Assessing the effects of Coenzyme Q10 supplementation in schizophrenia and schizoaffective disorder:
A double-blind, randomised, placebo-controlled trial

A thesis submitted for the degree of
Doctor of Philosophy

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Declaration:

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work, with contributions from others duly acknowledged within the text.

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A significant portion of Chapter 1 was published as Maguire et al. (2018), a peer-reviewed journal article. It was co-authored with April Hargreaves and Michael Gill and was published in *Nutritional Neuroscience*.

Signed

___________________________
Summary

Background: Schizophrenia is a complex, heterogeneous, neurodevelopmental disorder. Cognitive impairments and negative symptoms such as avolition and asociality are prevalent in the majority of patients with a diagnosis of schizophrenia. They are considered a major source of disability and strongly associated with functional and psychosocial outcomes, as well as ability to engage with psychological interventions. While anti-psychotic medication is typically a mainstay treatment for positive symptoms, there are few widely accessible and low-cost therapies for the remaining features available. Further, there has been a shift towards interventions which not only target symptoms or impairments, but also enhance quality of life and overall functioning. Thus alternative interventions to support people living with schizophrenia, including those which enhance cognition and reduce negative symptoms are receiving increasing attention. One encouraging line of enquiry in the development of effective interventions is based on the hypothesis that the symptoms of schizophrenia, particularly affective and negative symptoms and cognitive impairments are related to mitochondrial function. Coenzyme Q10 (CoQ10) is an endogenous compound that is essential for energy production within the mitochondria, but also functions as a potent anti-oxidant, inhibiting oxidative stress and damage. However, endogenous levels of CoQ10 can decline due to genetic and environmental factors, and associated mitochondrial impairment. Often deficits of CoQ10 are associated with fatigue, myopathy, and cognitive impairment. In light of its many functions, CoQ10 supplementation to minimise decline and improve symptoms has been investigated in multiple disorders associated with mitochondrial dysfunction, including neurological and neuropsychiatric disorders. This thesis investigated the potential role of CoQ10 supplementation in schizophrenia and schizoaffective disorder.

Aims and structure of thesis: The primary aim of this thesis was to examine the potential effect of CoQ10 supplementation on 1) cognitive function and 2) psychological and physical health in schizophrenia. A double-blind, randomised, placebo-controlled trial (RCT) was conducted to assess the effects of CoQ10 supplementation (300mg/day) on the pre-specified primary outcomes of attention and working memory performance after 3 and 6 months of supplementation. Secondary cognitive outcomes were: processing speed, executive function, and estimated current IQ. Secondary psychological symptom outcomes were depression, anxiety, and negative symptoms: avolition, asociality, blunted affect and alogia. Secondary health-related outcomes were: energy, diastolic and systolic blood pressure, physical activity, quality of life, and functional status. Secondary biochemical outcomes were CoQ10 status and mitochondrial function. Chapter 1 discusses findings in the literature supporting the use of CoQ10 supplementation in neurological and neuropsychiatric disorders. Chapter 2 describes the methods employed during the RCT. Methodological issues that presented during the conduct of the RCT and influenced subsequent analyses and interpretation of findings are discussed in Chapter 3. Chapter 4 outlines the results of CoQ10 supplementation on
primary and secondary cognitive outcomes. Chapter 5 outlines the results of CoQ10 supplementation on secondary outcomes: CoQ10 levels, mitochondrial function, energy, psychological, and health-related outcomes. Finally, Chapter 6 presents a general discussion of the findings.

Results: In total 70 patients with a diagnosis of schizophrenia and schizoaffective disorders were randomised to the CoQ10 (300mg/day) and placebo intervention groups. The effects of CoQ10 supplementation were compared to placebo at 3 and 6 months on primary and secondary outcomes. The primary analysis of outcomes was based on complete cases for each outcome variable. Sensitivity analysis followed an Intention to Treat (ITT) approach that used multiple imputations to account for missing values. Overall, there was no effect of CoQ10 supplementation on the primary or secondary cognitive outcome measures at either time point. This is despite observing an increase in plasma CoQ10 concentration at 3 months in the CoQ10 group compared to placebo, a comparative plasma increase which subsequently disappeared at 6 month analysis. Further CoQ10 supplementation also had no effect on mitochondrial function (plasma lactate concentration), energy, psychological and health-related outcomes outcome measures at either time point. Post-hoc secondary analyses including only patients who fully adhered to assigned intervention and those who remained on the same concomitant medication throughout the study also showed no effect of CoQ10.

Conclusion: While a number of limitations including modest sample size, attrition, and adherence may reduce estimates of effect, the results of the study indicate that CoQ10 supplementation confers minimal benefit on cognitive, energy, psychological and health-related outcomes in schizophrenia and schizoaffective disorder. It appears likely that the non-significant findings related to an absence of CoQ10 deficit within schizophrenia.
Role of the Candidate

This thesis includes research that was conducted in collaboration with others. The candidate’s role in the research is detailed below.

Planning: The rationale for the CoQ10 study was conceived by Dr April Hargreaves. Initial ethical approval for the study was obtained from St James’ Hospital/Tallaght University Hospital research ethics committee by Dr April Hargreaves and Prof Michael Gill on 11th April 2016. The candidate contributed to all subsequent ethical applications and amendments. Funding for the study was obtained by Prof Michael Gill and Dr April Hargreaves. Pharma Nord provided the placebo and CoQ10 capsules without charge to this study; this agreement was obtained by Dr April Hargreaves. Pharma Nord had no role in the design, conduct, analysis or interpretation.

Design: The randomised controlled trial was designed by Dr April Hargreaves and Prof Michael Gill. With their supervision, the candidate amended the research protocol to include measures of quality of life, functional status, physical activity and negative symptoms and changed the measure of attention to the Continuous Performance Task-Identical Pairs. Dr Iain Hargreaves (Liverpool John Moores University) developed the blood sample protocol and provided advice regarding blood sample collection, processing and storage. The candidate designed the Study within a Trial (Chapter 3) with advice from Prof Valerie Smith (School of Nursing and Midwifery, TCD).

Conduct: The candidate was responsible for the administration, management, conduct of the CoQ10 study. The candidate was responsible for all participant recruitment and data collection between November 2016 and October 2017. From November 2017 to March 2019 Clinical Research Nurse Christina Mooney assisted the candidate with participant recruitment and assessment. The candidate recruited and conducted assessments with 74% of participants included in this thesis. The study was hosted by the Clinical Research Facility (CRF), St James’ Hospital.

Analysis and interpretation: Dr April Hargreaves defined the sample size calculations and statistical analysis plan to use analysis of covariance to determine between group differences at follow up assessment points. The remaining analyses were defined by the candidate. The candidate consulted Dr Eleisa Heron, Department of Psychiatry, for statistical advice regarding assumptions of general linear models. All statistical analyses included in this thesis were conducted by the candidate. Plasma CoQ10 levels were analysed by Dr Iain Hargreaves and Mr Robert Heaton, Liverpool John Moores University, UK. Dr Iain Hargreaves provided advice regarding interpretation of plasma CoQ10 levels. Dr Suzannah Phillips, Jean Devine and Angela Lambert conducted the lactate biochemical analysis for the study at Liverpool Clinical Laboratories, UK. All interpretations of the results included in this thesis are the candidate’s own. Prof Michael Gill and Dr April Hargreaves provided supervision and direction throughout the study.
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I would like to dedicate this in loving memory of Packy Maguire.
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1 INTRODUCTION

1.1 Introduction

Schizophrenia is a heterogeneous, neurodevelopmental disorder characterised by a range of positive (delusions or hallucinations or both), negative (affective and motivational disturbances) and cognitive symptoms (impaired attention, memory, processing speed, executive function and social cognition). Approximately 0.3% of the population are living with a diagnosis of schizophrenia at any given time (Behan et al., 2008; Saha et al., 2005). Schizophrenia is one of the world’s leading causes of disability (Tandon et al., 2008). The high personal, economic and social burden of the disorder is due to its early onset and persistent symptoms that impact on the individual’s social and occupational functioning, quality of life, physical health, and life expectancy (Schaefer et al., 2013).

Cognitive impairments, which are prevalent in almost all patients with schizophrenia, are considered a major source of disability and strongly associated with functional and psychosocial outcomes, as well as ability to engage with psychological interventions (Galderisi et al., 2014; Kalache et al., 2015; O’Reilly et al., 2016; Schaefer et al., 2013; Wells et al., 2015). Cognitive impairments typically present prior to the manifestation of other symptoms associated with the disorder; abnormal development of the brain including hypomyelination and disrupted connectivity due to genetic and environmental factors appear to result in delayed or impaired acquisition and maintenance of normal cognitive abilities (Bora et al., 2017; Kuhn & Keefe, 2013; Maas et al., 2017). Further, the trajectory of impairments post-onset of the illness may be influenced by multiple factors including anticholinergic burden, substance abuse, and multi-morbidity (Bora et al., 2017; Grover et al., 2019; Lindenmayer et al., 2012; O’Reilly et al., 2016).

Nevertheless, while a general global impairment of cognition is evident in many patients with a diagnosis of schizophrenia, not every person is affected to the same extent (Donohoe et al., 2006; Weickert et al., 2000; Wells et al., 2015). The severity and scope of cognitive impairment in patients is highly heterogeneous reflecting considerable inter- and intra-individual variability (Bosia et al., 2019; Wells et al., 2015). The majority of patients appear to either experience deterioration in general cognitive function from premorbid function or generally compromised low premorbid and current IQ (Weickert et al., 2000; Wells et al., 2015; Donohoe et al., 2006). Patients with deteriorated general cognitive function tend to exhibit greatest dysfunction in verbal and spatial working memory, processing speed and attentional control, whereas those with compromised cognitive function exhibit more severe impairments on almost all cognitive domains including: attention, working memory, processing speed, and executive functions (Weickert et al., 2000; Wells et al., 2015). On the other hand, approximately one quarter of patients’ current IQ or global cognitive functioning is preserved and near to above average, though problems of attention and executive function may still be present (Bosia et al., 2019; Donohoe et al., 2006; Elliott et al., 2019).
The severity and range of cognitive functions affected appear to represent separate cognitive phenotypes in schizophrenia in which different illness trajectories may occur (Wells et al., 2015). Thus though affected to varying degrees at different phases of the condition, core cognitive domains that are typically impaired in schizophrenia include: attention, memory (particularly working memory), processing speed, and executive function (Kanchanatawan et al., 2018; McCleery et al., 2015; Nuechterlein et al., 2004). Impairments within individual cognitive domains as well as global cognitive function have been associated with poor functional and social outcomes and low quality of life (Alpteckin et al., 2005; Green et al., 2000; Nuechterlein et al., 2011; Ritsner et al., 2012). As such they present as meaningful outcomes for intervention and recovery in schizophrenia and related disorders such as schizoaffective disorder.

However, it is important to recognise that though cognition is associated with long-term outcomes, other symptoms of schizophrenia and related disorders also influence quality of life and functional outcomes. For instance, negative symptoms of schizophrenia are also associated with low quality of life, unmet social needs, increased distress, and poor physical health (Galderisi et al., 2014; Kaiser et al., 2017; Milev et al., 2005; Rabinowitz et al., 2013; Selten et al., 2000). Interestingly, cognitive impairments present in schizophrenia are associated with several other symptoms, in particular the presence of negative symptoms. Patients with generally preserved cognitive function tend to present with less severe negative symptoms, while more severe cognitive impairments are associated with increased negative symptoms and fatigue (Bora et al., 2017; Donohoe et al., 2006; Kanchanatawan et al., 2018; Milev et al., 2005). It has been hypothesized that over time, enduring cognitive impairments lead to decreases in motivation and the manifestation of negative symptoms, as the person develops dysfunctional beliefs surrounding their abilities or interactions with others (Green & Harvey, 2014). Symptoms of depression and anxiety are also prevalent in patients with schizophrenia, which in turn are also associated with fatigue, negative symptoms, pain, cognition, and overall quality of life (Gozdzik-Zelazny et al., 2011; Kanchanatawan et al., 2018; Priebe et al., 2011; Reine et al., 2003). As a result there are multiple interlinked symptoms of schizophrenia that influence patient quality of life and functional recovery, and interventions which may target any one or a selection of these interrelated symptoms are of considerable value (Bobes et al., 2007).

Critically, patients with schizophrenia are at increased risk of cardiovascular mortality (Westman et al., 2018). Patients with a diagnosis of schizophrenia frequently present with at least one physical health condition, which is generally related to metabolic disturbances (De Hert et al., 2010; Liao et al., 2011; Lindenmayer et al., 2012). In particular patients are at higher risk of metabolic syndrome, diabetes, hypertension, and hyperlipidaemia compared to the general population; disorders which in themselves are associated with cognitive impairments without psychiatric diagnoses (Liao et al., 2011; Nasrallah et al., 2006). Notably, patients with such metabolic morbidities, poor functional
mobility, and lower cardiorespiratory function tend to exhibit poorer cognitive function compared to patients without (Kim et al., 2019; Lindenmayer et al., 2012).

Cognition and motivational negative symptoms have been identified as the largest unmet treatment needs in schizophrenia (Green & Harvey, 2014). Currently, while antipsychotic medication can be effective in treating the positive symptoms in schizophrenia, they have little positive effect on cognitive function, variable effects on negative symptoms, and minimal evidence for effect on comorbid symptoms (Aquila & Citrome, 2015; Fervaha et al., 2013). Further the aggregative effects of multiple medications to manage comorbid symptoms of anxiety and depression, as well as adverse effects of antipsychotics, can inadvertently add to cognitive impairments (O’Reilly et al., 2016). For example, long term use of benzodiazepines is related to impairments in attention and working memory, while anticholinergic burden appears to not only impair cognitive and social functioning, but also as a consequence impairs ability to participate in psychosocial interventions (Fond et al., 2018; O’Reilly et al., 2016; Tsoutsoulas et al., 2017).

There is also increasing awareness that interventions should enhance quality of life and overall functioning, rather than merely the minimisation of symptoms. As such a number of non-pharmacological interventions to support people living with schizophrenia, including interventions to enhance cognition and reduce negative symptoms have been developed. In particular cognitive remediation and aerobic exercise show robust effects in improving cognitive function and alleviating negative and affective symptoms in schizophrenia and schizoaffective (Firth et al., 2016; Wykes et al., 2008). Aerobic exercise also bestows positive and meaningful effects on cardiovascular and respiratory health (Schmitt et al., 2018; Stubbs et al., 2017). However, engaging patients with a diagnosis in which a core feature is lack of motivation and current treatments are associated with fatigue and lethargy can be difficult (Firth et al., 2016). Further, such interventions can be costly and may not be readily available in rural or under-resourced areas. As such there remains an unmet need for accessible, affordable treatments which may help improve cognition and negative symptoms.

One alternative line of research enquiry in the development of effective intervention is based on the hypothesis that the symptoms of schizophrenia, particularly, fatigue, affective and negative symptoms and cognitive impairments are related to mitochondrial dysfunction. Mitochondrial dysfunction refers to an abnormality (or abnormalities) in essential mitochondrial functions including energy generation via oxidative phosphorylation (OXPHOS), the regulation of apoptosis and cellular calcium levels, and the generation of reactive oxygen species (ROS) (Ben-Shachar, 2002). Oxidative stress may accompany mitochondrial dysfunction and is defined as an imbalance between pro-oxidants, such ROS, and antioxidants, that results in cell damage and disruption to ROS-dependent cellular processes including intercellular communication (Do et al., 2015; Maas et al., 2017). A growing body of evidence implicates mitochondrial dysfunction and oxidative stress in the negative and cognitive symptoms in schizophrenia (Ben-Shachar, 2002; Bergman & Ben-
Recent trials of N-acetylcysteine, a precursor to glutathione that enhances antioxidant capacity, have demonstrated meaningful effects on executive function, working memory, negative symptoms and white-matter integrity in chronic schizophrenia and early psychosis (Berk et al., 2008; Klauser et al., 2018; Rapado-Castro et al., 2015). Thus targeting mitochondrial dysfunction presents as a reasonable avenue to support patients with a diagnosis of schizophrenia or related disorders. Mitochondria are the main energy producers within the cell and coenzyme Q10 (CoQ10) is essential for this energy production within the mitochondria but also functions as an anti-oxidant. CoQ10 can be taken as a nutritional supplement with minimal side effects and has potential value as a supplement intervention in schizophrenia.

1.2 The potential of CoQ10 supplementation in schizophrenia

The following sections review the many functions of CoQ10 and discuss its potential as an adjunctive therapy in schizophrenia.

1.2.1 Functions of CoQ10

CoQ10 is a lipid-soluble compound, synthesised in the inner mitochondrial membrane and is vital for mitochondrial function (Crane, 2007; Turunen et al., 2004). CoQ10 is a critical component of the OXPHOS process in the mitochondrial electron transport chain (ETC) (Turunen et al., 2004). As an electron carrier from complexes I and II to complex III in the ETC, CoQ10 is essential for the synthesis of adenosine triphosphate (ATP), a high energy molecule that stores and transports chemical energy within the cell (Figure 1.1) (Hargreaves, 2014). CoQ10 also helps to maintain mitochondrial membrane potential, which is involved in ATP production (Somayajulu et al., 2005; Turunen et al., 2004). Downregulation of the ATP synthesis pathway and impaired ATP production lead to synaptic fatigue and dysfunction, which have been implicated in the manifestation of several neurological and psychiatric disorders (Manji et al., 2012; Prabakaran et al., 2004; Sun et al., 2006).
ROS are the by-products of ATP production and other biological reactions in the cell. The induction of ROS is necessary for many cellular functions including growth, signalling, synaptic plasticity, learning and memory (Manji et al., 2012). However, chronic exposure or excessive levels of ROS leads to oxidative stress, and can result in damage to lipids, proteins and nucleic acids, contributing to mitochondrial dysfunction and the pathogenesis of disease (Anderson et al., 2013; Ishikawa et al., 2008; Ray et al., 2012). Mitochondrial dysfunction is associated with a shift from OXPHOS to less efficient anaerobic glycolysis in order to meet the cell’s energy requirements, often signified by elevated lactate concentrations (Regenold et al., 2009). When cells are subjected to oxidative stress, CoQ10 enhances DNA resistance to damage and in its reduced form (ubiquinol) CoQ10 acts by removing excessive ROS before they cause critical damage (Somayajulu et al., 2005; Turunen et al., 2004). Elevated ROS levels can also be produced by cytokine activity. This in turn can cause cell injury and death, thereby activating further cytokine pathways (Morris & Berk, 2015; Reuter et al., 2010). By removing ROS, CoQ10 may help mediate this bidirectional relationship between immune-inflammatory pathways and mitochondrial dysfunction (Morris & Berk, 2015). CoQ10 also indirectly supports the regeneration of other antioxidants such as α-tocopherol (Kohen & Nyska, 2002).

Though only 2% of the body’s weight, at rest the human brain utilizes 20% of total oxygen consumption in the body, and approximately 90% of its energy supply is produced through mitochondrial OXPHOS (Erecińska & Silver, 1989; Rolfe & Brown, 1997). This energy is used for
dendritic spine formation, synaptic transmission, maintenance of ionic homeostasis in synaptic terminals, synaptic vesicle recycling, and long-term potentiation (Hjelm et al., 2015). The heavy reliance on oxygen, mitochondrial ATP, and its high lipid content make the brain especially vulnerable to damage due to ROS and dysfunctional OXPHOS (Erecińska & Silver, 1989; Niedzielska et al., 2016). As such, mitochondrial dysfunction, metabolic shifts toward anaerobic glycolysis, and insufficient endogenous CoQ10 may contribute to the manifestation of neurological or neuropsychiatric disorders including schizophrenia.

1.2.2 The relevance of CoQ10 for schizophrenia

Mitochondrial dysfunction has been implicated in the pathophysiology of schizophrenia, both in patients receiving psychotropic medication and medication-free patients (Ben-Shachar, 2002, 2017; Hjelm et al., 2015; Prabakaran et al., 2004). Brains of patients with schizophrenia exhibit abnormal energy metabolism profiles such as altered OXPHOS and increased lactate levels, indicating overreliance upon anaerobic respiration to meet energy demands in the brain (Prabakaran et al., 2004; Rowland et al., 2016). Abnormalities within the mitochondrial ETC may contribute to these altered profiles, and there is evidence for the decreased expression of OXPHOS and ATP synthesis related genes in schizophrenia (Hjelm et al., 2015; Prabakaran et al., 2004). Additionally, complex I activity appears to be positively related to acute positive symptoms, while decreased activity has been observed in patients with residual schizophrenia (Ben-Shachar et al., 2007; Dror et al., 2002; Rosenfeld et al., 2011; Whatley et al., 1996). However, though dysregulation of complex I of the ETC in schizophrenia has been observed, the direction and extent of the dysregulation are inconsistent and highly heterogeneous (Holper et al., 2019). It is likely that the heterogeneity within these bioenergetics findings is influenced by the small sample sizes, brain regions examined, tissue-specific differences between blood samples and post-mortem brain samples, and critically antipsychotic medication (Elmorsy et al., 2017; Hjelm et al., 2015; Holper et al., 2019). There is consistent evidence that antipsychotic medication interferes with mitochondrial ATP generation and ETC complex activity and gene expression, particularly for complex I (Elmorsy et al., 2017; Hjelm et al., 2015; Scaini et al., 2018). Further research is required to disentangle the extent to which mitochondrial abnormalities are intrinsic to schizophrenia from those abnormalities that are induced or exacerbated by antipsychotic medication (Hjelm et al., 2015). Nonetheless, abnormal complex activity in the ETC (whether intrinsic to the disorder or attributable to environmental sources such as antipsychotic medication) may contribute to impairments in ATP production and mitochondrial function in schizophrenia. CoQ10 presents as a potential intervention to support mitochondrial function, due to its ability to restore electron flow in the ETC and thus improve ATP production (Hargreaves, 2014).
Impaired ETC activity may contribute to the presence of oxidative stress in schizophrenia, as dysfunctional mitochondria become less efficient ATP generators but produce more ROS (Prabakaran et al., 2004). Markers of oxidative damage including thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) are elevated in the disorder, and increased levels are associated with a decreased complex I activity (Gubert et al., 2013). Critical antioxidants such as glutathione (GSH) and α-tocopherol are reduced in schizophrenia, further suggesting disturbance of oxidative capacity in schizophrenia (Dadheech et al., 2012; Do et al., 2000). However, findings are conflicting with regard to the relationship between such antioxidant levels and symptom presentation. For example, lower levels of GSH in the posterior medial PFC have been associated with negative symptoms severity (Matsuzawa et al., 2008). However, plasma GSH levels were negatively correlated with positive symptoms but not negative symptoms (Nucifora et al., 2017). There is also some evidence of oxidative damage to DNA and RNA in schizophrenia, potentially due to defects in the ETC and increased ROS generation (Che, 2010; Jorgensen et al., 2013). As a free radical scavenger, CoQ10 may protect the cell from oxidative damage caused by dysfunctional OXPHOS and elevated ROS, whilst also indirectly regenerating anti-oxidants such as α-tocopherol (Duberley et al., 2014; Jahangard et al., 2019; Kohen & Nyska, 2002; Sanoobar et al., 2013; Somayajulu et al., 2005). For example, CoQ10 supplementation attenuated oxidative stress in CoQ10 deficient human neuronal cells, and reduced peripheral markers of oxidative stress in bipolar disorder and multiple sclerosis (Duberley et al., 2014; Jahangard et al., 2019; Sanoobar et al., 2013). Thus, CoQ10 supplementation may help to mitigate the oxidative stress evident in schizophrenia and support mitochondrial function.

