

I agree to take part in phase one (baseline phase) of the study:

YES/NO

I agree to take part in phase two (pre-quit) of the study:

YES/NO

I agree to take part in phase three of this study, the quit phase where I will attempt to quit smoking to the best of my ability:

YES/NO

I agree to the phase four of this study, and open-label phase where I know I will be taking the active micronutrient, Daily Essential Nutrients

YES/NO

I wish to receive a copy of the results YES/NO

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

I consent to being contacted 3 months after completion of the study regardless of whether I chose to continue to take the micronutrients and at that point I can choose whether to complete questionnaires.

YES/NO

I consent to my name being placed in a separate database so that I can be contacted in the future should there be other studies for me to participate in with the understanding that I can choose whether to participate in such studies or not.

YES/NO

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

I hereby consent to participate.

Signed:		Date:	
Printed name:			
Signature of person who gained consent:			

The person who may be contacted about the research is:

Principal Investigator: phillipa.newton@pg.canterbury.ac.nz

Or: Julia Rucklidge and Neville Blampied

A signed copy of this consent form has been given to you to keep for your records and reference. Ingredients of Daily Essential Nutrients attached.

Appendix VII. Information sheet Study two.

05-02-2015

Using Micronutrients in Smoking Cessation: A randomized controlled trial

Information Sheet for Participants

Principal Investigator: Phillipa Newton (phillipa.newton@pg.canterbury.ac.nz)

Mobile: 0273909422

Other investigators: Professor Neville Blampied (Neville.blampied@canterbury.ac.nz), Professor Julia Rucklidge (Julia.Rucklidge@canterbury.ac.nz),

What is the purpose of the study?

This study is interested in investigating the impact of a micronutrient formula (vitamins and minerals) on quit success, symptoms of withdrawal and low mood related to the withdrawal from nicotine dependence because of cigarette smoking. The supplement we are studying is called Daily Essential Nutrients. You are invited to participate in this study as you are a current smoker with no acute or chronic illness and are not currently on psychoactive medication (e.g. anti-depressants).

What would I have to do?

The study has four phases and if you agree to take part you will be asked to do the following during each phase (each visit to the University will take approximately an hour and free parking is provided):

Baseline (1-2 weeks): You will be asked to come in to the University of Canterbury to complete baseline questionnaires on smoking history, nicotine dependence and withdrawal, and associated psychological measures. After the first meeting you will complete a daily diary for one-two weeks that asks questions on smoking habits and withdrawal. Please do not change your smoking habits during this phase.

Pre-quit (4 weeks): After the 2 baseline phase you will be asked to come back to the University and complete questionnaires again. The pre-quit phase is a four-week phase of taking the capsules (non-active placebo or active micronutrient) to prepare you for quitting smoking. You will titrate up to your full dose of 12 capsules per day over seven days, once you are at the full dose you take four capsules three times daily until the end of the four weeks. In the first and last week of this phase you will monitor for cigarette smoking and withdrawal using the daily diary. At the end of this phase you will receive an email of things to do to prepare you to quit smoking.

Quit Phase (12 weeks*): After the four weeks of taking the capsules you will attempt to quit smoking on a target quit date.You will follow Quitline New Zealand's structured program to help you quit as well as continuing to consume 12 capsules every day. The researcher will help you to set up with Quitline. For the first month of phase three you will complete a daily diary of smoking habits and withdrawal, every two weeks you will receive an email and text reminder to complete online questionnaires. At weeks four and eight of this phase you come back in to the University to complete questionnaires, receive more capsules, and have a talk with the researcher about your smoking cessation plan. During week 7 and week 11 of this phase you will complete the daily dairy asking about smoking and withdrawal, you will be reminded of this by a text message and email. If you smoke at any time please text, call, or email the researcher. If you smoke for 3 days in a row this is counted as having a relapse and the researcher will call you to make another quit date.

What are the risks?

You may experience some physical effects of withdrawal and/or become stressed during smoking cessation. You may also experience some emotional distress of increased stress and negative affect (low mood) during from attempting to quit smoking. Quitline has many resources to minimize this risk.