To date, two small studies have examined CoQ10 levels in schizophrenia, with conflicting results (Imagawa, 1989; Kumar & Kurup, 2001). Imagawa (1989) noted lower CoQ10 levels in erythrocytes, but not plasma, of patients with schizophrenia compared to healthy controls. The lower erythrocyte levels were observed in patients receiving antipsychotic medication and patients who had never been treated with antipsychotic medication. However, no comparison between medicated and medication-free participants was reported. Therefore it is not possible to fully ascertain whether the difference from controls can be attributed to naturally occurring lower levels of CoQ10 or lipid peroxidation due to oxidative stress, potentially induced by antipsychotic use (Eftekhari et al., 2016; Ficarra et al., 2016; Herken et al., 2001). Further, as erythrocytes do not contain mitochondria they have little functional requirement for CoQ10 compared to other tissues and their utility for clinical assessment of CoQ10 status is uncertain (Molyneux, Young et al., 2008; Niklowitz et al., 2004). CoQ10 concentration within these cells is also thought to be independent of exogenous CoQ10 supply (Niklowitz et al., 2004). A subsequent study documented lower serum CoQ10 levels in 15 patients recently diagnosed with schizophrenia compared to controls (Kumar & Kurup, 2001). Blood CoQ10 concentration is dependent on both liver biosynthesis and dietary sources, therefore values reflect functional CoQ10 status in humans (Molyneux, Young, et al., 2008). In the absence of tissue samples, plasma acts as a suitable
surrogate marker to screen for suspected CoQ10 deficiency and monitoring response to CoQ10 supplementation (Molyneux, Young, et al., 2008). In the two studies, plasma and serum CoQ10 concentration appeared, on average, to be within the normal range (Molyneux, Young et al., 2008; Duncan et al., 2005). Unfortunately, neither study reported evaluating clinical symptoms or features alongside CoQ10 levels. To the author’s knowledge there are no other investigations of CoQ10 levels in schizophrenia. Further, little is known about the effects of antipsychotic medication on CoQ10 levels specifically, though it does appear that antipsychotic administration decreases complex I activity and ATP generation, and increases ROS generation and lipid peroxidation (Balijepalli et al., 2001; Chan et al., 2019; Elmorsy et al., 2016, 2017). However, it has been reported that amitriptyline a tricyclic antidepressant decreased CoQ10 levels and increased lipid peroxidation in peripheral blood mononuclear cells of patients with depression (Moreno-Fernández et al., 2012). Larger studies with patients with and without medications are required to further consider whether CoQ10 levels, particularly plasma CoQ10 levels, are related to mitochondrial function, clinical diagnosis and the presentation of symptoms in schizophrenia.

Compromised brain energy metabolism and impaired mitochondria in schizophrenia may contribute to cognitive deficits and negative and affective symptoms due to an inability to meet neuronal energy demands and consequential synaptic fatigue and disturbances in long- and short-term potentiation (Ben-Shachar & Laifenfeld, 2004; Scaini et al., 2016). Although the underpinning evidence base for CoQ10 status in schizophrenia is incomplete, there is increasing evidence that energy production is impaired and oxidative stress increased in schizophrenia. It is reasonable to suggest that such processes may be repaired and cognitive function and negative symptoms improved through the use of CoQ10 supplementation to improve ATP production and reduce oxidative stress in neuropsychiatric disorder such as schizophrenia. However, the potential for CoQ10 supplementation to improve cognitive function and clinical symptoms in schizophrenia has yet to be determined.

Several trials have examined the effect of CoQ10 supplementation in neurological and neuropsychiatric disorders, and the most robust studies have examined the effects on maintaining global function in the context of disease progression rather than improvement (Huntington Study Group, 2001; McGarry et al., 2017). Likewise, fatigue and depression which frequently present in schizophrenia and other disorders associated with OXPHOS dysfunction such as fibromyalgia and CFS/ME, may improve with CoQ10 supplementation. Tentative evidence arises from small-scale RCTs and observational studies in which supplementation with the coenzyme has improved redox status, reduced inflammatory cytokines and restored gene expression in disorders in which depression, fatigue and cognitive impairments are clinical features (Alcocer-Gómez, Sánchez-Alcázar, & Cordero, 2014; Fukuda et al., 2016; Moccia et al., 2017).

The following section will provide a review of CoQ10 supplementation and its effects in neurological and neuropsychiatric disorders and cardiac health.
1.2.3 Disorders treated with CoQ10

CoQ10 therapy has been investigated across multiple mitochondrial diseases, and neurological and neuropsychiatric disorders associated with mitochondrial dysfunction, due to its involvement in the regulation of mitochondrial bioenergetics and oxidative homeostasis. Fatigue, cognitive impairments and affective disturbances, alongside OXPHOS dysfunction and elevated levels of oxidative biomarkers are features of many such disorders including Parkinson’s disease, multiple sclerosis, and bipolar disorder (Morris et al., 2013; Morris & Berk, 2015; Niedzielska et al., 2016). CoQ10 demonstrates therapeutic effects in mitochondrial diseases, including primary CoQ10 diseases and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) and is used in their treatment (Hargreaves, 2014). However, there is less certainty regarding the effectiveness of CoQ10 therapy in neurological and neuropsychiatric disorders.

1.2.4 Neurological and neuropsychiatric disorders treated with CoQ10

The following section reviews the current evidence for CoQ10 therapy in various neurological and neuropsychiatric disorders, all of which exhibit evidence of mitochondrial dysfunction, but are not attributed to primary mitochondrial disease. Though the majority of research has been conducted in progressive, degenerative disorders, recently CoQ10 therapy has been investigated in chronic neuropsychiatric disorders. The study characteristics (Tables 1.1 and 1.2) and outcomes (Tables 1.3 and 1.4) of double-blind, randomised controlled trials (RCTs) and open-label studies that investigated the effect of CoQ10 as a single intervention across eight different neurological and neuropsychiatric disorders in adults are described in the following sections.

Fundamental differences in methodologies lead to difficulties in determining CoQ10’s therapeutic potential across the disorders examined. In particular there is little consensus across studies with regard to dosage (between 100mg and 2700mg per day), and duration of intervention (between four weeks and 30 months). This variation is both within and between disorders, and more favourable effects of CoQ10 are typically reported in studies of shorter duration. The following sections summarise the outcomes of CoQ10 intervention studies according to each disorder.

1.2.4.1 Parkinson’s Disease

Parkinson’s disease is a progressive neurodegenerative condition associated with mitochondrial pathology such as a reduction in complex I activity, elevated ROS, and reduced levels of CoQ10 (Schapira et al., 1990; Shults et al., 1997). The effects of CoQ10 on delaying functional decline and improving symptoms in Parkinson’s disease have been examined in RCTs (Table 1.1). CoQ10 therapy initially indicated protective effects against decline in Parkinson’s disease. Patients treated with 1200mg of CoQ10 declined less compared to patients receiving placebo or CoQ10 at doses of 300mg and 600mg following eight months of treatment (Shults et al., 2002). Mild symptom improvements were also reported in a small RCT (n=28) following four weeks of CoQ10 treatment (Müller, Büttner, Gholipour, & Kuhn, 2003). A futility trial determined that CoQ10 delivered at
2,400mg warranted further investigation at a phase III trial, as change in primary outcome UPDRS was less than 30% of historical progression rates (The NINDS NET-PD Investigators, 2007). However, subsequent, larger, RCTs did not find benefit of CoQ10 in early- and mid- stage Parkinson’s disease with regard to disease status or disability (Beal et al., 2014; Storch et al., 2007). Additionally, there was no effect of CoQ10 supplementation on quality of life, global cognitive function (measured using the Symbol Digit Modality Test) or the mentation subscale of the Unified Parkinson’s Disease Rating Scale (Beal et al., 2014). More recently, total disease status improved following reduced CoQ10 (ubiquinol) supplementation in patients experiencing a gradual wearing off of the therapeutic effects of levodopa. However, this effect was not maintained post-treatment and there was no benefit of CoQ10 in its reduced form in patients who had not previously been treated with levodopa (Yoritaka et al., 2015). In light of these findings, it is unlikely that long-term treatment with CoQ10 confers meaningful benefit in Parkinson’s disease, though more research into the efficacy of CoQ10 in its reduced form may be warranted.

1.2.4.2 Huntington’s Disease

Huntington’s disease is a genetic, degenerative condition in which cognitive decline and psychiatric disturbances are clinical features. Mitochondrial impairments such as ATP depletion, decreased activity of complexes II, III, and IV, elevated lactate and increased levels of 8OHDg, a biomarker of oxidative DNA damage have been implicated in its pathogenesis (Farshbaf & Ghaedi, 2017; Lin & Beal, 2006). Serum levels of CoQ10 in untreated Huntington’s disease patients have been found to be significantly lower than healthy controls or treated HD patients (Andrich et al., 2004). Three double-blind RCTs (Table 1.3) and two open-label studies investigated the effects of CoQ10 therapy for maintaining or improving clinical outcomes in Huntington’s disease, but the results are equivocal. Mitochondrial function as measured by cortical lactate concentration using 1H magnetic resonance spectroscopy improved following open-label treatment of CoQ10. These changes were not maintained however and reversed with withdrawal of therapy, emphasizing an endogenous CoQ10 deficit in the disease (Koroshetz et al., 1997). A small improvement in function and a trend towards slower total functional capacity decline with CoQ10 supplementation were reported in one RCT (Huntington Study Group, 2001). Additionally, attention performance improved in those receiving CoQ10. However, the most recent RCT published was concluded prematurely after an interim analysis, as there was insufficient evidence that CoQ10 treatment impeded functional decline (McGarry et al., 2017). The single statistically significant outcome of the RCT was a small effect on attention performance, as measured by Stroop Word Reading score. However, as this was a lone significant finding it is likely to be a spurious result. Overall, clinically meaningful improvements in total functional capacity, motor and neuropsychological function, or decelerated functional decline following CoQ10 treatment have not been identified in open-label studies or RCTs in Huntington’s disease (Feigin et al., 1996; Huntington Study Group, 2001;
CoQ10 may have some small, short-term beneficial effects, but limited or no long-term efficacy in Huntington’s disease.

1.2.4.3 Progressive Supranuclear Palsy

Changes in mitochondrial energy metabolism such as reduced complex I activity, depleted ATP and increased low energy adenosine diphosphate, as well as amplified anti-oxidant superoxide dismutase activity and glutathione (GSH) levels have been reported in Progressive Supranuclear Palsy (PSP) (Stamelou et al., 2010). Two RCTs examined the effects of CoQ10 treatment in PSP, although findings are conflicting (Table 1.3). During a small-scale, six-week RCT (n=21), patients with PSP treated with CoQ10 demonstrated mild clinical improvements in disease status and executive dysfunction (Stamelou et al., 2008). The short term treatment was hypothesized to have induced beneficial effects via restoring energy levels within individual neurons, rather than inducing regeneration (Stamelou et al., 2008). CoQ10 had no treatment effect on general cognitive impairment, as measured by the Mini Mental State Examination (MMSE) (Stamelou et al., 2008). However, more recently, in a larger 12-month RCT (n=61) no improvement in clinical symptoms, functional status or cognitive function was induced with CoQ10 treatment (Apetauerova et al., 2016). However, there was a trend towards slower decline in the CoQ10 group (Apetauerova et al., 2016). With a high withdrawal rate from the study in both CoQ10 (n=11) and placebo (n=14) groups, and analyses conducted on completers only, the support for CoQ10 supplementation to improve functional status, cognition or minimise decline in PSP is minimal. An appropriately powered trial that includes an intention to treat analyses is required to confirm or refute the utility of CoQ10 supplementation in PSP, particularly with regard to cognitive function.

1.2.4.4 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, neuro-immune disorder in which fatigue, sensory disturbances, cognitive impairment and muscular paralysis occur. Changes in mitochondrial function are hypothesised to correspond to progression of neurological symptoms (Sadeghian et al., 2016). These mitochondrial changes include ATP depletion, reduced activity of complexes I, III, and IV, elevated serum lactate, and evidence of elevated oxidative stress (Amorini et al., 2014; Dutta et al., 2006; Hargreaves et al., 2018; Lazzarino et al., 2010; van Horssen et al., 2008). Impairment of ATP synthesis in MS is also highly correlated with extent of physical disability (Lazzarino et al., 2010). Two recent studies explored the therapeutic potential of CoQ10 in MS (Tables 1.1 and 1.2). Results from the small, RCT (n=48) suggest that CoQ10 may be beneficial for depression and fatigue in this disorder, through its effects on inflammatory cytokines and markers of oxidative stress (Sanoobar et al., 2013, 2015, 2016). Over twelve weeks, depression and fatigue improved in participants treated with CoQ10, whilst the placebo group reported increased depression and fatigue (Sanoobar et al., 2016). Levels of inflammatory markers TNF-α, IL-6, MMP-9 and malondialdehyde (MDA) a marker of oxidative stress reduced, whilst antioxidant enzyme SOD increased in the CoQ10 treated group compared to the placebo group (Sanoobar et
al., 2013, 2015). An observation that self-reported cognitive function and pain improved and oxidative balance was restored in relapsing-remitting multiple sclerosis, following 3 months of CoQ10 supplementation in an open-label study, warrants further investigation (Moccia et al., 2019). However, without a placebo comparator it is difficult to determine whether the cognitive and pain improvements reflect placebo or other effects, or a true effect of CoQ10 on cognition and pain. Further double-blind trials are warranted in MS as CoQ10 supplementation appears to decrease inflammatory cytokines and ameliorate oxidative stress, and in doing so improve fatigue, depression, and cognitive function in MS.

1.2.4.5 Bipolar Disorder

Bipolar disorder, is a chronic neuropsychiatric condition with recurrent euthymic and depressive episodes, that is up to twenty times more prevalent in patients with mitochondrial disease than the general population (Goodwin & Jamison, 2007). Impairments in complex I activity in the prefrontal cortex, elevated lactate levels in cerebral spinal fluid, and caudate and anterior cingulate cortices, and mitochondrial structure abnormalities in the prefrontal cortex, fibroblasts and lymphocytes have been identified in patients with bipolar disorder but without mitochondrial disease (Andreazza et al., 2010; Cataldo et al., 2010; Chu et al., 2013; Quiroz et al., 2008; Regenold et al., 2009; Soeiro-de-Souza et al., 2016; Sun et al., 2006). Additionally while euthymic or manic states are associated with increased brain energy production, depression is associated with decreased energy generation (Baxter et al., 1985). In light of the evidence of mitochondrial dysfunction, the effects of CoQ10 supplementation during depressive episodes in bipolar disorder have been examined in one RCT (Jahangard et al., 2019; Mehrpooya et al., 2018) and two open-label studies (Forester et al., 2012, 2015). Results obtained from the small, short-term, open-label studies in geriatric bipolar disorder indicate that CoQ10 supplementation may be beneficial for depressive symptoms. However, with a small sample size and no placebo comparator it is not possible to determine if the improvement in mood is as a result of CoQ10 intervention, placebo effects or the natural phases within the disorder. More recently, one RCT indicated CoQ10 supplementation reduced symptoms of depression (Mehrpooya et al., 2018). Additionally, positive effects on oxidative stress and inflammatory markers were noted, with total anti-oxidant capacity and total thiol groups increasing, and IL-10, nitric oxide, and TNF-a decreasing (Jahangard et al., 2019). However, though 89 patients were randomised, twenty participants did not complete the eight-week trial or were excluded due to non-adherence and results presented were per protocol. Thus, while the results suggest efficacy of CoQ10 treatment among adherent completers, their external validity to the entire treatment population is limited. In light of the apparent effect that CoQ10 may have on depression, a larger RCT presenting both per protocol and intent to treat analyses, alongside physiological data such as change in CoQ10 may be warranted as mitochondrial dysfunction is heavily implicated in the pathogenesis of bipolar disorder.
1.2.4.6 Fibromyalgia

Markers of mitochondrial dysfunction including elevated ROS, lipid peroxidation, decreased mitochondrial membrane protection, and low levels of CoQ10 are evident in the pathophysiology of fibromyalgia, a chronic pain syndrome (Cordero et al., 2010). Three open-label studies and one RCT investigated the effect of CoQ10 supplementation in fibromyalgia (Tables 1.1 and 1.2). Preliminary evidence from open-label studies indicate beneficial effects of CoQ10 on oxidative stress, mitochondrial function, sleep, self-reports of pain, depression, anxiety and fatigue (Cordero, Alcocer-Gómez, Cano-García, et al., 2011; Cordero, Alcocer-Gómez, de Miguel, et al., 2011; Cordero, Cano-García, et al., 2012; Cordero, Díaz-Parrado, et al., 2012; Cordero, Santos-García, et al., 2012). One small RCT (n=20) reported significant clinical and molecular benefits following 40 days of CoQ10 supplementation in fibromyalgia compared to placebo. Clinically meaningful improvements in symptoms of depression, anxiety, pain, fatigue, tender points and increased platelet serotonin levels occurred in patients treated with CoQ10 for 40 days (Alcocer-Gómez et al., 2014; Cordero et al., 2013). Psychopathological symptoms including anxiety, depression, somatization, paranoid ideation and obsessive compulsive symptoms, as measured by the Symptom Checklist-90-R, also improved following CoQ10 intervention, while no benefit was reported for the placebo group (Alcocer-Gómez et al., 2017). At a molecular level, CoQ10 supplementation restored altered gene expression for inflammatory markers, mitochondrial biogenesis, and antioxidant response in blood mononuclear cells (Cordero et al., 2013, 2014). Platelet serotonin levels increased whilst and serum levels of pro-inflammatory cytokines decreased following CoQ10 treatment during this small sample RCT in fibromyalgia (Alcocer-Gómez et al., 2014; Cordero et al., 2014). In conclusion, though existing studies of CoQ10 in fibromyalgia are small, there is preliminary support for its use as an intervention. Larger RCTs are required to determine the extent of CoQ10’s treatment effect in fibromyalgia.

1.2.4.7 Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a chronic condition characterised by fatigue, pain, depression and cognitive impairments, with evidence of CoQ10 deficiency and mitochondrial dysfunction including increased lactate and decreased ATP synthesis and concentration (Maes et al., 2009; Myhill et al., 2009). Additionally, patients with very low CoQ10 experience significantly worse concentration and memory disturbances (Maes et al., 2009). Yet, only one open-label study (n=20) and one RCT (n=43) have been conducted to assess the benefit of CoQ10 on its symptoms (Fukuda et al., 2016). CoQ10 (ubiquinol) improved attention (cognitive effort) and depression in both studies, but had no effect on fatigue. Though these studies provide initial support for CoQ10 treatment in CFS/ME, the strength of the evidence is reduced by small sample sizes and single follow-up assessment. Further research is warranted to determine its efficacy as an intervention for CFS/ME, given the known CoQ10 deficiency in the disorder and these initial promising results.
Amyotrophic Lateral Sclerosis (ALS) is a degenerative, neuromuscular disease in which generalized weakness, fatigue and progressive muscle atrophy are features. OXPHOS disruption including reduced complex I, II, III, and IV activity and ATP production and oxidative stress are heavily implicated in ALS and are hypothesised to contribute significantly to neuronal loss (Smith et al., 2017). Initially, CoQ10 administration demonstrated neuroprotective effects and prolonged survival in transgenic mouse models of the disorder (Matthews et al., 1998). However, only one large, phase II RCT has been conducted in ALS. The adaptive trial which incorporated dose-selection and futility test found no clinical benefits of CoQ10 supplementation. As a result, the authors determined that there was not sufficient evidence to support further investigation of CoQ10 supplementation in ALS (Kaufmann et al., 2009).
Table 1.1 Characteristics of double-blind, randomised controlled trials investigating the effect of Coenzyme Q10 (CoQ10) in neurological and neuropsychiatric disorders. Outcome results are outlined in Table 1.3. Caption on page 16.

<table>
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<th>Disorder</th>
<th>Reference/Registration number</th>
<th>N</th>
<th>Male</th>
<th>Age</th>
<th>Mean (SD)</th>
<th>Age</th>
<th>CoQ10</th>
<th>Age</th>
<th>Control</th>
<th>Duration (weeks)</th>
<th>COQ10 (dose/day)</th>
<th>Control *</th>
<th>Outcome measures</th>
<th>Predetermined primary outcomes</th>
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<td>Amyotrophic Lateral Sclerosis</td>
<td>Kaufmann et al., 2009 NCT00243932</td>
<td>150</td>
<td>86</td>
<td></td>
<td></td>
<td>56.5</td>
<td>(10.8)</td>
<td>57.4</td>
<td>(11)</td>
<td>36</td>
<td>2700mg</td>
<td></td>
<td>ALS Functional Rating Scale-Revised, Forced Vital Capacity, Fatigue Severity Scale; SF-36, 8OHdG</td>
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<td>Bipolar disorder</td>
<td>Mehrpooya et al., 2018 IRCT2016092622 965N4</td>
<td>69</td>
<td>11</td>
<td></td>
<td></td>
<td>37.47</td>
<td>(10.7)</td>
<td>39.52</td>
<td>(10.8)</td>
<td>8</td>
<td>200mg</td>
<td></td>
<td>MADRS, adverse events</td>
<td>Yes (Change in MADRS)</td>
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<tr>
<td>Chronic Fatigue Syndrome</td>
<td>Fukuda et al., 2016</td>
<td>43</td>
<td>7</td>
<td></td>
<td></td>
<td>34.8</td>
<td>(9.36)</td>
<td>39.5</td>
<td>(9.36)</td>
<td>12</td>
<td>150mg</td>
<td></td>
<td>Chalder's Fatigue Scale, CES-D, sleep-wake cycle, Uchida-Kraepelin Psychodiagnostic test, reduced &amp; oxidative plasma CoQ10, serum oxidation &amp; antioxidant activity, autonomic nervous function</td>
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</tr>
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<td>Fibromyalgia</td>
<td>Alcocer-Gómez et al., 2017 Cordero et al., 2014 Cordero et al., 2013</td>
<td>20</td>
<td>0</td>
<td>49</td>
<td>(9)</td>
<td>44</td>
<td>(9.7)</td>
<td>55</td>
<td>(5)</td>
<td>6</td>
<td>300mg</td>
<td></td>
<td>Symptom Checklist-90-R’ subscales, Body Mass Index Platelet CoQ10 &amp; serotonin, BDI Inflammasone gene expression &amp; inflammasone serum markers (IL-1β, IL-18) FIQ, Tender points, VAS, Pittsburgh Sleep Quality Index, antioxidants, mitochondrial biogenesis, AMP-activated protein kinase phosphorylation</td>
<td>Yes. 1. CoQ10 levels by High-performance liquid chromatography (HPLC) 2. Oxidative stress 3. Inflammation parameters 4. Clinical symptoms using diagnostic criteria ACR 1990, FIQ, VAS, BDI (depression), and Pittsburgh Sleep Quality Index</td>
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<td>McGarry et al., 2017</td>
<td>609</td>
<td>296</td>
<td></td>
<td>50.5(11.9)</td>
<td>50.7(11.6)</td>
<td>260</td>
<td>2400mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UHDRS, Total Functional Capacity Score, Functional Checklist Score, Independence Scale, UHDRS subscales, Stroop Interference Task, Verbal Fluency, Symbol digit modality, Tolerability, serum CoQ10 &amp; 8OHdG UHDRS, UHDRS subscales, Stroop Test, Independence Scale, Hopkins Verbal Learning Task, Brief Test of Attention, Trail Making Task, Conditional Associative Learning Test</td>
<td>Yes (Joint rank of change in Total Functional Capacity Score/Time to Death) Yes (Tolerability) Yes (Total Functional Capacity change baseline to 30 months; Huntington Study Group, 2001)</td>
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<td></td>
<td>Ross et al., 2014 Huntington Study Group, 2001</td>
<td>90</td>
<td>43</td>
<td>39.5(10.9)</td>
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<td>600-2400mg</td>
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<th>Age Mean (SD)</th>
<th>Age CoQ10</th>
<th>Age Control</th>
<th>Duration (weeks)</th>
<th>COQ10 (dose/day)</th>
<th>Control *</th>
<th>Outcome measures</th>
<th>Predetermined primary outcomes</th>
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<td>Multiple Sclerosis</td>
<td>Sanober et al., 2016;2015;2013</td>
<td>48</td>
<td>4</td>
<td>33.1(7.6)</td>
<td>33.1(7.6)</td>
<td>30.9(7.7)</td>
<td>12</td>
<td>500mg</td>
<td>FSS, BDI</td>
<td>Expanded Disability Status Scale, serum TNF-α, IL-6, IL-4, MMP-9, TGF-β</td>
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<tr>
<td></td>
<td>IRCT 201102052602N4/5</td>
<td>48</td>
<td>4</td>
<td>33.1(7.6)</td>
<td>33.1(7.6)</td>
<td>30.9(7.7)</td>
<td>12</td>
<td>500mg</td>
<td>SOD &amp; GSH-Px activity</td>
<td>Yes (decrease of serum MDA, increase of GSH-Px, SOD &amp; total antioxidant capacity)</td>
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<tr>
<td>Parkinson's Disease</td>
<td>Yoritaka et al., 2015</td>
<td>31</td>
<td>14</td>
<td>62.7(11.4)</td>
<td>61.5(11)</td>
<td>64.1(11.4)</td>
<td>48</td>
<td>300mg*</td>
<td>UPDRS, UPDRS parts II &amp; III, HYS</td>
<td>Yes (Total UPDRS score change; per Yoritaka et al., 2015)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beal et al., 2014 NCT00740714</td>
<td>33</td>
<td>19</td>
<td>62.5(8.9)</td>
<td>34.9(9.4)</td>
<td>59.8(7.5)</td>
<td>96</td>
<td>1200, 2400mg</td>
<td>Total UPDRS, UPDRS subscales, Modified SE ADL, Modified Rankin Score, Symbol Digit Scores, Parkinson's Disease Quality of Life</td>
<td>Yes (Total UPDRS score change)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Storch et al., 2007 NCT00180037</td>
<td>131</td>
<td>91</td>
<td>60.7(9.1)</td>
<td>62.3(7.9)</td>
<td>59.8(7.5)</td>
<td>13</td>
<td>300mg</td>
<td>UPDRS, UPDRS parts II &amp; III, HYS, Schwab &amp; England Activities of Daily Living, Parkinson's Disease Questionnaire-39, Global Clinical Impression Score, MADRS</td>
<td>Yes (Sum of UPDRS parts II &amp; III change)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muller et al., 2003 NCT00180037</td>
<td>14</td>
<td></td>
<td>66.2(9.33)</td>
<td>64.36(7.69)</td>
<td>61.3(10.5)</td>
<td>65</td>
<td>300mg</td>
<td>UPDRS, UPDRS subscale III, Farnsworth-Munsell 100 Hue test</td>
<td>Yes (Total UPDRS, UPDRS part III &amp; Farnsworth-Munsell 100 Hue test error score change)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shults et al., 2002 NCT00004731</td>
<td>80</td>
<td>52</td>
<td>60.8(11.1)</td>
<td>63.1(12.1)</td>
<td>61.3(10.5)</td>
<td>65</td>
<td>300, 600, 1200mg</td>
<td>Total UPDRS, UPDRS subscales parts I, II, &amp; III, HYS, Schwab &amp; England Activities of change</td>
<td>Yes (Total UPDRS score change)</td>
<td></td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy (PSP)</td>
<td>Apetauerova et al., 2016 NCT00382824</td>
<td>61</td>
<td>37</td>
<td>65.6(9.5)</td>
<td>67.6(7.8)</td>
<td>67.6(7.8)</td>
<td>52</td>
<td>2400mg</td>
<td>Total PSP Rating Scale, PSP Rating Scale subscales, total UPDRS, UPDRS subscales, SE ADL, MMSE, Parkinson's Disease Questionnaire, SF- 36</td>
<td>Yes (Total PSP Rating Scale &amp; UPDRS change)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stamelou et al., 2008 NCT00328874</td>
<td>21</td>
<td>10</td>
<td>62.2(6.3)</td>
<td>68</td>
<td>63.5</td>
<td>6</td>
<td>5mg/kg</td>
<td>Brain metabolite concentrations, PSP Rating Scale, PSP staging system, HYS, Frontal Assessment Battery, MMSE, MADRS, SE, UPDRS II &amp; III</td>
<td>Yes (Adenosine diphosphate concentration change)</td>
<td></td>
</tr>
</tbody>
</table>

Table1. * If other than placebo. 8OHdG 8-hydroxy-2 deoxyguanosine, ATP adenosine triphosphate, BDI Beck's Depression Inventory, BMC blood mononuclear cell, FIQ Fibromyalgia Impact Questionnaire, GSH-Px glutathione peroxidase, HYS Hoehn and Yahr scale, MADRS Montgomery-Asberg Depression Rating Scale, MDA malondialdehyde, MMSE Mini Mental State Examination, SE ADL Schwab & England Activities of Daily Living SOD superoxide dismutase, UHDRS Unified Huntington's Disease Rating Scale, UPDRS Unified Parkinson's Disease Rating Scale, VAS Visual Analogue Scale
### Table 1.2 Characteristics of open-label, single arm studies investigating the effect of Coenzyme Q10 (CoQ10) in neurological and neuropsychiatric disorders. Outcome results are outlined in Table 4.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Reference</th>
<th>N</th>
<th>Male</th>
<th>Age</th>
<th>Duration (weeks)</th>
<th>COQ10 (dose/day)</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Forester et al., 2015</td>
<td>19</td>
<td>10</td>
<td>63.6(5.4)</td>
<td>4</td>
<td>400-800mg</td>
<td>MADRS, Young Mania Rating Scale</td>
</tr>
<tr>
<td></td>
<td>Forester et al., 2012</td>
<td>10</td>
<td>4</td>
<td>63.4(7.5)</td>
<td>8</td>
<td>400-1200mg</td>
<td>MADRS, creatine kinase activity (K_fo)</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome</td>
<td>Fukuda et al., 2016</td>
<td>20</td>
<td>5</td>
<td>36.8(6.88)</td>
<td>8</td>
<td>150mg</td>
<td>Chalder’s fatigue scale, Centre for Epidemiologic Studies Depression Scale, reduced and oxidative plasma CoQ10, oxidative stress index, sleep-wake cycle, Uchida-Kraepelin Psychodiagnostic test</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Cordero et al., 2013</td>
<td>1</td>
<td>0</td>
<td>45</td>
<td>13</td>
<td>300mg</td>
<td>Tender points, FIQ, VAS, Headache Impact Test, Migraine Disability Assessment, BMC lipid peroxidation, ATP, and PGC-1α, Tfam, NRF-1 mRNA expression levels</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2012a,2012b</td>
<td>10</td>
<td>0</td>
<td>45.3(10)</td>
<td>13</td>
<td>300mg</td>
<td>Tender points, FIQ, VAS, BDI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>0</td>
<td>45.3(10)</td>
<td>13</td>
<td>300mg</td>
<td>Tender points, FIQ, VAS, Headache Impact Test, ATP, BMC catalase and lipid peroxidation, MDA</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2011a</td>
<td>5</td>
<td>1</td>
<td>50.2(16.6)</td>
<td>39</td>
<td>300mg</td>
<td>VAS, FIQ, Headache Impact Test, Migraine Disability Assessment, plasma and BMC lipid peroxidation</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2011b</td>
<td>2</td>
<td>1</td>
<td>42.16</td>
<td>26</td>
<td>300mg</td>
<td>Tender points, VAS, FIQ, BMC lipid peroxidation</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Biglan et al., 2012</td>
<td>14</td>
<td></td>
<td>52.65(8.61)</td>
<td>20</td>
<td>1200-3600mg</td>
<td>Serum 8OHdG, plasma CoQ10</td>
</tr>
<tr>
<td></td>
<td>Koroshetz et al., 1997</td>
<td>18</td>
<td></td>
<td>50.4(13.4)</td>
<td>26</td>
<td>360mg</td>
<td>Cortical lactate</td>
</tr>
<tr>
<td></td>
<td>Feigin et al., 1996</td>
<td>10</td>
<td>5</td>
<td>50.4(13.4)</td>
<td>26</td>
<td>600-1200mg</td>
<td>Adverse events, Huntington’s Disease Rating Scale, Huntington’s Disease Functional Capacity Scale, Trail Making Task, Paired Associate Learning, Verbal Fluency, Symbol-Digit Modalities, Stroop Interference</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Moccia et al., 2019</td>
<td>60</td>
<td>22</td>
<td>41.5(1.8)</td>
<td>13</td>
<td>200mg</td>
<td>Multiple Sclerosis Neuropsychological Questionnaire, Expanded Disability Status Scale, VAS, BDI, Modified Fatigue Impact Scale, 8OHdG levels, uric acid, bilirubin, IL-2, IL-4, IL-6, IL-10, IL-17, TNF, IFN-γ</td>
</tr>
</tbody>
</table>

8OHdG 8-hydroxy-2 deoxyguanosine, ATP adenosine triphosphate, BDI Beck’s Depression Inventory, BMC blood mononuclear cell, FIQ Fibromyalgia Impact Questionnaire, GSH-Px glutathione peroxidase, HYS Hoehn and Yahr scale, MADRS Montgomery-Asberg Depression Rating Scale, MDA malondialdehyde, MMSE Mini Mental State Examination, SOD superoxide dismutase, UHDRS Unified Huntington’s Disease Rating Scale, UPDRS Unified Parkinson’s Disease Rating Scale, VAS Visual Analogue Scale
Table 1.3 Outcomes of double-blind RCTs investigating the effect of single-agent Coenzyme Q10 (CoQ10) in neurological and neuropsychiatric disorders.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Reference</th>
<th>Primary outcome</th>
<th>Effect on CoQ10</th>
<th>Physiological effects</th>
<th>Disease/functional status</th>
<th>Psychiatric symptoms</th>
<th>Fatigue</th>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Kaufmann et al., 2009</td>
<td>No effect</td>
<td>Increased</td>
<td>**</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>**</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>Mehrpooya et al., 2018</td>
<td>Depression improved</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Improved (MADRS)</td>
<td>**</td>
<td>no effect</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome</td>
<td>Fukuda et al., 2016</td>
<td>*</td>
<td>Increased</td>
<td>Autonomic nervous function increased</td>
<td>No effect</td>
<td>No effect</td>
<td>Improved (UKPD)</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Alcocer-Gómez et al., 2017</td>
<td>*</td>
<td>Increased</td>
<td>Serotonin levels increased</td>
<td>Gene expression NLRP3 &amp; IL-1β &amp; IL-18 decreased</td>
<td>Improved (PCL subscales)</td>
<td>Improved (BDI)</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Alcocer-Gómez et al., 2014</td>
<td>Depression improved, CoQ10 increased</td>
<td>Inflammasone gene expression (NLRP3 IL-1BGENE) and inflammasone serum markers (IL-1B, IL-18) increased</td>
<td>Improved (Depression &amp; anxiety FIQ subscales)</td>
<td>Improved (Fatigue &amp; morning tiredness FIQ subscales)</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2014</td>
<td>Depression improved, CoQ10 increased</td>
<td>Inflammasone gene expression (NLRP3 IL-1BGENE) and inflammasone serum markers (IL-1B, IL-18) increased</td>
<td>Improved (FIQ)</td>
<td>Improved (Depression &amp; anxiety FIQ subscales)</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2013</td>
<td>FIQ total improved</td>
<td>**</td>
<td>Gene expression IL-6, IL-8, TNF-a downregulated, PGC-1α, TFAM, NRF1, SOD1, SOD2, AMPK upregulated</td>
<td>Improved (Depression &amp; anxiety FIQ subscales)</td>
<td>Improved (Fatigue &amp; morning tiredness FIQ subscales)</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>McGarry et al., 2017</td>
<td>No effect</td>
<td>**</td>
<td>No effect</td>
<td>**</td>
<td>**</td>
<td>Improved (Stroop Word Reading)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ross et al., 2014</td>
<td>Accepted</td>
<td>Increased</td>
<td>No effect on 8OHdG</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Huntington Study Group, 2001</td>
<td>No effect</td>
<td>**</td>
<td>Improved (Functional Assessment Checklist of UHDRS)</td>
<td>**</td>
<td>**</td>
<td>Improved (Brief Test of Attention)</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Sanoobar et al., 2016</td>
<td>*</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Improved (BDI)</td>
<td>Improved (FSS)</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Sanoobar et al., 2015</td>
<td>Decreased serum levels of TNF-α, IL-6, and MMP-9</td>
<td>Serum TNF-α, IL-6, &amp; MMP-9 decreased</td>
<td>No effect</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sanoobar et al., 2013</td>
<td>SOD activity increased, MDA levels decreased</td>
<td>SOD activity increased, MDA levels decreased</td>
<td>No effect</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
</tbody>
</table>

continued next page
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Reference</th>
<th>Primary outcome</th>
<th>Effect on CoQ10 levels</th>
<th>Physiological effects</th>
<th>Disease/functional status</th>
<th>Psychiatric symptoms</th>
<th>Fatigue</th>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>Yoritaka et al., 2015</td>
<td>Total UPDRS improved</td>
<td>Increased</td>
<td>**</td>
<td>Improved (Total UPDRS)</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beal et al., 2014</td>
<td>No effect</td>
<td>Increased</td>
<td>**</td>
<td>No effect</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Storch et al., 2007</td>
<td>No effect</td>
<td>Increased</td>
<td>**</td>
<td>No effect</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Müller et al., 2003</td>
<td>Total UPDRS &amp; FMT improved</td>
<td>**</td>
<td>**</td>
<td>Improved (Total UPDRS &amp; FMT)</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shults et al., 2002</td>
<td>Total UPDRS score improved</td>
<td>Increased</td>
<td>ETC activity increased</td>
<td>Improved (UPDRS ADL, Schwab &amp; England)</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy</td>
<td>Apetauerova et al., 2016</td>
<td>No effect</td>
<td>Increased</td>
<td>**</td>
<td>No effect</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stamelou et al., 2008</td>
<td>Reduction in ADP</td>
<td>Increased</td>
<td>Reduced ADP &amp; uCre</td>
<td>Improved (Total PSPRS)</td>
<td>No effect</td>
<td>**</td>
<td>Improved (FAB)</td>
</tr>
</tbody>
</table>

*primary outcome not specified, **Not reported

8OH2dG (8-hydroxy-2-deoxyguanosine), ADL (activities of daily living), ADP (adenosine diphosphate), ALSFRSr (ALS Functional rating scale revised), ATP (adenosine triphosphate), BDI (Beck’s Depression Inventory), BMC (Blood mononuclear cell), CES-D (Centre for Epidemiologic Studies Depression Scale), EDSS (Expanded Disability Status Scale), FAB (Frontal Assessment Battery), FIQ (Fibromyalgia Impact Questionnaire), FMT (Farnsworth-Munsell 100 Hue test), FSS (Fatigue Severity Scale), FVC (Forced Vital Capacity), MADRS (Montgomery-Asberg Depression Rating Scale), MDA (malondialdehyde) levels, MFIS (Modified Fatigue Impact Scale), MMSE (Mini Mental State Examination), MSNQ (Multiple Sclerosis Neuropsychological Questionnaire), PSPRS (Progressive Supranuclear Palsy Rating Scale), SCL-90-R (Symptom Checklist-90-R), SF-36 (Short Form Health Survey-36), SOD (superoxide dismutase), TAC (total antioxidant capacity), uCRE (unphosphorylated creatine), UHDRS (Unified Huntington’s Disease Rating Scale), UKPD (Uchida-Kraepelin Psychodiagnostic test), VAS (Visual Analogue Scale)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Reference</th>
<th>Effect on CoQ10 levels</th>
<th>Physiological effects</th>
<th>Disease/functional status</th>
<th>Psychiatric symptoms</th>
<th>Fatigue</th>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Forester et al., 2015</td>
<td>**</td>
<td>**</td>
<td>Improved (MADRS)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Forester et al., 2012</td>
<td>**</td>
<td>Kfor of Creatine Kinase activity increased</td>
<td></td>
<td>No effect</td>
<td></td>
<td>**</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome</td>
<td>Fukuda et al., 2016</td>
<td>Increased</td>
<td>oxidative stress decreased</td>
<td>**</td>
<td>Improved (CES-D)</td>
<td>No effect</td>
<td>Improved (UKPD)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Cordero et al., 2013</td>
<td>Increased</td>
<td>BMC lipid peroxidation decreased, ATP increased, PGC-1α, Tfam, NRF-1 mRNA expression increased</td>
<td>Improved (FIQ)</td>
<td></td>
<td></td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2012a</td>
<td>Increased</td>
<td>**</td>
<td>Improved (FIQ)</td>
<td>Improved (BDI &amp; depression FIQ subscale)</td>
<td></td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2012b</td>
<td>Increased</td>
<td>ATP &amp; catalase increased, MDA decreased</td>
<td>Improved (FIQ)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Cordero et al., 2011a</td>
<td>Increased</td>
<td>Plasma &amp; BMC lipid peroxidation decreased</td>
<td>Improved (FIQ)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>Biglan et al., 2012</td>
<td>Increased</td>
<td>BMC lipid peroxidation decreased</td>
<td>Improved (FIQ)</td>
<td></td>
<td></td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Koroshetz et al., 1997</td>
<td>**</td>
<td>**</td>
<td>Cortical lactate concentration decreased</td>
<td></td>
<td></td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Feigin et al., 1996</td>
<td>**</td>
<td>**</td>
<td>No effect</td>
<td>**</td>
<td>**</td>
<td>No effect</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Moccia et al., 2019</td>
<td>**</td>
<td>8OHdG levels decreased</td>
<td>Improved (EDSS)</td>
<td>**</td>
<td>Improved (MFIS)</td>
<td>Improved (MSNQ)</td>
</tr>
</tbody>
</table>

**Not reported**

8OHdG (8-hydroxy-2 deoxyguanosine), ADL (activities of daily living), ADP (adenosine diphosphate), ALSFRSr (ALS Functional rating scale revised), ATP (adenosine triphosphate), BDI (Beck's Depression Inventory), BMC (Blood mononuclear cell), CES-D (Centre for Epidemiologic Studies Depression Scale), EDSS (Expanded Disability Status Scale), FAB (Frontal Assessment Battery), FIQ (Fibromyalgia Impact Questionnaire), FMT (Farnsworth-Munsell 100 Hue test), FSS (Fatigue Severity Scale), FVC (Forced Vital Capacity), MADRS (Montgomery-Asberg Depression Rating Scale), MDA (malondialdehyde) levels, MFIS (Modified Fatigue Impact Scale), MMSE (Mini Mental State Examination), MSNQ (Multiple Sclerosis Neuropsychological Questionnaire), PSPRS (Progressive Supranuclear Palsy Rating Scale), SCL-90-R (Symptom Checklist-90-R), SF-36 (Short Form Health Survey-36), SOD (superoxide dismutase), TAC (total antioxidant capacity), uCRE (unphosphorylated creatine), UHDRS (Unified Huntington's Disease Rating Scale), UKPD (Uchida-Kraepelin Psychodiagnostic test), VAS (Visual Analogue Scale).
1.2.4.9 Summary of review of CoQ10 supplementation in neurological and neuropsychiatric disorders

Though some support for CoQ10 supplementation in neurological and neuropsychiatric conditions has arisen from RCTs, considerable evidence in support of CoQ10 supplementation in neuropsychiatric symptoms and disorders stems from open-label studies which are subject to bias. Many RCTs are also inadequately powered (Table 1.1) and even moderate but potentially meaningful clinical effects relevant to each disorder may be missed (Table 1.3). Some findings reported are nominally significant and therefore potentially false positive (Button et al., 2013). RCTs are considered the gold-standard of trial methodology, and it is only through the implementation of RCTs that one can draw reliable conclusions about treatment efficacy. In order to be sure of the efficacy or otherwise of CoQ10, larger RCTs are required that are powered to detect clinically meaningful effects and present intention to treat analysis. This is particularly relevant for neuropsychiatric disorders that are thought to be associated with mitochondrial dysfunction, such as those with reduced activity in OXPHOS complexes and elevated ROS. Schizophrenia is one such disorder that may benefit from CoQ10 supplementation.

The next section will briefly summarise the effects of CoQ10 in cardiac health, which is important as cardiovascular diseases are a leading cause of death in patients with a diagnosis of schizophrenia (Westman et al., 2018).

1.2.5 CoQ10 in cardiac health

The role of CoQ10 in cardiac health has been extensively examined. Several meta-analysis and systematic reviews on the effects of CoQ10 supplementation in a range of cardiovascular conditions have been conducted in an attempt to consolidate the work (Flowers & Rees, 2014; Lei & Liu, 2017; Tabrizi et al., 2018; Zozina et al., 2018). Meta-analytic evidence demonstrates that CoQ10 supplementation in heart failure lowers mortality and improves exercise capacity, although dose was not taken into account in the analysis (100mg- 400mg/day; Lei & Liu, 2017). The therapeutic potential of CoQ10 may derive from its ability to promote OXPHOS and enhance energy production in cardiac muscle (Kumar et al., 2009; Lei & Liu, 2017; Molyneux, Florkowski, et al., 2008). Further, patients with cardiac failure often exhibit deficits of circulating CoQ10, which may be attributable to decline in endogenous synthesis with age, and also the use of beta-blockers and statins which inhibit the mevalonate pathway which is involved in CoQ10 synthesis (DiNicolantonio et al., 2015; Madmani et al., 2014). Deficits in CoQ10 are an independent predictor of cardiac failure (Molyneux et al., 2008). CoQ10 supplementation may also be beneficial for reducing hypertension (Rosenfeldt et al., 2007). In patients with metabolic disease, CoQ10 augmentation (100-150mg/day) may reduce systolic blood pressure levels, though diastolic blood pressure levels appear to be unaffected by supplementation (Tabrizi et al., 2018). However, there is
currently insufficient evidence supporting long-term use of CoQ10 in clinical hypertension (Ho et al., 2016). Nonetheless, given the high risk of cardiac related mortality and prevalent use of beta-blockers and statins in schizophrenia, the effects of CoQ10 supplementation on cardiac health may be valuable.