Although we have no reason to suspect that this supplement can harm a physically healthy individual in any way, we will monitor you throughout the trial by asking you whether you are experiencing side effects or other changes to your physical or mental health.

This type of supplement has been used by many people for many years without any unpleasant results reported. More recently, investigators in Canada have published a research paper outlining the safety of the micronutrients being studied. Data were assembled from all the known published and unpublished studies for the complex formula with the largest amount of published research in mental health. Biological safety data from 144 children and adults were available from six sources: there were no occurrences of clinically meaningful negative outcomes/effects or abnormal blood tests that could be attributed to toxicity. The company 'Nutratek' provides nutrients for other studies in the department of psychology at the University of Canterbury under the supervision of Julia Rucklidge and Neville Blampied. These studies have all received ethical approval through

either HEC or HDEC. In our trials conducted here at Canterbury, we have assessed to date over 100 participants taking micronutrients for up to 4 months. There were no abnormal blood results that concluded that these micronutrients were having an adverse effect on liver and kidney function. Further, any side effects reported by this sample were temporary and mild.

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. Other side effects that are reported by people taking micronutrients are headaches and stomach aches, although they are typically mild and transitory. These difficulties can be avoided by taking capsules on a full stomach, and so we suggest you *always take your capsules with food and plenty of water.* We will review side effects fortnightly 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+.

Micronutrients have the potential to interact with other medicines or drugs so you should avoid taking 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 to take other medications, such as over-the-counter medications to treat colds, flu, stomach upset and sleep problems, because they may interact with the micronutrients, 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 limited whilst on the micronutrients 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 DEN. 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 DEN.

If you need to take an antibiotic or antifungal agent orally at any time during the trial, please let us know. We ask this because antibiotics and antifungal drugs may interfere with the absorption of the micronutrients. You will be asked to not try any alternative medicines or other forms of therapy until after completing this study.

For safety reasons if you are, or become pregnant, *you will have to withdraw from the study.* Pregnancy should be avoided while taking the supplements. Further, we advise that during the trial, if relevant, you use appropriate contraception.

Will I benefit if I take part?

There may or may not be a direct medical benefit to you. Your withdrawal symptoms may be improved during the study, and your mood may improve during your quit attempt, but there is no guarantee that this research will help you. There is a chance you may receive a placebo (a non-active capsule), this is a double blind study so both you and the researcher will not know whether you receive DEN or placebo. All other aspects of the study will be identical for all participants and you may still benefit from Quitline New Zealand's five-step program and being actively involved in a study. The information we obtain from this study may help us to provide better interventions in the future for patients suffering from tobacco smoking addiction.

Do I have to participate?

Participation is your choice and you can stop at any time.

If you decide not to participate in this study, or if you decide part-way through that you want to stop, you are certainly free to do so. This decision will not influence your ongoing health care in any way. Similarly, the study's investigators might choose to end your participation in the study at any time for any reason. If new information becomes available that might affect your willingness to participate in the study, you will be informed as soon as possible.

Will I be paid for participating, or do I have to pay for anything?

Arrangements will be made with each individual participant to ensure that your transportation costs to the university (to meet with the investigator) and parking are covered. The capsules that you will take during the study will be provided at no cost.

Will my records be kept private?

I will take particular care to ensure the confidentiality of all data gathered for the study. I will also take care to ensure anonymity in publications of the findings. Neville Blampied and Julia Rucklidge will also have access to the data obtained during the study. Data will be stored on password protected computer files on the UC system with paper records held in locked storage in the Psychology Department for 10 years. It will then be destroyed.

What happens after the study?

If you feel you have benefited at the end of the trial, and want to continue taking the supplement, it is commercially available. The researcher will ask at the end of the study if you would like to purchase DEN and contact information so that you can obtain it will be given at this time. Quitline New Zealand (www.quit.org.nz) is a free service that will be

available after the end of the study if you would like to continue using their services. The researcher will ask at the end of the study if you would like to come in to the laboratory to further discuss the five-step program and the services that Quitline offers. The username and password for Quitline made with the help of the researcher will not expire at the end of the study and you can continue to use this for support for smoking cessation.