1.2.6 Conclusion

Though different in aetiology and presentation from neurological disorders such as Huntington’s disease and Amyotrophic Lateral Sclerosis, some similarities in mitochondrial impairments exist between schizophrenia and the neurological and neuropsychiatric disorders in which CoQ10 therapy was investigated. In particular altered ETC complex activity and associated depleted ATP, oxidative stress, and increased lactate have been reported in schizophrenia and the discussed disorders (Dror et al., 2002; Gubert et al., 2013; Rowland et al., 2016; Somerville et al., 2011). Further, primary mitochondrial diseases such as MELAS, Kearns–Sayre syndrome, and non-syndromic encephalomyopathy also present with psychosis, mood disturbances and cognitive impairments similar to schizophrenia (Anglin et al., 2012; Fattal et al., 2006; Kraya et al., 2018). Metabolic syndrome, hypertension, and diabetes are also highly prevalent in schizophrenia, conditions which are independently associated with chronic oxidative stress and inflammation (Baptista et al., 2011; De Hert et al., 2010; Lindenmayer et al., 2012).

CoQ10 is essential for normal, healthy functioning in humans. It demonstrates a clear role in mitochondrial function and disease pathogenesis. While benefits of supplementation in certain disorders are evident, robust evidence in support of its therapeutic role in other neurological and psychiatric disorders is limited, often due to underpowered studies and confounding variables. More robust methods, such as carefully designed RCTs in large patient samples, are required to reliably evaluate therapeutic intervention with CoQ10 in neuropsychiatric disorders, including schizophrenia.

Schizophrenia is a highly heterogeneous disorder characterised by a variety of symptoms, including cognitive impairments, negative and affective symptoms. Importantly, the extent of cognitive impairment is a critical correlate and determinant of functioning and recovery in schizophrenia, across phases of the illness (Green & Harvey, 2014). In particular, attention and working memory are predictive of social competence and work and education skills (Bosia et al., 2019; Bowie et al., 2008; Gonzalez-Blanco et al., 2019). It has recently been suggested that mitochondrial dysfunction, including OXPHOS abnormalities, contributes to such impairments in these cognitive functions. For example, reduced ETC activity, particularly complex I activity, as indicated by under-expression of mitochondrial complex genes NDUFA1 and NDUFB11, may contribute to the manifestation of attention deficits in schizophrenia (Haghishatfard et al., 2018). Energy hypometabolism in the rostral anterior cingulate cortex and downregulation of NDUFA1, NDUFB10
and NDUFB11 may influence working memory performance (Haghighatfard et al., 2018). Further, in early psychosis, patients with low levels of oxidative stress performed better on attention and working memory tasks compared to those with higher levels of oxidative stress (Alameda et al., 2018).

CoQ10 supplementation may help support mitochondrial function through restoring ETC activity and increasing ATP energy supply to neurons. Further, as an anti-oxidant CoQ10 removes excessive ROS and promoting the regeneration and activity of other antioxidants, thereby reducing further ROS-induced damage to cells (Crane, 2007; Duberley et al., 2014; Feher et al., 2007; Sanoobar et al., 2013). Through these properties, CoQ10 may have beneficial effects on cognition. Several animal and case-report studies suggest neuroprotective and potentially restorative effects of CoQ10 administration on memory and cognitive function (Langsjoen et al., 2005; Monsef et al., 2019; Okeahialam, 2015; Omidi et al., 2019; Sandhir et al., 2014; Shinkai et al., 2000). However, as reviewed in the preceding sections, the results of RCTs and open-label studies in human participants are highly inconsistent, and robust evidence is lacking. For example, CoQ10 may have a protective effect against cognitive decline in progressive disorders, but such benefits are not maintained with longer follow-up and may be lone or spurious findings. The effect of adjunctive CoQ10 supplementation on stable cognitive dysfunction, specifically attention and working memory impairments, is yet to be determined. Nonetheless, given the relationship between cognition, in particular attention and working memory and recovery in schizophrenia, and evidence of mitochondrial dysfunction in schizophrenia, CoQ10 presents as a reasonable therapeutic strategy which merits further investigation.

1.3 Aims of this thesis

To date, there are no RCTs investigating the effects of CoQ10 administration in schizophrenia. There is a reasonable rationale for a study of CoQ10 supplementation in schizophrenia, though a stronger evidence base regarding CoQ10 status in schizophrenia would be preferred. Nonetheless, there is considerable overlap in symptoms and pathophysiology between schizophrenia and disorders with known mitochondrial dysfunction and CoQ10 deficiencies, and evidence for abnormal mitochondrial function and oxidative stress in schizophrenia. Additionally, RCTs have demonstrated beneficial effects of CoQ10 supplementation on co-morbid depressive, fatigue and cognitive symptoms in several neurological and neuropsychiatric disorders. Given the aforementioned overlaps and CoQ10’s initially promising results in multiple sclerosis, fibromyalgia, and bipolar disorder, the following question was raised:

Does CoQ10 supplementation have a role in the treatment and management of cognitive, clinical and functional outcomes in schizophrenia and schizoaffective disorder?

The work described in the following chapters attempted to answer this question.
To this end, a double-blind RCT was conducted to determine the effects of CoQ10 supplementation on cognitive function, CoQ10 status, mitochondrial function, energy, psychological symptoms, and health-related outcomes in schizophrenia.

The following hypotheses were generated:

1. There would be improvements in sustained attention in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

2. There would be improvements in working memory performance in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

3. There would be improvements in processing speed in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

4. There would be improvements in executive function in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

5. There would be improvements in general cognitive function in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

6. There would be an increase in CoQ10 levels in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

7. There would be improvement in the measure of mitochondrial function between patients who received CoQ10 supplementation and patients who received placebo after 3 months and 6 months supplementation.

8. There would be improvement in levels of energy in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

9. There would be less severity of depression symptoms in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

10. There would be less severity of anxiety symptoms in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

11. There would be less severity of negative symptoms avolition, asociality, blunted affect and alogia in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.
12. There would be improvement in self-reported quality of life in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

13. There would be improvement in physical activity levels in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

14. There would be improvement in functional status in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

15. There would be lower systolic and diastolic blood pressure in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

The study design and methods to test these hypotheses are detailed in Chapter 2. Chapter 3 describes and discusses methodological issues that occurred during the conduct of the RCT that influenced the analysis and interpretation of the RCT results. Chapter 4 addresses the effects of CoQ10 supplementation on cognitive function. Chapter 5 addresses the effects of CoQ10 supplementation on the secondary outcomes that are CoQ10 status, mitochondrial function, energy, psychological symptoms and health-related outcomes. Chapter 6 provides a general discussion of the overall findings.
2 METHODS

2.1 Study design

This double-blind, placebo-controlled, randomised, parallel group trial (RCT) compared neurocognitive performance and clinical symptoms of CoQ10 supplemented schizophrenia and schizoaffective disorder patients to patients who received placebo. Assessment of outcome measures took place at three time points: baseline, three months and six months post randomisation (Figure 2.1).

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**Figure 2.1 Study design and procedures.**
2.2 Ethical approval

Ethical approval for this study was granted by St James’ Hospital/Tallaght University Hospital and Newcastle Hospital research ethics committees (Appendix A). Subsequent amendments to the research protocol were also approved by the committees (Table 2.1). This study was carried out according to the principles of the Declaration of Helsinki (Amendment 2008) and ICH Good Clinical Practice guidelines - ICH E6 (R2). All patients signed informed consent upon enrolment to the study. The Patient Information Leaflet and Informed Consent Form are provided in Appendix B.

Table 2.1 Dates of REC initial study approval and approval of subsequent protocol amendments.

<table>
<thead>
<tr>
<th>Ethics approval</th>
<th>Ethics amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>St James’/Tallaght</td>
<td>St James’/Tallaght</td>
</tr>
<tr>
<td>11(^{th}) April 2016</td>
<td>27(^{th}) October 2016</td>
</tr>
<tr>
<td>Newcastle</td>
<td>8(^{th}) October 2018</td>
</tr>
<tr>
<td>23(^{rd}) March 2018</td>
<td>23(^{rd}) March 2017</td>
</tr>
<tr>
<td></td>
<td>18(^{th}) January 2018</td>
</tr>
<tr>
<td></td>
<td>13(^{th}) August 2018</td>
</tr>
</tbody>
</table>

2.3 Study classification and registration

In Ireland, the Health Products Regulatory Authority classifies coenzyme Q10 as a food supplement, rather than a medicinal product. Thus, the RCT was not classified as a clinical trial, rather an interventional study of a nutritional supplement. The RCT was registered on clinicaltrials.gov [identifier: NCT03576911] on 4\(^{th}\) July 2018.

2.4 Research setting

The study was conducted in association with the Clinical Research Facility (CRF), St James’s Hospital, Dublin. The CRF supplied pharmacy services, blood sample processing and storage facilities, phlebotomy consumables and clinic rooms. Quality and regulatory affairs guidance was provided throughout the study by the CRF Quality and Regulatory Affairs Manager (QRAM). Research nursing services were also available for phlebotomy and clinical observation where required. Venepuncture supervision, training and assessment of competency were also provided by clinical research nurses on site.

2.5 Intervention

CoQ10 was delivered in soft gelatine capsules containing 100mg of ubiquinone. Placebo capsules were identical in appearance and contained the same non-active ingredient (Table 2.2). The selected daily dose of CoQ10 for this study was 300mg, divided into 100mg doses to be taken 3 times daily. A dosage of 300mg CoQ10 per day was decided upon following a review of the literature where it was found to be effective for a variety of symptoms including pain, depression
and fatigue, with minimal adverse effects (Alcocer-Gómez et al., 2014; Cordero, Cano-García, et al., 2012; Cordero et al., 2014).

Table 2.2 Ingredients in CoQ10 and placebo capsules.

<table>
<thead>
<tr>
<th>CoQ10 capsule ingredients</th>
<th>Placebo capsule ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100mg of ubiquinone</strong></td>
<td></td>
</tr>
<tr>
<td>Palm oil</td>
<td>Palm oil</td>
</tr>
<tr>
<td>Gelatine (bovine)</td>
<td>Gelatine (bovine)</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Glycerol</td>
</tr>
<tr>
<td>Ammonia caramel</td>
<td>Ammonia caramel</td>
</tr>
<tr>
<td>Purified water</td>
<td>Purified water</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Titanium dioxide</td>
</tr>
</tbody>
</table>

CoQ10 is considered very safe and well tolerated in humans up to high doses (Hidaka et al., 2008). The observed safety level for CoQ10, derived from clinical trial data, is 1200mg/day for supplementation (Hidaka et al., 2008). Reported minor adverse effects include skin itching (100mg/day), fatigue (600-1200mg/day), headache (600-1200mg/day), increased involuntary movement (600-1200mg/day), and gastrointestinal disturbances including heartburn (600-1200mg/day), stomach upset (300mg/day), abdominal pain and soft faeces (0 to 900mg/day). However, as there is no dose-response relationship, adverse events cannot be definitively attributed to active ingredient ubiquinone. In placebo controlled trials similar adverse events have occurred in placebo groups in trials (Hidaka et al., 2008; Ikematsu et al., 2006; The Huntington Study Group, 2010). The oil or non-active ingredients in the capsules or wafers may induce nausea and other gastrointestinal disturbances (Hidaka et al., 2008).

CoQ10 is a lipid soluble compound that is most readily absorbed through an oil-based medium; absorption can be further increased when ingested with a fatty meal (Bhagavan & Chopra, 2006). It is indicated that the higher the ingested dose of CoQ10, the lower the percentage of dose absorbed. Thus, to maximise absorption and reduce the risk of nausea, it is recommended to split the dosage throughout the day and consume the capsules with food (Bhagavan & Chopra, 2006).

In the present study, participants were instructed to take one capsule three times daily with food. Capsules were supplied to participants after their baseline and three month visit in batches of three months (270 capsules). All capsules were provided without charge by Pharma Nord, Denmark. Pharma Nord label this product as a medicinal standard food supplement, and have previously supplied controlled trials in humans. Pharma Nord was not involved in study planning, design, conduct, analysis or interpretation. The company signed a renouncement of rights and responsibilities agreement with the Initiator (Dr April Hargreaves).
2.6 Interactions and safety concerns

CoQ10 may possess pro-coagulant properties, due to its structural similarity to vitamin K (De Smet, 2005). As such it is contraindicated in those taking coumarin-derived anticoagulants such as warfarin, phenprocoumon, and acenocumarol (De Smet, 2005). It is recommended that increased International Normalised Ratio monitoring take place in those taking coumarin-derived anticoagulants and CoQ10 (Tran et al., 2001). Due to the potential safety concern, concomitant coumarin-derived anticoagulants, heparins, or other blood thinning medication was an exclusion criterion (Section 2.8) in this study.

CoQ10 concentrations may be reduced by concomitant administration of statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) (Banach et al., 2015; Littarru & Langsjoen, 2007). The inhibition of HMG-CoA reductase appears to also inhibit endogenous CoQ10. A meta-analysis demonstrated that taking atorvastatin, simvastatin, rosvastatin, and pravastatin reduced plasma CoQ10 (Banach et al., 2015). However, the effects on tissue levels may differ depending on the statin; for example atorvastatin, but not pitavastatin, reduces tissue levels of coenzyme Q10 (Kawashiri et al., 2008). Though this is not a safety concern, statin use was recorded as this may have impacted results.

CoQ10 concentrations may also be affected by the presence of thyroid conditions in patients. Patients with hypothyroidism may exhibit elevated CoQ10 circulating levels, whereas hyperthyroidism is associated with reduced levels (Mancini et al., 2013). Patients receiving treatment for thyroid dysfunction were considered eligible for participation; however patients could be withdrawn from the study if concomitant thyroid medication changes were required during the study.

2.7 Safety reporting

An adverse event (AE) is defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, which does not necessarily have a causal relationship with the product (ICH-GCP Guidelines). Suspected AEs were documented in the participant’s case report form and reported to the principal investigator.

2.8 Participants

Adults with a clinical diagnosis of schizophrenia or schizoaffective disorder were recruited to the study from St James’s, Tallaght and Wicklow mental health services. The majority of participants were outpatients within these services and recruited through psychiatric outpatient clinics and day support services. Diagnosis was confirmed by the patient’s treating clinician and chart review. Two patients self-referred to the study outside of these services upon hearing of the study. Their diagnosis was confirmed through speaking with a member of their mental health team/GP and a structured clinical interview for DSM-IV (SCID).
Inclusion and exclusion criteria are listed in Table 2.3. Along with a clinical diagnosis of schizophrenia or schizoaffective disorder, the inclusion criteria required participants to be aged between 18-70 years on entry to the study. Exclusion criteria were a history of seizures, co-morbid substance abuse or psychiatric diagnosis in the preceding 6 months, currently pregnant or breastfeeding, previous head injury with loss of consciousness (>3 minutes), uncontrolled thyroid dysfunction, and taking warfarin or another anti-coagulant (as per contraindicated medication, Section 2.6.1).

Table 2.3 Inclusion and exclusion criteria for enrolment into the study.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical diagnosis of schizophrenia or schizoaffective disorder</td>
<td>1. History of seizures</td>
</tr>
<tr>
<td>2. 18-70 years of age</td>
<td>2. Co-morbid substance abuse or psychiatric diagnosis in the preceding 6 months,</td>
</tr>
<tr>
<td></td>
<td>3. Currently pregnant or breastfeeding,</td>
</tr>
<tr>
<td></td>
<td>4. Previous head injury with loss of consciousness (&gt;3 minutes)</td>
</tr>
<tr>
<td></td>
<td>5. Uncontrolled thyroid dysfunction, and</td>
</tr>
<tr>
<td></td>
<td>6. Taking warfarin or another anti-coagulant</td>
</tr>
</tbody>
</table>

2.9 Screening and informed consent

Patients were initially identified by a member of their mental health treating team. The patient was then informed of the study by either a member of their treating team or a member of the research team (Christina Mooney, clinical research nurse, or the author). The patient received verbal and written information about the study from the clinical research nurse or the author. Those who were interested in the study and met the inclusion criteria were invited to participate in the research. Patients were encouraged to raise any questions or concerns about the study with the researchers and to speak with the treating team or GP about the research study before agreeing to take part. The first study visit occurred approximately one week after initial provision of information by the research team. The time lag between provision of information and signing consent was allowed time for patients to query details of the study and consider their participation (ICH-GCP guidelines). Before any study related procedures took place, including chart review to obtain medication lists, freely given informed consent was obtained in writing by the researcher at the first study visit (Baseline visit). Informed consent was obtained after the study was explained in full and the patient had the opportunity to ask questions; to ensure the patient understood the content the researcher read the information sheet and consent form with the patient at the first visit.
2.10 Baseline assessment

Upon signing consent, participants completed a baseline assessment. Concurrent medication details were obtained from the participants and checked subsequently in a chart review (see contraindicated medication in Section 2.6). Antipsychotic doses were converted to chlorpromazine equivalents. Sociodemographic details of age, education, marital status, living arrangements and clinical information regarding clinical diagnosis, duration of illness and comorbid conditions were collected to check the representativeness of the outpatient sample. Alcohol, tobacco and illicit drug use were also recorded. A comprehensive battery of neuropsychological, clinical and physical outcome measures was administered (described in detail Sections 2.12 – 2.13).

2.11 Outcome assessment

Participants completed a comprehensive neuropsychological and clinical assessment at baseline, 3 months post-randomisation (midpoint) and 6 months post-randomisation (endpoint), to evaluate differences between CoQ10 and placebo groups at each time point (Table 2.4). With the exception of four participants, the participants completed the outcome assessment with the same assessor at each visit. Christina Mooney and I conducted the assessments.

2.12 Primary outcomes

2.12.1 Sustained attention

The first primary outcome was sustained attention performance, as measured with the Continuous Performance Task - Identical Pairs (CPT-IP) (Cornblatt et al., 1988). CPT-IP is the recommended attention assessment measure for clinical trials of cognitive deficits in schizophrenia (Nuechterlein et al., 2008). The measure demonstrates good test-retest reliability (Table 2.5), minimal practice effects and sensitivity to treatment effects in patient samples (Kahn et al., 2012; Keefe et al., 2017). Typically, small to moderate effect sizes of improvement or deterioration in attention following treatment have been reported (.3 - .5 Cohen’s d).

During the 10 minute task, a series of rapidly presented digits appear on a computer screen. Participants are required to respond to the second stimulus in any identical pair of digits, but withhold responses from random and nearly identical pairs (Kahn et al., 2012). The task is divided into three testing conditions (2-digits, 3-digits and 4-digits) with a break between each condition. The outcome for each condition is d’; a signal/noise discrimination index derived from correct target response rates and false alarms to nearly identical pairs (Nuechterlein et al., 2015) (Neucterlein et al., 2015). The anticipated range for d’ is from -4.24 to 4.24; higher d’ indicates better performance (Rapisarda et al., 2014).
2.12.2 Working memory

Working memory performance was the second primary outcome. This was measured with two measures: the between errors score of Spatial Working Memory task (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB; (Robbins et al., 1994) and total score on the Letter Number Sequencing (LNS) subscale from the WMS-III (Wechsler, 1997b).

SWM is acceptable as a repeated measure in intervention studies due to adequate test-retest reliability (Table 2.5), acceptable practice effects, and sensitivity to treatment effects (Barnett et al., 2010; Goghari et al., 2014). SWM is a 10-minute serial search task administered on a touch screen computer that increases working memory load at each task level. In each set, participants must search for tokens hidden behind coloured boxes on the screen. Once participants find a token they must place it in a “bank” and continue to find the remaining tokens. Participants are told that once a token has been found behind a particular box, another token would not be hidden there again. Thus the participants were required to remember under which boxes that they had already found tokens, and avoid searching those boxes again. Trials increased in difficulty as the task progressed. Between-trial errors, which is searching a box in which a token had been found on a previous trial in a set, was the outcome selected. Age and gender standardized scores are provided and higher scores indicate better working memory.

LNS is a reliable measure of verbal working memory that is correlated with global functioning, and is a recommended outcome measure for working memory in clinical trials of schizophrenia (Nuechterlein et al., 2008). During the task participants are read a list of numbers and letters and required to reorder the stimuli into ascending number then letter classes (Wechsler, 1997b). Each item consists of three different number-letter combination trials. The trials start with two number-letter combinations and progress to eight number-letters. The task continues until a participant gets three trials in an item wrong. Higher scores indicate better verbal working performance. Analyses of LNS were conducted using age corrected scores.
Table 2.4 List of primary and secondary outcomes administered during baseline, midpoint and endpoint assessments.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measure</th>
<th>Direction of scores for improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Continuous Performance Task - Identical Pairs D'prime: 2 digits</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>3 digits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 digits</td>
<td></td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>Spatial Working Memory (Errors)</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Letter number sequencing</td>
<td>Higher</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>Trail Making Task A (seconds)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Verbal fluency (FAS)</td>
<td>Higher</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail Making Task B (seconds)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Spatial Working Memory (Strategy)</td>
<td>Higher</td>
</tr>
<tr>
<td>Current IQ</td>
<td>WAIS-III subtest: Similarities</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>WAIS-III subtest: Matrix reasoning</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Estimated Full Scale IQ</td>
<td>Higher</td>
</tr>
<tr>
<td>Energy</td>
<td>Functional Assessment of Chronic Illness Therapy Fatigue Scale</td>
<td>Higher</td>
</tr>
<tr>
<td>Depression</td>
<td>Beck Depression Inventory II</td>
<td>Lower</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Beck Anxiety Inventory</td>
<td>Lower</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Brief negative symptoms scale subscales: Asociality Avolition Blunted affect Alogia</td>
<td>Lower</td>
</tr>
<tr>
<td>Quality of life</td>
<td>World Health Organisation Quality of Life-Short Form domains: Physical health Psychological functioning Social relationships Environmental opportunities</td>
<td>Higher</td>
</tr>
<tr>
<td>Functional status</td>
<td>Social and Occupational Functioning Assessment Scale</td>
<td>Higher</td>
</tr>
<tr>
<td>Physical activity</td>
<td>International Physical Activity Questionnaire Short Form (MET-min/week)</td>
<td>Higher</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic blood pressure (mmhg)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure (mmhg)</td>
<td></td>
</tr>
<tr>
<td>CoQ10 levels</td>
<td>Plasma CoQ10 levels</td>
<td>Higher</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td>Plasma lactate levels</td>
<td>Lower</td>
</tr>
</tbody>
</table>

Improvement on measure is indicated if change occurs in the direction listed above.
2.13 Secondary outcomes

2.13.1 Secondary cognitive outcome measures

2.13.1.1 Processing speed

Processing speed was assessed at 3 and 6 months post-supplementation using the FAS test of verbal fluency and the Trail Making Task Form A (Strauss et al., 2006).

The FAS test (Spreen & Benton, 1977) is a phonemic verbal fluency task that demonstrates good test-retest reliability (Table 2.5) and is sensitive to treatment effects. Small to moderate effects post-treatment have been reported using the task (Harvey & Keefe, 2001). During the verbal fluency task, participants generate as many words as possible for a given letter in one minute. The letter F, A and S were used. Higher scores indicate faster processing speed.

Trail Making Task form A is another reliable measure of processing speed that is commonly used in trials and interventions in schizophrenia (Bowie & Harvey, 2006; Keefe et al., 2017). The task demonstrates good test-retest reliability (Table 2.5) and is sensitive to treatment effects (Keefe et al., 2017). Participants are required to connect 25 circled numbers in numerical order as quickly as possible. Time in seconds to completion is the outcome of interest. Lower scores indicate faster processing speed (Bowie & Harvey, 2006).

2.13.1.2 Executive functioning

Executive functioning was measured with two measures: the strategy score of SWM (CANTAB; Robbins et al., 1994) and the Trail Making Task Form B (Strauss et al., 2006).

Alongside the “Between Errors” score (see primary outcome measures) the SWM task also provides a strategy score that is indicative of executive function. Effective strategy is considered when the participant begins with a particular box and returns to that box upon finding a token to start a new search. Standardized scores are provided and higher scores indicate better performance, while lower scores indicate poor choice of strategy and suggest executive dysfunction (Martoni et al., 2015).

Form B of the Trail Making Task is a validated measure of executive functioning, specifically cognitive flexibility (Bowie & Harvey, 2006; Kortte et al., 2002; Tombaugh, 2004). The task demonstrates good test-retest reliability (Table 2.5) (Strauss et al., 2006; Tombaugh, 2004). Participants are required to connect 25 circled numbers and letters in an ascending pattern but alternating between numbers and letters with each move (i.e. 1-A-2-B-3 etc.) as quickly as possible. Time in seconds to completion was the outcome of interest. A maximum score of 300 seconds was allotted and the task was discontinued after 300 seconds (Bowie & Harvey, 2006). Lower scores (time to complete task in seconds) indicated better executive functioning, while higher scores suggest executive dysfunction (Bowie & Harvey, 2001).
2.13.1.3 General cognitive function (Current IQ)

Estimates of current IQ were assessed 3 and 6 months post-randomisation.

The Similarities and Matrix Reasoning subtests from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III; Wechsler, 1997a) were administered in order to derive estimates of current full scale IQ. Where comprehensive full scale IQ testing may be too time consuming or taxing on participants, short-forms and subtest dyads of the WAIS are frequently used in clinical and research settings to estimate global cognitive functioning (Denney et al., 2015). Though increasing the number of subtests administered increases accuracy of IQ estimate, Denney et al. (2015) demonstrated that the Similarities and Matrix Reasoning dyad is a valid predictor of full scale IQ ($R^2 = .71$). This dyad has previously been used within a psychosis sample to derive estimates of full scale IQ from published norms available for the two subtests (Hargreaves et al., 2015).

The Similarities subtest measures verbal reasoning and concept formation. Participants are read two related words and required to state how the two words are alike or similar. The test is discontinued when a participant gets four consecutive items wrong (Wechsler 1997a). Matrix reasoning is a subtest of abstract problem solving that measures four types of nonverbal reasoning: pattern completion, classification, analogy and serial reasoning. Participants are presented with an incomplete matrix for each item and required to complete the matrix by selecting one of five response options. The trial is discontinued when a participant scores 0 on four out of five consecutive items (Wechsler, 1997a).

Table 2.5 Test-retest properties, RCI, and cut-point value for clinical significance on cognitive measures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$R_{12}$</th>
<th>RCI</th>
<th>Normative mean</th>
<th>Clinical significance cut point*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-IP-2 digits</td>
<td>0.64</td>
<td>1.052</td>
<td>4.060</td>
<td>3.343</td>
</tr>
<tr>
<td>CPT-IP-3 digits</td>
<td>0.57</td>
<td>1.379</td>
<td>3.560</td>
<td>2.674</td>
</tr>
<tr>
<td>CPT-IP-4 digits</td>
<td>0.79</td>
<td>0.884</td>
<td>2.270</td>
<td>1.634</td>
</tr>
<tr>
<td>SWM Errors</td>
<td>0.70</td>
<td>26.417</td>
<td>15.7</td>
<td>35.3</td>
</tr>
<tr>
<td>LNS</td>
<td>0.61</td>
<td>3.603</td>
<td>9.9</td>
<td>8.764</td>
</tr>
<tr>
<td>FAS</td>
<td>0.82</td>
<td>14.683</td>
<td>34.78</td>
<td>33.651</td>
</tr>
<tr>
<td>Trail Making Task-A</td>
<td>0.79</td>
<td>14.810</td>
<td>26.52</td>
<td>38.81</td>
</tr>
<tr>
<td>SWM (Strategy)</td>
<td>0.63</td>
<td>9.273</td>
<td>30.6</td>
<td>33.393</td>
</tr>
<tr>
<td>Trail Making Task-B</td>
<td>0.89</td>
<td>41.571</td>
<td>72.05</td>
<td>104.515</td>
</tr>
<tr>
<td>Estimated FSIQ</td>
<td>0.850</td>
<td>6.375</td>
<td>99.6</td>
<td>94.959</td>
</tr>
<tr>
<td>Similarities</td>
<td>0.690</td>
<td>3.104</td>
<td>10.1</td>
<td>9.396</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>0.880</td>
<td>2.688</td>
<td>10.1</td>
<td>9.262</td>
</tr>
</tbody>
</table>

*midpoint between cohort sample mean at baseline and normative mean.

See Section 2.15.17 for details on RCI and clinical significance.
2.13.2 Biochemical outcome measures

2.13.2.1 CoQ10 concentration

Plasma CoQ10 concentration was used to determine CoQ10 status in participants. Normal plasma CoQ10 is within the reference range of 0.5 – 1.7 μmol/l (Molyneux, Young, et al., 2008). Total oxidised CoQ10 was measured to determine whether CoQ10 levels change following CoQ10 supplementation, and whether any change may be correlated with change in neuropsychological or clinical outcomes. Plasma CoQ10 reflects the amount of absorbed CoQ10 (Button et al., 2015).

Plasma CoQ10 levels were measured using high-performance liquid chromatography at Liverpool John Moore University, UK by Dr Iain Hargreaves and Robert Heaton.

2.13.2.2 Mitochondrial function

Plasma lactate concentration was used as an estimator of mitochondrial function. Increased lactate may indicate a shift from oxidative phosphorylation to greater reliance on less efficient anaerobic glycolysis for energy production (Regenold et al., 2009; Rowland et al., 2016). Reduction in lactate levels may indicate improved mitochondrial function. The laboratory reference range for normal lactate concentration was 0.5 - 2.2 mmol/l.

Plasma lactate analysis was conducted at Liverpool Clinical Laboratories by Dr Suzannah Phillips, Jean Devine and Angela Lambert.

2.13.2.3 Sample collection for biochemical outcomes

Blood samples to measure plasma CoQ10 and lactate were taken using a butterfly vacuum set and Vacuette® blood tubes at baseline, 3 months and 6 months post-randomisation. Samples for lactate analysis were collected in fluoride/oxalate tubes and samples for CoQ10 analysis were collected in EDTA tubes. The 4ml samples were centrifuged at 4° Celsius for five minutes, and plasma was then pipetted into 2ml aliquot tubes. The aliquots were frozen in a -80° Celsius freezer until sample analysis. Where it was not possible to process the blood samples immediately, the samples were stored upright on ice until processing as lactate is highly unstable in whole blood. Sample were kept upright on ice and then centrifuged and separated within one hour.
2.13.3 Energy outcome measure

Energy levels were assessed at baseline, 3 and 6 months post-randomisation using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F; Cella, 1997). FACIT-F is a self-report questionnaire that was initially developed to evaluate fatigue associated with cancer anaemia, and its impact on function and daily activities. The questionnaire has since shown good reliability and validity in a variety of chronic diseases including lupus, Crohn’s disease and rheumatoid arthritis (Loftus et al., 2008; Pettersson et al., 2015; Pouchot et al., 2008). Lower scores on the scale indicate higher levels of illness related fatigue.

2.13.4 Psychological symptom outcome measures

Affective and negative symptoms between the CoQ10 and placebo groups were assessed using the following measures at baseline, and 3 and 6 months post-randomisation.

2.13.4.1 Depression

Depression was assessed using Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996). BDI-II is a 21-item scale with excellent internal consistency ($\alpha = .92$) (Beck et al., 1996) that is routinely used to assess depression severity and determine treatment effects in clinical and research settings. Level of depression can be categorised into four groups using the BDI-II: 0-13 minimal range, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (Beck et al., 1996). The estimated minimal clinically important difference on the BDI-II is between 17.5% and 32% reduction in scores from baseline, with anti-depressant resistant depression requiring the greater reduction (Button et al., 2015). Reliable change in depressive symptoms occurs when a participant’s score changes by 8.46 points from baseline, and the change is clinically significant if a reduction of at least 8.46 points occurs and the total score is less than or equal to 14 points (Seggar et al., 2002).

2.13.4.2 Anxiety

Anxiety was assessed using Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). BAI possesses sound psychometric properties including excellent internal consistency ($\alpha = .92$) and good test–retest reliability ($r = .75$) (Beck et al., 1988). BAI is routinely used in clinical practice and research setting to establish baseline anxiety severity and determine effects of interventions on anxiety severity. Anxiety scores can be classified at 4 levels using the BAI: 0-9 normal range, 10–19 mild to moderate anxiety, 19–29 moderate anxiety, and 30–63 severe anxiety (Westbrook & Kirk, 2005). Reliable change has been estimated as 10 point change from baseline score and clinically significant change as 10 point reduction in score from baseline and end score less than or equal to 10 (Westbrook & Kirk, 2005).
2.13.4.3 **Negative symptoms**

Negative symptoms of avolition, asociality, alogia and blunted affect were assessed using their respective subscales from the Brief Negative Symptoms scale (BNSS; Kirkpatrick et al., 2011). The Brief Negative Symptom Scale is a short semi-structured interview that was designed for use in clinical trials, as well as epidemiological and psychological studies in schizophrenia. It consists of six subscales that evaluate five currently accepted negative symptoms, and one additional subscale: lack of normal distress. The BNSS has demonstrated good psychometric properties and appears sensitive to psychosocial and pharmacological treatment effects. The BNSS has been proposed to allow researchers to examine treatment effects on separate aspects of negative symptoms. Due to the extensive testing battery only the avolition and asociality questions were administered, and alogia and blunted affect were rated on expression and speech throughout the testing session. The anhedonia and lack of normal distress subscales of the measure were not administered. Higher scores on the subscales indicate higher levels of negative symptoms.

2.13.5 **Additional health related outcome measures**

Differences in physical activity, quality of life, functional status, and systolic and diastolic blood pressure between the CoQ10 and placebo groups were assessed using the following measures at 3 and 6 months post-randomisation.

2.13.5.1 **Physical activity levels**

Physical activity levels were measured using the International Physical Activity Questionnaire Short Form (IPAQ-SF; Craig et al., 2003). IPAQ-SF is an interviewer administered questionnaire. Participants are asked about their various physical activities in the preceding seven days. Activities are split between walking, moderate and vigorous physical activities that took place for at least ten minutes at a time. Using the IPAQ-SF scoring guidelines weekly metabolic equivalent task minutes (MET-min/Week) were estimated from reported weekly physical activity. A MET-minute is the rate of energy expended during an activity relative to energy expended at rest (Craig et al., 2003). They are calculated by multiplying the time spent doing an activity by the rate of energy expenditure for that activity (Craig et al., 2003). MET-min/week is then used to classify participants’ activity levels into the physical activity categories of low, moderate and high health enhancing physical activity.

2.13.5.2 **Subjective quality of life**

Subjective quality of life was measured using the World Health Organisation Quality of Life short form (WHOQOL-SF; Skevington et al., 2004). This scale consists of 26 questions which are scored and transformed to provide domain scores of physical health, psychological functioning, social relationships and environmental opportunities. Higher scores indicate higher well-being within the attached domain. There are also two general questions which address participants’ perception of
their quality of life and overall health. WHOQOL-SF is sensitive to detecting changes in quality of life in patients with schizophrenia (Van de Willige et al., 2005).

2.13.5.3 Functional status

Functional status was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992). The SOFAS provides a rating from 0 to 100 of current global social and occupational function. Ratings are made independent of psychological symptoms, and impairments must be considered direct consequences of mental and physical conditions, rather than an absence of opportunity or context. Higher scores represent higher levels of functioning (Rybarczyk, 2011). Impaired memory and insight for patients with schizophrenia can render self-reported accounts of their capabilities and competencies inaccurate, whereas both caregiver and clinician ratings can produce more reliable data (Brown & Velligan, 2016). Where possible this proxy measure was completed in collaboration with a member of the participant’s treating team, caregiver or close friend.

2.13.5.4 Blood pressure

Systolic and diastolic blood pressure was assessed at 3- and 6-months post-randomisation.

Systolic and diastolic blood pressure was taken using a portable blood pressure monitor (Omron M10-IT). Clinically significant readings were defined as systolic pressure above 140 mmhg or below 90 mmhg and diastolic pressure above 90 mmhg or below 60mmhg. Where a clinically significant reading occurred, a second reading was taken ten minutes later. In the event of a repeated clinically significant reading, a clinical research nurse was requested to take a manual reading. The values of all readings were recorded and given to the participant. They were requested to bring that information to their GP. Follow up phone calls were made with the participants to ensure they had attended their GP.
2.14 Randomisation, concealment and blinding procedures

Upon signing consent, completing the baseline assessment and ensuring participation was not contraindicated, participants were randomised to receive CoQ10 or placebo capsules during the study (Figure 2.2 illustrates the CONSORT flow diagram). Randomisation was conducted by a research pharmacist using a randomisation table stratified by blocks according to age and sex (males aged 18-39 years, females aged 18-39 years, males aged 40+ years, and females aged 40+ years). The randomisation table was created by an independent statistician. No member of the research team observed the randomisation table during the course of the study. Study personnel, clinical teams and participants remained blinded to treatment group allocation, throughout the study and outcome assessment. Upon completion or withdrawal from the study participants were asked to indicate whether they thought they were receiving CoQ10 or placebo.

Pharma Nord provided the placebo and CoQ10 capsules in blister sheets that were packed in plain white boxes. Each blister sheet contained 30 capsules. These were delivered by Pharma Nord directly to the research pharmacist at the CRF. The research pharmacist over labelled the boxes with the requisite information which included instructions for intake, date dispensed, and expiry date. Each label stated “270 CoQ10 or Placebo Capsules”. As the capsules were not considered an investigational medicinal product (IMP) the pharmacist was permitted to over label.

Blinding success was evaluated using the James’ blinding index (James et al., 1996). At the end of the study, the assessors and participants recorded their own guess as to which group the participant had been enrolled (do not know, placebo group, treatment group). Successful blinding is indicated by a high number of “do not know” answers, and approximately equal numbers of correct and incorrect guesses. Emergency un-blinding procedures were in place for the principle investigator (PI) in the event of a severe adverse event or suspected severe adverse reaction during the course of the study, though these did not occur. Disclosure of treatment group label was made by the research pharmacist at the end of data collection, once the analysis plan was finalised and reviewed with the PI.
2.15 Statistical methods

Statistical package SPSS 25 for Windows (SPSS, 2018) was used in the analysis. A summary of the analyses protocol is presented in Table 2.6.

Table 2.6 Summary of analyses used within this thesis.

<table>
<thead>
<tr>
<th>Analysis step</th>
<th>Statistical test(s)</th>
<th>Cases analysed</th>
<th>Chapter presenting results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of demographic and health status information between groups</td>
<td>Independent t-test, Chi-square test</td>
<td>ITT</td>
<td>Chapter 3</td>
</tr>
<tr>
<td>Comparison of baseline values on primary and secondary outcomes measures between groups</td>
<td>Independent t-test, Mann Whitney U, Chi-square test</td>
<td>ITT</td>
<td>Chapters 4,5</td>
</tr>
<tr>
<td>Within group change on primary and secondary cognitive outcomes</td>
<td>Paired sample t-test, McNemar test</td>
<td>CC</td>
<td>Chapter 4</td>
</tr>
<tr>
<td>Between group difference on primary and secondary cognitive outcomes</td>
<td>ANCOVA</td>
<td>CC ITT (sensitivity)</td>
<td>Chapter 4</td>
</tr>
<tr>
<td>Post-hoc analyses: Between group difference on primary and secondary cognitive outcomes</td>
<td>ANCOVA</td>
<td>CC</td>
<td>Chapter 4</td>
</tr>
<tr>
<td>Reliable and clinically significant change on primary and secondary cognitive outcomes</td>
<td>Chi square test NNT</td>
<td>CC</td>
<td>Chapter 4</td>
</tr>
<tr>
<td>Within group change on secondary outcomes</td>
<td>Paired sample t-test, McNemar test</td>
<td>CC</td>
<td>Chapter 5</td>
</tr>
<tr>
<td>Between group difference on secondary outcomes</td>
<td>ANCOVA, GEE</td>
<td>CC ITT (sensitivity)</td>
<td>Chapter 5</td>
</tr>
<tr>
<td>Post-hoc analyses: Between group difference on secondary outcomes</td>
<td>ANCOVA, GEE</td>
<td>CC</td>
<td>Chapter 5</td>
</tr>
<tr>
<td>Minimal clinically important, reliable and clinically significant change on secondary outcomes</td>
<td>Chi square test NNT</td>
<td>CC</td>
<td>Chapter 5</td>
</tr>
<tr>
<td>Relationship between CoQ10 and lactate levels and remaining outcomes</td>
<td>Spearman’s rho</td>
<td>CC</td>
<td>Chapter 5</td>
</tr>
<tr>
<td>Relationship between change in CoQ10 and lactate levels and change on remaining outcomes</td>
<td>Spearman’s rho</td>
<td>CC</td>
<td>Chapter 5</td>
</tr>
</tbody>
</table>

ANCOVA Analysis of covariance, CC Complete Cases, GEE Generalised estimating equation, ITT Intention to Treat, NNT Number needed to treat
2.15.1 Sample size calculation

Sample size determination is a critical step in study and RCT planning; the trial must be have an adequate sample size to detect a clinically significant effect that is also statistically significant, whilst also minimising the number of participants potentially exposed to harmful or ineffective treatments (Button et al., 2013; Lenth, 2001). This RCT had dual primary outcome measures: Attention and Working Memory performance. To compare differences between treatment groups on the outcomes at each follow-up assessment, analysis of covariance (ANCOVA) was used. The required sample size for ANCOVA was calculated using the method described by Borm et al. (2007). An online sample size calculator was used: http://www.biostathandbook.com/ancova.html.

The sample size was calculated based on estimates of treatment effect, variability, correlation between covariate and outcome, desired power and required significance level for the dual primary outcomes. For the RCT, the conventional power of 0.8 was desired; the probability of detecting a statistically significant effect, given that an effect occurred with treatment, was 80%. The significance level was 0.05; the risk of Type 1 error was 5%. A medium effect size of 0.4 was selected. This effect size was considered a treatment advantage of clinical interest, and had previously been obtained in trials of cognitive behavioural therapy in schizophrenia (Wykes et al., 2008). Standard deviation (SD) was used as an estimate of variability, these values were obtained from previous work within the cohort (Donohoe et al., 2013). Finally, a medium correlation of 0.5 ($R^2=0.25$) between covariate and outcome variables was presumed.

Based on the above assumptions, sample size calculation for the first primary outcome of attention indicated that 69 participants per treatment group would be required, assuming standard deviation (SD) of .96. For the second primary outcome of working memory, a total sample size of 250 participants were required, based on the above assumptions, changing SD to 1.3 for standardized scores on SWM. To guard against potential loss of power due to attrition, a dropout rate of approximately 20% was factored into the recruitment target. This approach has been recommended by others (Szymczynska et al., 2017). Thus the study aimed to recruit a total of 300 participants in order to detect a medium effect of CoQ10 on both attention and working memory performance.

There are alternative recommendations for calculating sample sizes in randomised controlled trial. Notably it has been recommended to use unstandardized or raw measures to estimate effect size, such as raw difference between group means and pooled standard deviation from the literature for a more accurate estimate (Lenth, 2001). Further, estimating sample size for each co-primary outcome may be overly conservative if outcome measures are correlated (Sugimoto et al., 2012).
2.15.2 Missing data

Missing data are defined as values which are not available but would be important for analyses if they were observed (Little et al., 2012). Missing data can reduce power and bias the interpretation of a trial’s results, particularly where large amounts of data may be missing or where missing values may be weighted by treatment allocation (European Medicines Agency (EMA), 2010). Missing data violate the Intention-to-Treat (ITT) principle of measurement and analysis of all patient outcomes according to their assigned randomised group, regardless of treatment or protocol adherence (EMA, 2010). Missing data may be the result of study discontinuation due to adverse events or inconvenience to the patient. In other cases, trial design may inadvertently encourage missing data through lengthy assessments and the collection of multiple outcome measures (Jakobsen et al., 2017).

Jakobsen and colleagues (2017) detail the three mechanisms behind missing data: missing completely as random (MCAR), missing at random (MAR) and missing not at random (MNAR). MCAR data are independent of observed and unobserved data, and though sample size is reduced thereby reducing power (Jakobsen et al., 2017). However, MCAR data typically do not inflate bias as the missing data is unlikely due to (Jakobsen et al., 2017). MAR data are dependent on observed values only; missing values can be predicted by other values from participants with complete data (Jakobsen et al., 2017). Prediction of MNAR values is dependent on both observed and unknown values. It is impossible to fully determine whether data is MAR or MNAR since unknown values cannot be used to predict the probability of unknown values (Jakobsen et al., 2017).

Where a substantial proportion of data is missing on primary variables (5% < 40%) it has been recommended to conduct the principle analysis using observed data within randomised treatment condition, and provide auxiliary sensitivity analysis to consider the influence of missing data on result interpretation thus missing data (Jakobsen et al., 2017). Such sensitivity analysis generally requires imputation of missing values, though there is no gold-standard method for replacing on observed data. Single imputation methods to replace missing values such as last observation carried forward or mean imputation have been heavily criticised however as these methods tend to underestimate variability within the sample and assume that the data is MAR (EMA, 2010; Molnar et al., 2009; Unnebrink & Windeler, 2001). Multiple imputation presents as an alternative method for handling missing data, accounting for existing variability within both outcomes and auxiliary variables (Jakobsen et al., 2017). However, where missing data can be predicted by other values within the data all imputation methods remain subject to bias.

Thus, the principle analysis of outcomes in this RCT was based on complete cases for each outcome variable. Sensitivity analysis followed an Intention to Treat (ITT) approach and used multiple imputation based on chained equations to impute missing values in SPSS 25 (SPSS, 2018).
2.15.3 Study population, demographics, health status information and outcome measures at baseline

As recommended in CONSORT guidelines (Moher et al., 2010) demographic and clinical characteristics for each treatment group are presented in Chapter 3-5 to provide a comprehensive picture of the recruited sample.

Between groups tests of demographic and outcome variables at baseline were conducted and included in this thesis to consider success of randomisation and identify potential imbalances between groups that should be included as a covariate. However, testing and reporting baseline differences between groups is discouraged by many (Austin et al., 2010; de Boer et al., 2015; European Medicines Agency, 2015; Knol et al., 2012; Moher et al., 2010; Senn, 1994). Such tests are considered redundant and potentially misleading for several reasons (Moher et al., 2010). First, if randomisation is conducted appropriately, any imbalances between groups will be random artefacts as both samples are from the same population. Reporting several null hypothesis statistical tests (NHSTs) will not supplement this fact. Rather, if α = 0.05, it is likely that 5% of tests will be significant, simply by chance (de Boer et al., 2015). Second, comparisons at baseline should consider the magnitude and prognostic value of chance imbalances, rather than their statistical significance (Moher et al., 2010). Covariates included within the model reduce the standard error of treatment effect by removing some of the unexplained variance, therefore providing a more precise estimate of treatment effect (de Boer et al., 2015). However, meaningful differences between treatment groups may go undetected due to low power and thus continue to confound results. Likewise, including a statistically significant but non-prognostic factor in an adjusted model may bias the results. Thus selection of covariates should be based on meaningful known prognostic factors obtained from the literature or clinical expertise rather than the results of NHSTs (de Boer et al., 2015; Senn, 1994). Nonetheless, the European Medicines Agency (2015) emphasise that if a chance imbalance in a baseline covariate is observed, and the experimental group has a better prognosis than the control group, adjusting the observed imbalance is important. Sensitivity analysis should be included to demonstrate that a positive treatment effect is not explained by imbalances in baseline and allow assessment of the robustness of primary analysis (European Medicines Agency, 2015).