The results of this research will be reported in a thesis held digitally in the UC library, reported at professional and scientific conferences, submitted for publication in peer reviewed scientific articles, and may be publicized in the media. You may request the reports from this study.

Who can I contact during the study if I have a question?

If you have any questions throughout the study you can contact me (details above) or the supervisors of this research by email Neville.blampied@canterbury.ac.nz and Julia.rucklidge@canterbury.ac.nz. This project has received ethical approval from the University of Canterbury Human Ethics Committee and you should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

If you understand and agree to take part in the study please complete the attached consent form.

I am looking forward to working with you and thank you in advance for your contributions.

Phillipa Newton

Appendix VIII. Study Two Ethics Approval Letter

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

HUMAN ETHICS COMMITTEE

Secretary, Lynda Griffioen
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2015/11

12 February 2015

Phillipa Newton
Department of Psychology
UNIVERSITY OF CANTERBURY

Dear Phillipa

The Human Ethics Committee advises that your research proposal "Using micro-nutrients in smoking cessation: a randomisted controlled trial" has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your email of 5 February 2015.

Best wishes for your project.

Yours sincerely

Lindsey MacDonald
Chair
University of Canterbury Human Ethics Committee

Appendix VIII Study Questionnaires

Demographic Information and Smoking History Questionnaire: Study One

First name:

Surname:

Middle(s) name:

Date of Birth: ___/___/___ Male/Female/Other:

Ethnicity:

Are you:
Married
De-Facto
Single
Divorced
Separated

Address: (please include suburb)

Do you have an email address? Yes / No Email address:

Home phone number:

Mobile phone number:

Are you taking any medication on a regular basis?
Yes / No
Please indicate medications:

Do you have any acute or chronic illnesses? Please list them here along with medications.

Smoking History Questionnaire

Please answer the following questions to the best of your ability.

Age when you had your first puff of a cigarette?

When did you begin regular smoking? (3 cigarettes a day for three consecutive days)

How many cigarettes on average have you smoked per day over the last month?

How many SERIOUS quit attempts have you made in your life? Note: a serious quit attempt lasted more than three days.

How many of these quit attempts lasted six months or over?

Study two baseline questionnaires

First Name:

Last Name:

Middle name(s):

What is your date of birth?

Are you:

Male

Female

Other:

What is your ethnicity?

New Zealand European

Maori

Samoan

Cook Island Maori

Tongan

Niuean

Chinese

Indian

Other

What is your residential address?

What is your email address?

Please write down the number you prefer to be contacted on:

Please write down another contact number:

Are you:
Married
De-Facto
Single
Divorced

Separated

What is your combined house hold income?

If you have ANY acute or chronic illness(es) please list them below (this includes any mental illness)

If you are taking ANY medication(s) on a regular basis please list them below (including psychoactive medication e.g. antidepressants or anti anxiety)

Have you ever been on any psychoactive medication (antidepressants, anti-anxiety etc)

At what age did you have your first cigarette?

At what age did you begin regular smoking? (3 cigarettes a day for three consecutive days)

How many cigarettes have you smoked per day over the last month?

How many SERIOUS quit attempt have you made in your life? (lasted more than three days)?

How many of these quit attempts last SIX months or over?

Are you currently taking any medications for smoking cessation or on nicotine replacement therapy (nicotine patches, e -cigarettes or lozenges)?

What are you currently using for smoking cessation?

Side Effects Questionnaire

Please indicate if, in the last 2 weeks, you have experienced any of the following symptoms.

Dry mouth

Urinary retention

Blurred vision

Constipation

Sedation/lethargy

Sleep disruption

Nightmares

Change in appetite

Skin rash

Weight gain

Headache

Nausea

Gastrointestinal disturbance/diarrhea

Abdominal pain

Inability to achieve an erection

Inability to achieve an orgasm

Loss of libido

Agitation

Anxiety

Other symptoms?

If you have experienced any of these symptoms, what action did you take to remedy them?