Within this thesis, comparisons between groups at baseline were made using NHSTs, however it is acknowledged that this information may be superfluous. Pre-randomisation differences were not included as additional covariates in the principal analyses reported in Chapters 4 and 5. The baseline score for each separate outcome variable was included as the only covariate in the associated analysis, regardless of statistical difference between groups. This approach allows for a more precise evaluation of treatment effect, which accounts for regression to the mean on the variable, but is not biased by the inclusion of potentially inappropriate factors (Twisk et al., 2018).
Finally, in the event that a treatment effect in favour of CoQ10 was observed sensitivity analysis including imbalanced covariates should be conducted.

Baseline characteristics and health status information are presented as mean and standard deviation (SD) or numbers and percentage (Chapter 3). Baseline characteristics and health status information were compared between groups using independent t-tests and Chi-Square tests. Medication details at baseline and changes to medication regime during study participation were compared using independent t-tests and Chi-Square tests. Fisher’s Exact Probability Test (FET) is reported alongside Chi-Square tests where less than 80% of cells meet the expected cell count of 5. Between groups differences on baseline scores of outcome measures for all randomised participants were analysed using independent t-tests, Mann Whitney U tests and Chi Square tests (Chapters 4 and 5). Variables are presented in terms of mean and SD or median and interquartile range (IQR). Due to extreme floor effects at baseline blunted affect and alogia are also presented in terms of the presence or absence of the symptoms, change in symptom presentation was analysed using McNemar’s test.

2.15.4 Within group change

Though reported frequently in the literature, separate paired comparisons of follow-up scores against baseline as a primary analysis are considered conceptually wrong and may be misleading for several reasons (Allison et al., 2016; Bland & Altman, 2011, 2015; Boutron et al., 2010). First, change within group, if it occurs, may not indicate treatment effect, but rather placebo effects, practice effects and regression towards the mean (Bland & Altman, 2011, 2015; Keefe et al., 2017). Treatment response during a RCT is likely to involve these effects; as such the null hypothesis that there was no mean change from baseline is questionable (Bland and Altman, 2015). Further, the approach is associated with increased Type 1 error rate. Bland and Altman's (2011) demonstrated that when there is no difference between two treatments, the Type 1 error rate can deviate from the nominal 5% to up to 50%. Finally, “significance” of a within group test does not indicate “difference” between treatments, and may be misinterpreted by the reader (Bland & Altman, 2015; Boutron et al., 2010). Focusing on within group effects rather than between-group effect may distort interpretations of results (Boutron et al., 2010).

Within this thesis, separate paired comparisons against baseline were made for each treatment group. These tests were conducted to build a comprehensive picture of the data within the placebo and CoQ10 groups. However it is acknowledged that this information may be superfluous. The tests were not intended as the primary analysis or to distort interpretations of treatment effects. The results of the tests allow for consideration of other factors beyond treatment effect, such as regression towards the mean and placebo effects. For descriptive purposes, within group change from baseline to 3 and 6 month outcome assessments for complete cases were analysed using paired t-tests with Bonferroni adjustments for within pairwise comparisons. The principal and
sensitivity analyses of primary and secondary outcomes used ANCOVA to estimate treatment effect of CoQ10 within the parallel group design.

### 2.15.5 Evaluation of treatment effects

To evaluate the effects of CoQ10 supplementation compared to placebo a series of analyses were conducted to evaluate:

1. The differences in mean scores of attention and working memory between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
2. The differences in mean scores of processing speed, executive function and current IQ between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
3. The differences in mean levels of energy, depression, and anxiety between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
4. The differences in mean levels of negative symptoms asociality, avolition, blunted affect and alogia between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA, GEE).
5. The differences in mean levels of quality of life domains, social and occupational functioning, weekly physical activity between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
6. The differences in mean systolic and diastolic blood pressure between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
7. The differences in mean levels of plasma CoQ10 and plasma lactate between the CoQ10 and placebo groups at 3 and 6 months (ANCOVA).
8. The relationship between plasma CoQ10 and plasma lactate in both CoQ10 and placebo groups at baseline, 3 and 6 months (Spearman’s rho correlation).

Analysis of covariance (ANCOVA) was selected to assess between-group differences at 3 months and 6 months. This method adjusts for baseline differences between groups and has multiple advantages over alternative analysis of treatment effects (Borm et al., 2007; Egbewale et al., 2014; Twisk et al., 2018). ANCOVA is more powerful than repeated measures analysis or analysis of change in cases where the baseline value is moderately or highly correlated with the outcome value (Egbewale et al., 2014). The method is also advantageous as it reduces bias in estimated treatment. When groups are drawn and randomised from the same population, random imbalances between groups may occur due to chance and measurement error (Twisk et al., 2018; de Boer et al., 2015). With regression towards the mean, over the course of an intervention study one group may increase while the other may decrease (Twisk et al., 2018). As a result the estimated treatment effect is likely to be biased in unadjusted analysis. In RCTs where the baseline value is related to the follow-up value, small but not statistically significant differences between groups in baseline value can have a confounding effect (Twisk et al., 2018; Egbewale et al., 2014). Further, including a covariate will reduce unexplained variance and the estimated treatment effect will be more precise
(Egbewale et al., 2014). It is therefore recommended to include baseline score on the outcome measure as a covariate in the analysis.

In each of the ANCOVAs, performance or score on the relevant measure at each outcomes assessment was entered as the dependent variable, group as the independent variable, and baseline performance or score on the measure at baseline as a covariate. Residuals of each model were inspected to ensure model fit.

Due to extreme floor effects at baseline the results for blunted affect and alogia are presented in terms of the presence or absence of the symptoms and analysed using a generalized estimating equations approach. Values for blunted affect and alogia were not included in the multiple imputation model. The results for the remaining variables are presented as the unadjusted mean difference between groups at follow up assessments and adjusted mean difference between groups after controlling for baseline performance.

The statistical significance level of 0.05 was adjusted for multiple testing within families of measures to minimise risk of false positive (Benjamini & Hochberg, 1995). The small sample size randomised to the trial resulted in reduced power to detect the hypothesised moderate effect of CoQ10 on attention and working memory. As such, this correction for multiple testing was employed as it is less conservative than Bonferroni adjustment, protecting against Type 2 error (Benjamini & Hochberg, 1995).

2.15.6 Exploratory post-hoc analyses

Exploratory analyses were conducted according to the following subsets:

1) Adherent participants – differences in mean scores between CoQ10 and placebo groups at 6 months for those participants who reported 90 percent treatment adherence at 6 months.
2) Stable medication - differences in mean scores between CoQ10 and placebo groups at 6 months for those participants whose prescribed medication remained unchanged during the study.
2.15.7 *Meaningful, reliable and clinically significant change*

Statistically significant difference refers to any difference in the outcome scores that are highly unlikely to have occurred due to chance, and reflect real difference between two groups rather than measurement error (Jacobson & Truax, 1991). An effect size of the difference may be determined, however even large effect sizes are not necessarily clinically significant for all participants (Duff et al., 2012). Thus it has been recommended to determine the extent to which clinically significant change occurs within participants (Duff, 2012; Jacobson & Truax, 1991).

Clinically significant change can be defined using a variety of methods and the change classified into four groups: recovered (clinically and statistically significant), improved (statistically significant only), unchanged (no significance), and deteriorated (statistically significant change but in a negative direction) (Brouwer et al., 2013; Jacobson & Truax, 1991). Statistical change per participant can be determined using a Reliable Change Index (RCI), while clinically significant change is typically accepted when scores on the outcome measure post-treatment fall within the normative population range, outside the range of the dysfunctional population mean, or are closer to the normative population mean than the dysfunctional mean (Brauwer et al. 2013; Jacobson & Truax, 1991).

A reliable change index (RCI) was calculated for the cognitive outcomes (Jacobson & Truax, 1991). A native control sample was not available for the outcome measures, thus for cognitive change, RCI was calculated using test-retest reliability norms from procedural manuals or normative studies of the cognitive tasks (Table 2.5). Clinical significance for the cognitive outcomes was determined when participants fell closer to the normative mean obtained from published resources than the sample baseline mean. Chi-square tests were then used to determine if the proportion of individuals who changed within each group differed within each measure. A number needed to treat analyses within each cognitive domain was then conducted comparing the proportion of change within the CoQ10 group to the placebo group.

Reliable and clinically significant changes in depression and anxiety symptoms were also considered using criteria previously reported in the literature for the BDI-II and BAI (Seggar et al., 2002; Westbrook & Kirk, 2005).

Minimum clinically important difference (MCID) is a threshold value for a change on patient reported outcomes that is perceived as meaningful and worthwhile by the patient (Jaeschke et al., 1989). MCID for continuous patient reported outcomes measures was estimated as 0.5SD of the baseline cohort scores (Norman et al., 2003).
3 METHODOLOGICAL ISSUES AND SAMPLE CHARACTERISTICS WITHIN THE COQ10 RANDOMISED CONTROLLED TRIAL

3.1 Introduction

Randomised control trials (RCTs) are often considered a “gold standard” in evidence based care, as they offer the opportunity to draw some causal conclusions surrounding the intervention of interest. Compared to single arm, case-control, or open-label trials, well-designed RCTs can control for known and unknown confounds including demographic characteristics and prognostic factors, as well as placebo and practice effects (Keefe et al., 2017; Sedgwick, 2014). However, RCTs can remain subject to methodological flaws that limit the interpretability of results and estimates of effectiveness (Spieth et al., 2016). Results of RCTs may be subject to biases (for example selection, attrition, or reporting biases) that may over or under estimate a treatment effect, or they may lack generalisability to the clinical population of interest (Leon et al., 2006; Nordon et al., 2016, 2018; Rothwell, 2005). Additionally, extent of treatment adherence during the RCT will influence applicability of the results (García et al., 2016) The aim of this chapter is to describe such methodological issues that occurred during the conduct of the CoQ10 RCT.

3.2 Background

Successful recruitment of patients is considered a key to success in clinical trials, as small sample sizes can reduce statistical power and the robustness of findings. As such, underpowered studies produce more false negatives than high powered studies (Ioannidis, 2005). Only 14% of discontinued RCTs reported significant effect sizes, which may indicate low power (Briel et al., 2016). Further, small sample sizes and or small effects reduce the likelihood that a statistically significant result, when identified, signals a true effect in the population (Button et al., 2013). Trials that are underpowered are also more prone to effect inflation; by chance they can detect a larger effect than what truly exists (Button et al., 2013). Underpowered trials are also more vulnerable to publication and reporting biases; selective reporting is more likely to occur, and a true “negative” trial is difficult to distinguish from an underpowered trial of a small but true effect (Bedard et al., 2007; Zakeri et al., 2018). Underpowered studies can be less generalizable, as the small number of participants is less likely to represent the true patient population and findings may be insufficient to inform clinical practice (Halpern et al., 2002; Manski & Tetenov, 2016).

3.2.1 Recruitment

Participant recruitment and enrolment challenges in particular may compromise the generalisability or estimation of intervention effectiveness; particularly if only a very small percentage of eligible patients are recruited overall or where patients recruited to the study do not represent the population for whom the intervention is intended (Donovan et al., 2016; McDonald et al., 2006; Nordon et al., 2018). Frequently reported barriers to successful recruitment of representative patients to RCTs include time constraints and staff shortages at investigational or clinical sites; lack
of clinical equipoise; overestimation of eligible patients; competing studies; patient mistrust of research and treatment misconception (Briel et al., 2016; Rendell et al., 2006; Walsh & Sheridan, 2016). In contrast, having a designated trial manager, embedding studies within clinical services, treating physician recommendation, and providing additional resources to promote and protect research activity within clinical services have been shown to facilitate successful recruitment and enrolment to RCTs (Briel et al., 2016; Correll et al., 2011; Liu et al., 2018; Peckham et al., 2015, 2018; Walsh & Sheridan, 2016).

Engaging and enrolling patients with a diagnosis of schizophrenia or other severe mental illnesses in RCTs and clinical research can be particularly challenging (Borschmann et al., 2014; Patterson et al., 2014). Considerable portions of potentially eligible research candidates may never be invited to participate in clinical research or trials due to organisational or clinical barriers. A recent cross-sectional study noted that only 20% of patients with a psychotic disorder were approached for consent to be contacted about research within a large inner city National Health Service (NHS) mental health trust (Patel et al., 2017). The majority of those approached were in hospital rather than community settings, potentially reflecting resource issues within services (Patel et al., 2017). Additionally, younger patients and patients with good clinical outcomes are more likely to be approached to participate in research (Patel et al., 2017). Patients with schizophrenia are also less likely to be referred to clinical research when capacity or perceived capacity to take on new information or consent to research may be limited (Jones & Cipriani, 2019). It has been proposed that incentivising patients and clinicians through financial support may help improve recruitment and enrolment to RCTs (Correll et al., 2011; Liu et al., 2018). Yet, potentially encouraging “professional subjects” to enrol, or creating “enrolment pressure” within services to identify and recruit patients may also bias results through deliberate or unconscious enrolment of ineligible or inappropriate participants, as well as creating additional ethical concerns surrounding freely given consent (Shiovitz et al., 2016).

The selective nature of research participation can also bias RCT findings in mental health trials (Lally et al., 2018). For example, 80-90% of patients with physical conditions consented to a permission to contact scheme for research participation (Cheah et al., 2013). In contrast, only two-thirds of patients with psychosis expressed willingness to be contacted about clinical research (Patel et al., 2017). This discrepancy in willingness to participate between patients with physical and psychotic disorders may in part be due to features associated with psychotic disorders such paranoia, avolition and degree of insight (Correll et al., 2011; Riedel et al., 2005). Further, patients with more severe symptoms are less inclined to participate in research than participants with less impairment and illness severity (Roberts et al., 2005). However, in contrast, others suggest that patients with schizophrenia express high-readiness to participate in clinical trials and research (Cummings et al., 2013; Donohoe et al., 2017; Jørgensen et al., 2014). The type of research and intervention under investigation is likely to influence patients’ willingness to participate. Fears of
side effects or symptom aggravation as a consequence of participation are frequently cited deterrents for participation (Briel et al., 2016; Kaminsky et al., 2003; Zullino et al., 2003).

3.2.2 Retention

Retaining patients once recruited presents as a further challenge during the conduct of RCTs. Effective randomisation that ensures participants are evenly matched on baseline characteristics between groups can be futile if differential attrition rates occur between groups. Patients who withdraw may exhibit different characteristics or responses to the intervention than those who complete the trial. High levels of attrition will influence efficacy and credibility claims, even if balanced between groups (Xia et al., 2009). Drop-out rates from trials with schizophrenia and psychotic disorders are particularly high and can vary from 4% to 71% (Moodie et al., 2016; Rabinowitz et al., 2013; Szymczynska et al., 2017). Overall estimates of the proportion of dropouts can be dependent on trial type; varying from approximately 20% in psychosocial trials to approximately 35% in pharmacological interventions (Leucht et al., 2013; Szymczynska et al., 2017; Villeneuve et al., 2010). Factors that influence likelihood of attrition in schizophrenia trials are related to both sample characteristics and study design including older age, being male, unemployment, poor insight into disorder, unpleasant side-effects of treatment, blinding and treatment preference, longer treatment and illness duration (Moodie et al., 2016; Nose et al., 2003; Schoemaker et al., 2019; Szymczynska et al., 2017; Villeneuve et al., 2010). Patient dissatisfaction with assigned treatment is also associated with withdrawal of consent (Schoemaker et al., 2019). To guard against potential loss of information, and therefore statistical power, due to attrition, it has been recommended that sample size should be increased in proportion to the anticipated loss of participants (Szymczynska et al., 2017).

3.2.3 Treatment adherence

Treatment adherence, once patients are enrolled and randomised, will also influence the applicability of RCT results, particularly when translating RCT efficacy to effectiveness in clinical care. Treatment adherence refers to the extent to which a patient or trial participant follows the prescribed intervention according to the medical or therapeutic advice given, and can partially explain the variability in treatment effects (Allemann et al., 2017). Treatment non-adherence is a common problem in clinical and research mental health settings; it has been estimated that between 40 and 60% of patients with schizophrenia do not take their medication as prescribed (Lacro et al., 2002; Valenstein et al., 2006). However, Kane and colleagues (2013) indicated that treatment non-adherence in RCTs is generally better, though more variable (2.3% to 37.1%) than naturalistic or observational studies (30% to 58.4%). Several factors are likely to influence the variability between trial and routine medication adherence. First, patients who actively consent to participate in a RCT may have exhibited greater motivation and treatment acceptance than when prescribed an intervention with limited consultation. Additionally, the frequent, comprehensive follow up visits to determine safety, tolerability and treatment effects that occur during RCTs offer greater
opportunity to monitor and encourage adherence compared to routine care (Correll et al., 2011; Shiovitz et al., 2016). Increased personal contact is in itself likely to increase adherence (Kane et al., 2013). Regardless of setting however, several patient and treatment related factors are associated with level of adherence; higher levels of education and immediacy of treatment response are related to better treatment adherence, whereas unemployment, substance abuse, hostility, cognitive impairment and complex treatment regimens are associated with treatment non-adherence (García et al., 2016; Kane et al., 2013; Nosé et al., 2003). Environmental factors also influence level adherence, particularly the quality of existing therapeutic relationships, living conditions and social support (García et al., 2016; Higashi et al., 2013; Kane et al., 2013). Importantly, prior adherence behaviour is predictive of future practice (Higashi et al., 2013).

### 3.2.4 Summary

Failure to achieve and retain the necessary sample size within the designated trial period has statistical, financial and ethical consequences. The RCT may require additional monetary resources to expand or extend recruitment (McDonald et al., 2006). Extending the recruitment period delays potentially viable intervention from reaching patients and extreme delays risk interventions becoming outdated before effects can be determined (Olsen et al., 2015). Further, extending recruitment periods is no guarantee that the recruitment target will be reached (Raftery et al., 2015). On the other hand if a RCT concludes prior to achieving the intended sample size it will be underpowered and results may be inconclusive or unreliable (McDonald et al., 2006; Donovan et al., 2016). Attrition level can also reduce statistical power and credibility of a trial. Additionally, enrolled sample characteristics and adherence behaviour will influence the generalisability of trial outcomes.
3.3 Methodological issues during the conduct of the CoQ10 RCT

3.3.1 Required sample size

The CoQ10 RCT was an investigation of the effect of CoQ10 supplementation on cognitive, psychological, health and quality of life outcomes in schizophrenia and schizoaffective disorder. The sample size required to achieve 80% power to detect a moderate effect of CoQ10 on attention was 69 participants per treatment group, and on working memory was 125 participants per treatment group (Chapter 2). Ultimately, 70 participants were randomised to either CoQ10 or placebo. As a result of the low enrolment numbers, the study was inadequately powered to detect the expected small effects of CoQ10 on cognition compared to placebo.

3.3.2 Recruitment process

Previous recruitment experiences to psychosis studies within the Department of Psychiatry, TCD indicated that approximately 20% of patients approached would decline to participate in clinical research studies (Cummings et al., 2013; Donohoe et al., 2017). Therefore it was estimated that 375 patients needed to be invited to participate in the CoQ10 study, in order to reach the recruitment goal of 300 patients. Within the mental health service catchment areas of St James’s, Tallaght University, and Newcastle hospitals, approximately 1,550 people should meet a diagnostic criteria for schizophrenia or schizoaffective disorder, based on a 0.3% prevalence rate (Behan et al., 2008). It was therefore anticipated that that the required sample size of 300 participants would be reached through these services.

To meet the sample size of 300, it was necessary to consent and randomise 12 eligible patients per month over 26 months. Weekly and monthly recruitment rates were plotted to monitor recruitment to the study. Actual recruitment of participants was consistently slower than required, leading to increased monthly targets; after seven months of recruitment 20 patients per month needed to be randomised in order to meet the planned sample size (see Figure 3.1 for actual and anticipated consent rates). To help overcome this recruitment lag, a clinical research nurse with prior experience of recruiting participants to psychosis studies was hired by the PI in November 2017, so that multiple outpatient clinics could be approached simultaneously. Additionally, a Study within a Trial (SWAT) to improve screening and consent rates was designed but unsuccessfully implemented.
3.3.2.1 Recruitment Study within a Trial

A SWAT is the embedding of a methodology related research question within an existing trial. The aim of the SWAT should be to inform future design or delivery of trials, and may address design, conduct, analysis or reporting of results (Smith et al., 2013).

During the CoQ10 RCT, it was noted that a large number of patients declined to speak with the researchers at outpatient clinics. In response to this challenge, a SWAT was designed to determine whether prior notification of the RCT increased patients willingness to speak to the researchers about the RCT and subsequent consent rates (Caldwell et al., 2010; Liu et al., 2018; Treweek et al., 2010). Ethical permission was sought and granted to send a pre-information letter to potentially eligible participants identified by their treating team. The letter explained that the service users may be contacted by the research team about voluntarily participating in the research study. The letter was to be signed by a member of the treating team. The letter was not a replacement for the existing information sheet. It was proposed to randomise potentially eligible research candidates to receive the letter or no letter (1:1 ratio) in order to evaluate the effect of the letter on participant consent rates. Appendix C contains the pre-information letter and correspondence with REC.

Figure 3.1 Monthly participant recruitment rate to CoQ10 study.
It was not possible to conduct and evaluate the SWAT due to several factors. Primarily, clinical teams approached did not maintain an up-to-date list of patients and their psychiatric diagnoses for contact. Secondly, due to data protection restrictions within the services, a chart review to identify potentially eligible patients by the author could not be conducted. Thirdly, some clinical team members expressed concern that receiving the pre-information letter about the study may deter patients from attending their mental health appointment to avoid speaking to the researchers or may complain about sharing their personal information with people outside their service. Enrolment to the overall RCT was also less effective during the attempted SWAT implementation period compared to the same period the previous year, despite a larger catchment area and twice the number of outpatient clinical teams. In light of these factors, the SWAT was discontinued.

3.3.3 Consent and retention

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for participant recruitment, inclusion and retention is presented in Figure 2. In total, 316 patients were identified as potentially eligible research candidates; of whom 260 were referred to the researchers. Of patients referred to the study team, 147 patients declined to participate in the study. Five broad reasons for declining included: anticipated burden of participation, misunderstanding purpose of placebo, apprehension about side-effects or the risk of becoming unwell, discomfort surrounding diagnosis and current (dis)satisfaction with treatment plan. Thirty-seven of patients introduced to researchers were ineligible due to contraindicated medication, age, current or recent history of substance abuse, co-morbid neurological condition, or general ill-health. Six patients consented to participate in the study but withdrew prior to randomisation. Reasons for withdrawal post-consent but prior to randomisation were: fatigue during baseline assessment (n=3), upon chart review contraindicated medication or medical condition (n=2), and not meeting diagnosis of schizophrenia or schizoaffective disorder (n=1).
Figure 3.2 CONSORT Flow Diagram for CoQ10 study

- Identified (n=316)
  - Assessed for eligibility (n=260)
  - Excluded (n=190)
    - Not meeting inclusion criteria (n=37)
    - Declined to participate (n=147)
    - Consented but not randomised (n=6)

- Randomized (n= 70)

- Allocation
  - Allocated to CoQ10 (n=31)
    - Received allocated CoQ10 (n=31)
  - Allocated to placebo (n=39)
    - Received allocated placebo (n=39)

- Follow-Up (3 months)
  - Follow-up (n=24)
    - Lost to follow-up (not contactable) (n=2)
    - Discontinued intervention (n=5)
      - Hospitalization due to psychosis (n=1)
      - Suspected adverse event (n=2)
      - Personal reasons (n=2)
  - Follow-up (n=27)
    - Lost to follow-up (not contactable) (n=2)
    - Not available for appointment (n=1)*
    - Discontinued intervention (n=9)
      - Suspected adverse event (n=2)
      - Personal reasons (n=7)

- Follow-Up (6 months)
  - Follow-up (n=21)
    - Lost to follow-up (not contactable) (n=2)
    - Discontinued intervention (n=1)
      - Personal reasons (n=1)
  - Follow-up (n=25)
    - Discontinued intervention (n=3)
      - Hospitalization due to psychosis (n=1)
      - Personal reasons (n=2)

- Analysis
  - Complete cases (n=46)
  - Intent to Treat (n=70)
The overall retention rate at 6 months was 66%; 26% of randomised participants withdrew from the study before the midpoint assessment at 3 months. One participant was unable to attend the midpoint assessment at 3 months but continued to adhere to allocated treatment regime and attended the final outcome assessment at 6 months. There was no statistically significant difference in the overall withdrawal rates between the two treatment groups, $\chi^2(1, N=70) = 0.59, p = .444$. Participants who completed the study had significantly higher levels of education ($Mdn = 14$) compared to those who withdrew from the study ($Mdn = 13$), $U = -2.11, p = .034$. Participants who completed the study had significantly lower levels of avolition at baseline ($Mdn = 2.5$) compared to those who completed the study ($Mdn = 5$), $U = -2.75, p = .006$. Participants who completed the study had significantly lower levels of lactate ($Mdn = 1.10$) compared to those who withdrew from the study ($Mdn = 1.45$), $U = -2.42, p = .015$.

There were no other baseline differences between completers and those who withdrew. Reasons for withdrawal from the study are outlined in Figure 3.3.

**Participant withdrawal**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow-up (not contactable)</td>
<td>6</td>
</tr>
<tr>
<td>Suspected adverse event</td>
<td>4</td>
</tr>
<tr>
<td>No longer wishing to participate in the study</td>
<td>4</td>
</tr>
<tr>
<td>Lack of perceived benefit from allocated treatment</td>
<td>4</td>
</tr>
<tr>
<td>Difficulty adhering to treatment</td>
<td>3</td>
</tr>
<tr>
<td>Hospitalization due to relapse of psychotic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Choosing to participate in a different research study</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 3.3 Reasons for participant withdrawal from study.**

### 3.3.4 Adverse events

Relapse of psychotic symptoms was not deemed attributable to treatment allocation or research participation and thus was not classified as an adverse event. One participant stopped taking all psychiatric medication without medical supervision resulting in relapse. The second participant was transitioning from one form of antipsychotic medication to another at time of relapse.

Suspected adverse events occurred in four participants in total, these participants withdrew from the study. In the CoQ10 group, one participant reported nausea and one reported joint pain. In the placebo group, one participant reported nausea and one reported light headedness.
3.3.5 Adherence to treatment regime

Adherence to study treatment was measured by means of a pill count at the follow-up assessments at 3 months and 6 months. Participants were requested to bring remaining capsules to their follow-up assessments. Seventeen participants at midpoint and eleven participants at endpoint did not bring remaining capsules to the appointment, nor could they recall or accurately report the number of capsules remaining on follow up contact. Information on remaining capsules after 6 months was available for 35 participants. Twenty-six participants either brought remaining capsules to their appointments or counted back remaining capsules during a follow-up phone call. Nine participants self-reported complete adherence to treatment regimen throughout the study. Median remaining capsules in the placebo group (n=16) was 26 (IQR = 77.25) and in the CoQ10 group (n=19) was 20 (IQR = 36). Participants were assumed to be fully adherent to the study treatment if < 10% of total capsules (54 capsules or less) remained at 6 months. There were no differences in demographic characteristics or baseline measure scores between participants who reported full adherence and those who did not. Participants were more likely to report full adherence when their medication had remained stable in the preceding 3 months, \( \chi^2 (1, N=44) = 6.51, p = .018 \).

3.3.6 Success of blinding

At the end of the study, the participants and the two assessors (ÁM & CM) independently recorded their own guess as to which group the participant had been enrolled. Successful blinding was indicated. Assessors guessed CoQ10 assignment 47% percent of the time and 57% of total assessor guesses were correct. Thirty-seven percent of participant guesses were correct. Thirty percent of participants indicated that they were unsure as to which group they had been assigned, the remaining participants guessed incorrectly.

3.4 Sample demographics and health status information at baseline

3.4.1 Baseline demographic and health status characteristics

The majority of participants had a diagnosis of schizophrenia (70%). On average participants had been living with a diagnosis of either schizophrenia or schizoaffective disorder for 18.33 years (SD = 11.41). The average age of all participants was 47.9 years (SD = 10.41). Participants had spent on average 14.13 years (SD = 3.57) in education. Eleven participants (16%) had completed degree level education or higher. Seventeen percent of participants were in full or part-time employment, 9% of the sample was currently attending vocational training or further education programmes. Most of the cohort was single (77%) and 73% of the sample were male.

In terms of health behaviours and status, less than half (44%) of the sample smoked tobacco and 47% drank alcohol at the time of baseline assessment. Casual illicit substance use at baseline was not reported in the sample. At baseline, 36% of the sample reported low levels physical activity, as
measured using IPAQ (Craig et al., 2003). Hypertension was the most commonly reported comorbid physical condition within the sample (24.3%). There was no statistically significant difference between treatment groups on baseline demographic and health status characteristics (Table 3.1).

Table 3.1 Baseline characteristics and health status information of participants by treatment allocation

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=39)</th>
<th>CoQ10 (N=31)</th>
<th>$\chi^2$</th>
<th>p</th>
<th>FET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>27(69.2)</td>
<td>22(71)</td>
<td>0.03</td>
<td>.875</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>12(30.8)</td>
<td>9(29)</td>
<td>0.03</td>
<td>.875</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29(74.4)</td>
<td>22(71)</td>
<td>0.10</td>
<td>.751</td>
<td></td>
</tr>
<tr>
<td>Marital status (single)</td>
<td>29(74.4)</td>
<td>25(80.6)</td>
<td>0.39</td>
<td>.534</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>7(17.9)</td>
<td>5(16.1)</td>
<td>0.66</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Currently in education</td>
<td>5(12.8)</td>
<td>1(3.2)</td>
<td>0.24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>t</td>
<td>p</td>
<td>df</td>
</tr>
<tr>
<td>Age</td>
<td>47.69 (10.23)</td>
<td>48.16 (10.18)</td>
<td>-0.19</td>
<td>.853</td>
<td>68</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>17.76 (12.29)</td>
<td>19.12 (10.26)</td>
<td>-0.47</td>
<td>.640</td>
<td>64</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.58 (3.6)</td>
<td>13.57 (3.6)</td>
<td>1.16</td>
<td>.249</td>
<td>66</td>
</tr>
<tr>
<td>Comorbid physical condition</td>
<td>n(%)</td>
<td>n(%)</td>
<td>$\chi^2$</td>
<td>p</td>
<td>FET</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4(10.3)</td>
<td>2(6.5)</td>
<td>0.32</td>
<td>.572</td>
<td>.687</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7(17.9)</td>
<td>10(32.3)</td>
<td>1.16</td>
<td>.281</td>
<td></td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>2(5.1)</td>
<td>4(12.9)</td>
<td>1.33</td>
<td>.248</td>
<td>.395</td>
</tr>
<tr>
<td>Health behaviour</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>t</td>
<td>p</td>
<td>df</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>24.59 (18.05)</td>
<td>17.15 (7.49)</td>
<td>1.53</td>
<td>.139</td>
<td>22.5</td>
</tr>
<tr>
<td>Units of alcohol per week</td>
<td>15.9 (20.56)</td>
<td>10.35 (11.65)</td>
<td>0.86</td>
<td>.398</td>
<td>31</td>
</tr>
<tr>
<td>Physical activity level</td>
<td>n(%)</td>
<td>n(%)</td>
<td>$\chi^2$</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>13(33.3)</td>
<td>12(38.7)</td>
<td>0.22</td>
<td>.641</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>19(48.7)</td>
<td>11(35.5)</td>
<td>1.24</td>
<td>.266</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6(15.4)</td>
<td>8(25.8)</td>
<td>1.17</td>
<td>.279</td>
<td></td>
</tr>
</tbody>
</table>

FET Fisher’s exact test, $\chi^2$ Chi-Square, t independent sample t-test
3.4.2 Participant medication status during the CoQ10 RCT

3.4.2.1 Antipsychotic medication status

All participants were taking at least one antipsychotic medication, with the average chlorpromazine equivalent dose being 418.79 mg/day ($SD = 273.39$) at baseline. The majority of participants were taking oral antipsychotics as the only form of antipsychotic (37%). The most frequently prescribed antipsychotic medication were atypical antipsychotics olanzapine (34%), clozapine (34%) and aripiprazole (23%). There were no statistically significant differences between treatment groups on baseline antipsychotic regimes (Table 3.2).

### Table 3.2 Baseline antipsychotic medication status

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=39</th>
<th>CoQ10 N=31</th>
<th>$t$</th>
<th>$p$</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose equivalent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>404.23(240.14)</td>
<td>437.1(313.44)</td>
<td>-0.50</td>
<td>.621</td>
<td>68</td>
</tr>
<tr>
<td><strong>Number of antipsychotic medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>22(56.4)</td>
<td>18(58.1)</td>
<td>0.02</td>
<td>.890</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>14(35.9)</td>
<td>11(35.5)</td>
<td>0.00</td>
<td>.971</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>3(7.7)</td>
<td>2(6.5)</td>
<td>0.04</td>
<td>.841</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type of antipsychotic medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Antipsychotics</td>
<td>26(66.7)</td>
<td>21(67.7)</td>
<td>0.01</td>
<td>.924</td>
<td></td>
</tr>
<tr>
<td>Depot antipsychotic</td>
<td>5(12.8)</td>
<td>4(12.9)</td>
<td>0.00</td>
<td>.992</td>
<td>1</td>
</tr>
<tr>
<td>Depot &amp; oral antipsychotics</td>
<td>8(20.5)</td>
<td>6(19.4)</td>
<td>0.02</td>
<td>.904</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotic drug name</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>14(35.9)</td>
<td>10(32.3)</td>
<td>0.10</td>
<td>.750</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>13(33.3)</td>
<td>11(35.5)</td>
<td>0.04</td>
<td>.851</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10(25.6)</td>
<td>6(19.4)</td>
<td>0.39</td>
<td>.534</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>5(12.8)</td>
<td>2(6.5)</td>
<td>0.78</td>
<td>.378</td>
<td>.452</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>5(12.8)</td>
<td>2(6.5)</td>
<td>0.78</td>
<td>.378</td>
<td>.452</td>
</tr>
<tr>
<td>Risperidol</td>
<td>3(7.7)</td>
<td>3(9.7)</td>
<td>0.09</td>
<td>.768</td>
<td>1</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>2(5.1)</td>
<td>2(6.5)</td>
<td>0.06</td>
<td>.813</td>
<td>1</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2(5.1)</td>
<td>2(6.5)</td>
<td>0.06</td>
<td>.813</td>
<td>1</td>
</tr>
<tr>
<td>trifluoperazine</td>
<td>2(5.1)</td>
<td>0</td>
<td>1.64</td>
<td>.201</td>
<td>.499</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2(5.1)</td>
<td>4(12.9)</td>
<td>1.33</td>
<td>.248</td>
<td>.395</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1(2.6)</td>
<td>0</td>
<td>0.81</td>
<td>.369</td>
<td>1</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>0</td>
<td>3(9.7)</td>
<td>3.94</td>
<td>.047</td>
<td>.082</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0</td>
<td>1(3.2)</td>
<td>1.28</td>
<td>.259</td>
<td>.443</td>
</tr>
<tr>
<td>Taking antipsychotics only</td>
<td>8(20.5)</td>
<td>8(25.8)</td>
<td>0.27</td>
<td>.600</td>
<td></td>
</tr>
</tbody>
</table>

*FET* Fisher’s exact test, $\chi^2$ Chi-Square, *t* independent sample *t*-test
3.4.2.2 Additional psychiatric medication

Seventy-seven percent of the sample were taking at least one other psychiatric medication as part of their treatment plan at baseline. Significantly more participants in the placebo group (56%) were taking only one additional psychiatric medication compared to 29% of CoQ10 group. Significantly more participants in the CoQ10 group were taking anxiolytic medication compared to the placebo group. There were no other statistically significant differences between treatment groups in terms of psychiatric medications (Table 3.3). Antidepressants were the most frequently prescribed additional psychiatric medication in the sample (44%).

Table 3.3 Additional psychiatric medication information

<table>
<thead>
<tr>
<th>Dose equivalent</th>
<th>Placebo mean(SD)</th>
<th>CoQ10 mean(SD)</th>
<th>t</th>
<th>p</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5.67 (3.21)</td>
<td>6.8 (3.76)</td>
<td>-0.46</td>
<td>.662</td>
<td>7</td>
</tr>
</tbody>
</table>

Additional medications

<table>
<thead>
<tr>
<th>Number of additional psychiatric medications</th>
<th>Placebo n(%)</th>
<th>CoQ10 n(%)</th>
<th>$\chi^2$</th>
<th>p</th>
<th>FET</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>22 (56.4)</td>
<td>9 (29)</td>
<td>5.25</td>
<td>.022</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>8 (20.5)</td>
<td>11 (35.5)</td>
<td>1.96</td>
<td>.162</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>1 (2.6)</td>
<td>3 (9.7)</td>
<td>1.62</td>
<td>.203</td>
<td>.315</td>
</tr>
</tbody>
</table>

Type of psychiatric medication

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Placebo 19(48.7)</th>
<th>CoQ10 14(45.2)</th>
<th>0.09</th>
<th>.767</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic</td>
<td>11(28.2)</td>
<td>9(29)</td>
<td>0.01</td>
<td>.939</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>4(10.3)</td>
<td>10(32.3)</td>
<td>5.23</td>
<td>.022</td>
</tr>
<tr>
<td>Hypnotic</td>
<td>4(10.3)</td>
<td>3(9.7)</td>
<td>0.01</td>
<td>.940</td>
</tr>
<tr>
<td>Lithium</td>
<td>3(7.7)</td>
<td>4(12.9)</td>
<td>0.52</td>
<td>.470</td>
</tr>
</tbody>
</table>

FET Fisher’s exact test, $\chi^2$ Chi-Square, t independent sample t-test

3.4.2.3 Additional physical health medications

In addition to medications for mental health, participants were also prescribed a number of medications for physical health conditions. Twenty-one percent of the sample reported taking statins for high levels of cholesterol. Beta-blockers were the next frequently prescribed physical health medication (14%), though beta-blockers may also be prescribed for symptoms of anxiety. There were no statistically significant differences between the two treatment groups regarding rate of physical health medication prescription (Table 3.4).
### Table 3.4 Medication for physical health conditions or adverse effects of psychiatric medication

<table>
<thead>
<tr>
<th>Type of physical condition medication</th>
<th>Placebo</th>
<th>CoQ10</th>
<th>( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>11(28.2)</td>
<td>4(12.9)</td>
<td>2.42</td>
<td>.121</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>4(10.3 )</td>
<td>6(19.4)</td>
<td>1.17</td>
<td>.28</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>6(15.4)</td>
<td>3(9.7 )</td>
<td>0.50</td>
<td>.479</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>4(10.3)</td>
<td>4(12.9)</td>
<td>0.12</td>
<td>.73</td>
</tr>
<tr>
<td>Metformin</td>
<td>3(7.7 )</td>
<td>2(6.5 )</td>
<td>0.04</td>
<td>.841</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2(5.1 )</td>
<td>4(12.9)</td>
<td>1.33</td>
<td>.25</td>
</tr>
<tr>
<td>Insulin</td>
<td>1(2.6 )</td>
<td>1(3.2 )</td>
<td>0.03</td>
<td>.869</td>
</tr>
</tbody>
</table>

*FET* Fisher’s exact test, \( \chi^2 \) Chi-Square, \( t \) independent sample \( t \)-test.

#### 3.4.2.4 Medication changes during course of the study

Changes in medication for physical or mental health occurred frequently between baseline and midpoint and between midpoint and final assessments. Fifteen percent of participants who completed the study had medication changes between baseline and midpoint assessment only, 13\% of participants changed medication between midpoint and final assessment only, and 15.2\% of participants who completed the study changed prescribed medication between baseline and midpoint and between midpoint and final assessment. More participants in the placebo group changed medication during the course of the study than in the CoQ10 group (Table 3.5).

### Table 3.5 Medication changes during course of the study.

<table>
<thead>
<tr>
<th>Medication changes during study</th>
<th>Placebo</th>
<th>CoQ10</th>
<th>( \chi^2 )</th>
<th>( p )</th>
<th>FET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication change during study (visit 2 and/or visit 3)</td>
<td>15(53.6)</td>
<td>5(20.8)</td>
<td>5.85</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td>Medication change at visit 2</td>
<td>11(40.7)</td>
<td>3(12.5)</td>
<td>5.09</td>
<td>.024</td>
<td></td>
</tr>
<tr>
<td>Medication change at visit 3</td>
<td>9(36.0)</td>
<td>4(19.1)</td>
<td>1.62</td>
<td>.203</td>
<td></td>
</tr>
<tr>
<td>Medication change at visits 2 and 3</td>
<td>5(21.7)</td>
<td>2(9.5)</td>
<td>1.22</td>
<td>.269</td>
<td>.416</td>
</tr>
</tbody>
</table>

*FET* Fisher’s exact test, \( \chi^2 \) Chi-Square, \( t \) independent sample \( t \)-test.
3.5 Discussion

The CoQ10 RCT ultimately enrolled and randomised 23% of its initial sample target over a 26 month recruitment period. This experience reflects a common trend in clinical trials and research. Up to 86% of trials do not meet recruitment targets within their pre-specified time frame, while up to one quarter of clinical trials are terminated due to inadequate accrual of patients (Carlisle et al., 2015; Huang et al., 2018; Sully et al., 2013). Gilbody et al. (2002) previously reported that less than 5% of clinical trials in schizophrenia have reached sufficient power over the preceding 50 years. Notably, 43% of trial extension requests to the Health Technology Assessment programme cite recruitment issues; yet trials that were granted an extension were no more likely to meet their recruitment goal compared to those without an extension (Raftery et al., 2015). The CoQ10 RCT is therefore not an exception to clinical trials in severe mental illness and other conditions, though potential factors that influence enrolment warrant discussion.

Assuming a 0.3% prevalence rate (Behan et al., 2008), I estimated that approximately 1190 people within the Dublin services catchment areas and 360 within the Wicklow service catchment area would meet a diagnosis for schizophrenia or schizoaffective disorder. However, only 20% of the prospective research population were identified by clinical teams as potentially eligible research candidates. This experience mirrors Patel and colleagues’ (2017) finding that 20% of patients with psychotic disorders are ultimately approached to participate in research. It is also possible that the proportion of eligible patients within the recruiting services was overestimated. However earlier observational studies in the same population identified and recruited proportionally more patients within the same services (Cummings et al., 2013).

Service and clinical team related factors may have influenced patient identification and enrolment rates. Two of the mental health services in which the CoQ10 RCT was conducted were attached to university teaching hospitals with high research outputs, while the third service also routinely engaged with clinical research and intervention trials. Additionally, several clinical team members within the services are clinician scientists. This positive research culture may have helped facilitate the study (Peckham et al., 2018); clinical team leads within the services were agreeable to researchers attending clinics for recruitment, meeting service staff, and service staff expressed an interest in study progress, outcomes and outputs. The pro-research environment was likely advantageous as others’ frequently cite poor knowledge surrounding research methods and trials within clinical teams as a barrier to recruitment for RCTs (Borschmann et al., 2014; Briel et al., 2016; Patterson et al., 2014). However, strains on resources including staff time and infrastructure within the services may have negatively affected patient identification and recruitment. Across the mental health sector in Ireland there is a “chronic shortage of staff” and staff turnover is increasing due to related stress and fatigue (Mental Health Commission, 2017). Where clinical staff experience time and caseload pressures, priority is given to clinical work over research recruitment (Patterson et al., 2014). Interest in research and the CoQ10 RCT was evident within the services.
and efforts were made to identify potential research candidates. However, requesting clinical staff to introduce the study and researchers to patients during busy clinic hours within strained services without incentive or compensation for the increased burden may have been an ineffective recruitment strategy.

Selective referral, a common barrier to recruitment of representative samples in mental health research and trails, may have also occurred in the CoQ10 RCT. During recruitment to the CoQ10 RCT some patients were identified by clinical staff as meeting the inclusion criteria but were deemed generally unsuitable, unable to complete the cognitive assessment, too unwell, or vulnerable to relapse by clinicians. Likewise, other patients were deemed more likely to engage with the research and potential benefits of participation were anticipated, and therefore recommended to participate. Similar experiences are reported in the literature (Howard et al., 2009; Patel et al., 2017). Clinicians tend to be selective in the patients that they do refer to a trial; they are more likely to refer patients when they consider research participation as potentially beneficial for that patient or those who already exhibit positive treatment outcomes (Patel et al., 2017; Howard et al., 2009). Clinician’s may also have ethical concerns regarding patients’ ability to comprehend the research process and consent to the research (Appelbaum et al., 2004; Candilis et al., 2008; Jones & Cipriani, 2019; Morris & Heinssen, 2014). A need to protect service users from distress or disappointment may also factor; perceived capacity to meet the research demands or the perceived detriment of study participation to patient health and therapeutic alliance are deterrents for referral or recommendation to participate (Howard et al., 2009; Borschmann et al., 2014). Thus, similar to other reports, some degree of selective referral of patients may have occurred during recruitment to the RCT. This may influence the generalisability of results or distort estimates of effect, as the prognostic factors within the referred sample may differ greatly from the target population (Gross et al., 2002; Katz et al., 2011).

Researchers have claimed that patients with schizophrenia express high-readiness to participate in clinical research trials once organizational and gate-keeper barriers were surpassed (Joegensen et al. 2014). It was expected that approximately 80% of eligible patients would agree to participate in the CoQ10 RCT, based on previous recruitment experiences within the services and findings in the literature (Cummings et al., 2013; Donohoe et al., 2017; Jørgensen et al., 2016). However, other work indicates that patients with psychosis are considerably less likely to consent to research; Patel et al. (2017) reported that only 65% of patients consent to be contacted about research. In the CoQ10 RCT the proportion of those invited to participate, who ultimately consented to take part, was 29%, with six participants withdrawing from the study prior to randomisation. It is likely that expressing willingness to be contacted about future research, does not necessarily translate to active participation when invited to participate. Additionally, the features of schizophrenia and schizoaffective disorder such as paranoia, avolition and cognitive impairment make it particularly
difficult to engage and consent patients to an RCT involving thrice daily supplement regime and multiple cognitive assessments.

Study design features may thus have influenced patients’ willingness to participate in the CoQ10 RCT. During recruitment patients often appeared to perceive CoQ10 as an additional or alternative medicine to their current medication regime; some patients did not want to take additional tablets but rather wanted to reduce the number they were taking, and others expressed fear of becoming unwell as a result of a new medication. Several patients also expressed concerns regarding the duration of and their ability to complete the cognitive assessment. Some patients stated that they did not want to be used in an experiment and expressed distrust regarding the use of placebo as a control group and did not want to be randomised. Other patients did not identify with the diagnostic label of “schizophrenia” which was used in the study title, information sheet and consent form. Similar patient concerns have been reported elsewhere in the literature (Briel et al., 2016; Jenkins et al., 2013; Zullino et al., 2003). On the other hand, referral by supportive and trusted clinicians to the RCT and knowing other patients already enrolled appeared to render patients more willing to discuss the study and consider enrolment themselves. Such facilitators have also been reported in various patient populations (Jenkins et al., 2013; Briel et al., 2016).

Due to several factors it was not possible to implement a SWAT aimed at improving screening and recruitment to the RCT. Consulting clinical team members and patients in advance of SWAT development and ethical approval is likely to have identified concerns and an alternative strategy to identification and contacting potential research candidates developed. Embedding RCTs within mental health services through engaging clinical team members to work directly on the trial appears to be an effective approach to recruiting sufficient participants (Peckham et al., 2018). This approach minimises data sharing concerns related to using patient lists for research purposes, and also helps reduce conflicting priorities between clinical and research work due to protected research time (Peckham et al., 2018).

The rate of participant attrition during the CoQ10 RCT was high (34%), but within the range of rates described elsewhere (Kane et al., 2013; Schoemaker et al., 2019; Szymczynska et al., 2017). However, a lower attrition rate was expected as supplementation and psychosocial intervention trials tend to report better retention rates than RCTs of pharmacological agents (Alvarez-Jimenez et al., 2008; Roffman et al., 2013; Szymczynska et al., 2017). Critically, participants who did not complete the CoQ10 RCT tended to exhibit worse mitochondrial function, higher levels of avolition and had spent fewer years in formal education. Additionally, inability to contact participants via phone or through their mental health team and schedule follow-up was the most frequent cause for missing data. This experience is similar to other reports; patients who intermittently use health care services, exhibit poorer social function, higher levels of negative symptoms and lower levels of education are less likely complete trials or treatments (Davis et al., 2002, Nosé et al., 2003). The selective nature of attrition during the CoQ10 RCT may limit the
generalisability of the results since remaining participants are less likely to represent the patient population (Szymczynska et al., 2017). Further, the rate of overall attrition reduces statistical power and may introduce confounding to the results. To consider the influence of potential biases resulting from high participant attrition, the primary analyses was conducted using complete cases, and an intent-to-treat (ITT) analysis with multiple imputation of missing data was conducted for sensitivity analyses. Study results can be interpreted with more confidence when the ITT and complete cases analyses draw equivalent conclusions.

Sixty-one percent of participants who completed the CoQ10 RCT indicated excellent adherence, as determined by less than 10% capsules remaining at endpoint (6 month assessment). Treatment non-adherence may reflect features of schizophrenia; cognitive impairment and functional status are associated adherence in outpatient services (Iasevoli et al., 2017). However, it is also likely that the CoQ10/placebo regimen, which was selected to optimise absorption of CoQ10, may have also influenced adherence. Adherence is poorer when a treatment regimen is complicated or interferes with daily routines and lifestyles (Brown & Bussell, 2011; García et al., 2016; Higashi et al., 2013; Holmes et al., 2014). This was reflected in the sample; patients who did not indicate full adherence reported forgetting to take the midday capsule as this was not a usual aspect to their existing medication regime. Additionally, three participants withdrew from the study as they found adhering to the treatment regimen too difficult. Patients were also less likely to adhere where concomitant medication had been changed in the preceding three months; the increasing changes to routine may have made it more difficult for participants to manage their medication and supplements. It is also possible that necessary changes to concomitant medication may be indicative of poor adherence behaviour generally (Higashi et al., 2013). Failing to adhere to assigned treatment however can reduce statistical power, due to increased and artefactual variability and attenuated estimates of treatment (Shiovitz et al., 2016). To consider the effect of treatment non-adherence on results, a secondary (exploratory) subgroup analysis using only patients who indicated complete adherence during the CoQ10 RCT was conducted.

Post-hoc baseline imbalances were observed between groups in terms of anxiolytic medication and number of psychiatric medications. However, the EMA states that such post-hoc imbalances should not be entered as a covariate in the primary analysis, as any observed imbalance is likely to be a random event (European Medicines Agency, 2015). Imbalances in prognostic factors may be considered for secondary analyses, however imbalances in baseline medication were not considered prognostic in the CoQ10 study. On the other hand, if a covariate measured after randomisation may potentially be affected by allocated treatment; exploratory subgroup analyses based on the affected covariate may offer useful insights (European Medicines Agency, 2015). Post-randomisation imbalances in concomitant medication occurred during the CoQ10 study. Exploratory subgroup analyses were conducted using participants with stable medication only to remove potential confounding from medication changes.
3.6 Conclusion and future considerations

Difficulties engaging and enrolling participants with severe mental illness into clinical trials have been well documented in the existing literature. Often challenges to recruitment have been attributed to organisational or clinical barriers which prevent access to potential research candidates. However though the number of patients identified as potentially eligible for the study by the clinical teams was close to the target goal, the majority of patients declined to participate. It is possible that elements of the study design and recruitment strategy deterred patients. Future research should consider consulting with clinical team members and patients prior to trial design and conduct to identify potential facilitators and deterrengnts to participating.

The recruitment period for the CoQ10 RCT was 26 months, during which one-quarter of the planned sample size was randomised. Extending this period and proceeding with the same recruitment strategy would have required researchers and clinical teams to identify approximately 1400 patients in order to meet the recruitment target. Pre-notifying potentially eligible patients of the study may have helped improve recruitment; however it was not possible to implement this. An alternative strategy to improve recruitment may be to engage specific clinical team members to champion recruitment within the services, as patients are more likely to enrol in trials when supported by trusted clinicians. However this approach is resource intense in terms of clinical time and finances. Another challenge in conducting the CoQ10 RCT was that only 66% of participants enrolled ultimately completed the study. Further, approximately two-thirds of the sample indicated full adherence to the intervention and a post-randomisation imbalance in changes to concomitant medication occurred. These challenges are likely to influence the generalisability of the results.
4 EFFECT OF COQ10 SUPPLEMENTATION ON PRIMARY AND SECONDARY COGNITIVE OUTCOMES.

This chapter presents and interprets the effects of oral CoQ10 supplementation on the primary and secondary cognitive outcomes in schizophrenia and schizoaffective disorder.

4.1 Background

Cognitive function depends on effective synaptic function and cell to cell communication (Sullivan et al., 2018). Mitochondria are essential players in providing the necessary energy for cellular function. Mitochondria generate adenosine triphosphate (ATP) to meet the energy demands for dendritic spine morphogenesis, synaptic transmission, synaptic vesicle recycling and long term potentiation (Harris et al., 2012; Hjelm et al., 2015; Li et al., 2004; Pathak et al., 2015; Scaini et al., 2016). Mitochondria are also involved in both neurogenesis and neurodegeneration; damage to mitochondria is thought to underlie the cognitive defects associated with several neurodevelopmental and neurodegenerative disorders (Do et al., 2009; Khacho et al., 2019; Maas et al., 2017). Impaired mitochondria are less effective ATP generators and also induce redox imbalance (Scaini et al., 2016). Thus, disruptions to oxidative phosphorylation (OXPHOS) and the electron transport chain (ETC) in particular may contribute to cognitive impairments in schizophrenia due to an inability to meet neuronal energy demands and increased oxidative stress (Ben-Shachar, 2017; Sullivan et al., 2018, 2019).

There is converging evidence that such disrupted bioenergetics and mitochondrial function contribute to the manifestation of the cognitive deficits in schizophrenia (Ben-Shachar, 2017; Bergman & Ben-Shachar, 2016; Prabakaran et al., 2004; Rowland et al., 2016). For example, hypomyelination in schizophrenia associated with cognitive symptoms has been attributed to redox imbalance induced in part by in disrupted OXPHOS (Maas et al., 2017). Reduction in the function of Disrupted-in-Schizophrenia 1 (DISC1), schizophrenia-susceptibility gene associated with mitochondrial dysfunction including decreased cellular ATP and mitochondrial NADH dehydrogenase activity, has been implicated in cognitive functions such as memory, attention and processing speed (Callicott et al., 2005; Park & Park, 2012; Vassos et al., 2010; Zai et al., 2017). Further, elevated lactate has also been observed in schizophrenia and this is an indicator of abnormal energy metabolism that suggests a shift toward anaerobic glycolysis (Rowland et al, 2016; Sullivan et al, 2019). This increase in lactate may be associated with cognitive impairment in schizophrenia (Rowland et al., 2016). More generally, metabolic syndromes including diabetes and hypertension occur frequently in schizophrenia and are associated with more severe cognitive impairments (Çelikbaş et al., 2019; Liao et al., 2011; Lindenmayer et al., 2012). Such abnormalities are also evident in drug-naïve patients, suggesting that bioenergetics dysfunction may be central to the aetiology of schizophrenia (Middleton et al., 2002).
Specific cognitive impairments, which are of critical importance for functional outcomes and recovery, have been associated with mitochondrial dysfunction in schizophrenia. For example, disrupted ETC activity, particularly complex I activity, as indicated by under-expression of mitochondrial complex genes NDUFA1 and NDUFB11, may contribute to the manifestation of attention deficits in schizophrenia (Haghighatfard et al., 2018). Energy hypo-metabolism in the rostral anterior cingulate cortex and downregulation of NDUFA1, NDUFB10 and NDUFB11 may influence working memory performance (Haghighatfard et al., 2018). Abnormal bioenergetics may also be involved in executive function, processing speed, and problem solving impairments in schizophrenia (Rowland et al., 2016; Haghighatfard et al., 2018).

Elevated lactate, indicating an energy shift towards anaerobic glycolysis, has been associated with slower processing speed and poorer general cognitive function and reasoning scores (Rowland et al., 2016). Thus agents that support mitochondrial function, particularly those related to OXPHOS, present as viable candidate interventions for cognitive impairment. CoQ10 is an essential component of the OXPHOS system. In addition to shuttling electrons through the ETC to produce ATP, CoQ10 possesses antioxidant properties, functioning as a ROS scavenger and a regenerator of other antioxidants (Crane, 2007). Failure in mitochondrial bioenergetics and compromised antioxidant capacity resulting from CoQ10 deficiencies are implicated in pathology of multiple diseases associated with cognitive disturbances and decline including Parkinson’s disease, ataxia, and CFS (Cooper et al., 2008; Maes et al., 2009; Myhill et al., 2009; Pieczenik & Neustadt, 2007; Schapira et al., 1990; Shults et al., 2002). However, it is remains unclear whether CoQ10 deficiency is a cause of the disease pathology or a consequence. CoQ10 supplementation has been investigated as a single, adjunctive and combination therapy for cognitive impairment in such disorders, with highly variable results. Initial trials of CoQ10 proved particularly promising for maintaining executive function and attention in Huntington’s disease and progressive supranuclear palsy, with large effect sizes; however subsequent larger RCTs found no evidence of reliable cognitive effect (Huntington Study Group, 2001; McGarry et al., 2017; Aperterouva et al., 2016; Stamelou et al., 2008). One small RCT of CoQ10 also improved attention (cognitive effort) in CFS (Fukuda et al., 2016), and one open label study indicated that self-reported cognitive complaints improved in multiple sclerosis (Moccia et al., 2019). In summary, CoQ10 may have a protective effect against cognitive decline in progressive disorders, but such benefits are not maintained with longer follow-up. However, the effect of adjunctive CoQ10 supplementation on chronic cognitive dysfunction is yet to be determined.

In light of the evidence that mitochondrial dysfunction is involved in schizophrenia and the suggestions in the literature that CoQ10 may be beneficial for restoring or maintaining cognitive function in other disorders, the effect of oral CoQ10 supplementation on the cognitive deficits experienced by patients with schizophrenia and schizoaffective disorder was investigated.
Specifically it was hypothesised that:

1) There would be improvements in sustained attention in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

2) There would be improvements in working memory performance in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

3) There would be improvements in processing speed in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

4) There would be improvements executive function in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

5) There would be improvements general cognitive function in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

The remainder of this chapter presents and discusses the effects of oral CoQ10 supplementation on the primary and secondary cognitive outcomes (Table 4.1) in schizophrenia and schizoaffective disorder.

Table 4.1 List of primary and secondary cognitive outcome measures and direction of change for improvement.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measure</th>
<th>Direction of scores for improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>Continuous Performance Task - Identical Pairs D'prime: 2 digits, 3 digits, 4 digits</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Spatial Working Memory (Errors)</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Letter number sequencing</td>
<td>Higher</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial Working Memory (Errors)</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Letter number sequencing</td>
<td>Higher</td>
</tr>
<tr>
<td>Secondary outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>Trail Making Task A (seconds)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Verbal fluency (FAS)</td>
<td>Higher</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail Making Task B (seconds)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Spatial Working Memory (Strategy)</td>
<td>Higher</td>
</tr>
<tr>
<td>Current IQ</td>
<td>WAIS-III subtest: Similarities</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>WAIS-III subtest: Matrix reasoning</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Estimated Full Scale IQ</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Improvement on measure is indicated if change occurs in the direction listed above.
4.2 Methods particular to this chapter

Chapter 2 provides a detailed description of the methods used in the CoQ10 RCT. Chapter 3 describes the study sample and methodological issues that influenced the analyses and interpretation of results. Below is a description of some methods that are particular to this chapter.

4.2.1 Analyses used

1. Potential differences in baseline scores of outcome measures between groups for all randomised participants were tested using independent t-tests. Variables are presented in terms of mean and SD.
2. For descriptive purposes, within group change from baseline to 3 and 6 month outcome assessments for complete cases were analysed using paired t-tests with Bonferroni adjustments for multiple pairwise comparisons. Tests were exploratory in nature and were not intended to generate claims of treatment effect.
3. To evaluate the effects of CoQ10 supplementation compared to placebo on primary (a) and secondary cognitive (b) outcomes, multiple analysis of covariance (ANCOVA) analyses were conducted to test:
   a. The differences in mean scores of attention and working memory between the CoQ10 and placebo groups at 3 and 6 months.
   b. The differences in mean scores of processing speed, executive function and current IQ between the CoQ10 and placebo groups at 3 and 6 months.

Due to the high attrition rate (>20%) the principle analysis was based on complete cases for each outcome variable at each time point. Sensitivity analysis followed an ITT approach and used multiple imputation based on chained equations to impute missing values in SPSS 25.

4. Secondary exploratory analyses using complete cases:
   a. Adherent participants – differences in mean scores between CoQ10 and placebo groups at 6 months for those participants who reported 90 percent treatment adherence at 6 months.
   b. Stable medication - differences in mean scores between CoQ10 and placebo groups at 6 months for those participants whose prescribed medication remained unchanged during the study.

5. Differences in the proportion of responders at 6 months in each group on cognitive measures as determined using reliable and clinically significant change criteria were tested using Chi Square test of independence. A number needed to treat analysis was conducted.
4.3 Results

4.3.1 Comparison of baseline outcome measure scores between groups.

4.3.1.1 Primary outcomes

Comparisons between groups at baseline were made using independent t-tests; however as discussed in Chapter 2 this information may be superfluous. If randomisation were conducted appropriately, any statistically significant imbalance between groups is due to chance. There were no statistically significant differences between groups at baseline for primary outcomes of attention and working memory (Table 4.2). Baseline data for the primary outcome measure of attention (CPT-IP) was missing for seven participants. One participant in the placebo group could not complete the test due to the malfunctioning of the test computer. Four participants in the placebo group and two participants in the CoQ10 group could not understand task instructions (n=6).

<table>
<thead>
<tr>
<th>Primary outcome measure</th>
<th>Placebo</th>
<th>CoQ10</th>
<th>Between group difference test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’prime: 2 digits</td>
<td>2.75</td>
<td>1.07</td>
<td>2.48</td>
</tr>
<tr>
<td>D’prime: 3 digits</td>
<td>1.88</td>
<td>0.91</td>
<td>1.69</td>
</tr>
<tr>
<td>D’prime: 4 digits</td>
<td>1.08</td>
<td>0.73</td>
<td>0.90</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory</td>
<td>-1.28</td>
<td>1.46</td>
<td>-1.68</td>
</tr>
<tr>
<td>Letter Number Sequencing</td>
<td>8.31</td>
<td>3.61</td>
<td>6.77</td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) within group at baseline for all randomised participants. Independent t-tests (equal variances assumed) and associated p-values.

4.3.1.2 Secondary cognitive outcomes

Comparisons between groups at baseline were made using independent t-tests for normally distributed variables and Mann Whitney U tests for variables that did not meet the assumptions of the independent t-test. As detailed in Chapter 2 this information may be unnecessary. If randomisation were conducted appropriately, any statistically significant imbalance between groups is due to chance. Groups were comparable across the secondary cognitive outcome measures. There were no statistically significant differences between groups at baseline on any of the secondary cognitive outcome measures for processing speed, executive function, or current IQ (Table 4.3).
Table 4.3 Descriptive statistics and comparison of secondary cognitive outcome measures between placebo and CoQ10 groups for randomised sample at baseline.

<table>
<thead>
<tr>
<th>Secondary cognitive measure</th>
<th>Placebo Mean/Mdn</th>
<th>SD/IQR</th>
<th>CoQ10 Mean/Mdn</th>
<th>SD/IQR</th>
<th>t/U</th>
<th>p</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Task A</td>
<td>46.18</td>
<td>25.86</td>
<td>51.65</td>
<td>22.21</td>
<td>492</td>
<td>.242</td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>34.15</td>
<td>13.41</td>
<td>30.40</td>
<td>12.05</td>
<td>1.20</td>
<td>.233</td>
<td>67</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Task B</td>
<td>109.93</td>
<td>41.55</td>
<td>120.06</td>
<td>91.00</td>
<td>517</td>
<td>.385</td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory (Strategy)</td>
<td>-1.02</td>
<td>1.26</td>
<td>-1.02</td>
<td>1.65</td>
<td>578</td>
<td>.754</td>
<td></td>
</tr>
<tr>
<td>Current IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>8.61</td>
<td>2.74</td>
<td>8.80</td>
<td>3.08</td>
<td>-0.28</td>
<td>.784</td>
<td></td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>8.32</td>
<td>2.97</td>
<td>8.55</td>
<td>3.28</td>
<td>-0.29</td>
<td>.769</td>
<td></td>
</tr>
<tr>
<td>Estimated Full Scale IQ</td>
<td>88.97</td>
<td>15.75</td>
<td>92.03</td>
<td>18.98</td>
<td>-0.72</td>
<td>.477</td>
<td></td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) or median (Mdn) and interquartile range (IQR) within group at baseline for all randomised participants. Independent t-tests (equal variances assumed) or non-parametric Mann Whitney U and associated p-values.

4.3.2 Within group change from baseline

4.3.2.1 Within group change on primary outcome measures at 3 and 6 months

Separate paired comparisons against baseline were made for each treatment group on the primary outcomes. These tests were conducted to build a comprehensive picture of the data within the placebo and CoQ10 groups. However it is acknowledged that this information may be superfluous. The tests were not intended as the primary analysis or to distort interpretations of treatment effects. The results of the tests allow for consideration of other factors beyond treatment effect, such as regression towards the mean and placebo effects.

For descriptive purposes, within group change from baseline to 3 and 6 month outcome assessments for complete cases were analysed using paired t-tests with Bonferroni adjustments for within pairwise comparisons. Means and standard deviations of the primary outcome measures for complete cases at baseline, midpoint and endpoint are shown in Table 4. Within group mean change from baseline to midpoint and from baseline to endpoint are also presented in the table. The statistical significance of the within group change was tested using paired t-tests; p values were adjusted using Bonferroni correction for repeated testing within pairs.

Attention

Results of the paired t-tests indicated that in the placebo group, performance improved from baseline to endpoint on the 3-digit condition, but not the 2- or 4-digit conditions, of attention task CPT-IP. The CoQ10 group’s attention performance improved from baseline to midpoint on the 3-digit condition and from baseline to endpoint on all CPT-IP task conditions.
Working memory

Paired t-tests of complete cases indicated that working memory did not change from baseline in the CoQ10 group on either the spatial working memory task or letter number sequencing. Spatial working memory performance improved in the placebo group from baseline to 6 months. Performance on the letter number sequencing task did not change from baseline to 3 or 6 months in the placebo group.
Table 4.4 Descriptive statistics and mean change in scores from baseline to midpoint (3 months) and endpoint (6 months) on primary outcome measures for complete cases at endpoint.

<table>
<thead>
<tr>
<th>Primary outcome measure</th>
<th>Placebo</th>
<th></th>
<th></th>
<th>CoQ10</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 0 Months</td>
<td>Midpoint 3 months</td>
<td>Endpoint 6 months</td>
<td>Within group change 0 to 3 months Mean (SD)</td>
<td>Change p</td>
<td>Within group change 0 to 6 months Mean (SD)</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 digits</td>
<td>2.74(0.90)</td>
<td>3.16(0.88)</td>
<td>3.07(0.73)</td>
<td>0.42</td>
<td>.119</td>
<td>2.39(0.98)</td>
</tr>
<tr>
<td>3 digits</td>
<td>1.85(0.80)</td>
<td>2.06(0.83)</td>
<td>2.62(0.92)</td>
<td>0.21</td>
<td>.444</td>
<td>1.60(1.02)</td>
</tr>
<tr>
<td>4 digits</td>
<td>1.10(0.56)</td>
<td>1.22(0.62)</td>
<td>1.29(0.67)</td>
<td>0.13</td>
<td>.551</td>
<td>0.93(0.81)</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory (Errors)</td>
<td>-1.43(1.26)</td>
<td>-1.12(1.49)</td>
<td>-1.00(1.31)</td>
<td>0.31</td>
<td>.182</td>
<td>-1.65(1.40)</td>
</tr>
<tr>
<td>Letter Number Sequencing</td>
<td>8.22(3.79)</td>
<td>9.39(3.73)</td>
<td>9.00(3.44)</td>
<td>1.17</td>
<td>.288</td>
<td>7.29(3.49)</td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) within group at baseline, midpoint, and endpoint assessments. Change within group is mean change in scores from baseline to follow up assessment. P-values for paired t-tests of within group change, Bonferroni adjustment was applied to control for multiple paired testing within group (2 tests), significance level was set at alpha < .05.
4.3.2.2 Within group change on secondary cognitive outcome measures at 3 and 6 months

Separate paired comparisons against baseline were made for each treatment group on the secondary cognitive outcomes. These tests were conducted to build a comprehensive picture of the data within the placebo and CoQ10 groups. The tests were not intended as the primary analysis or to distort interpretations of treatment effects. The results of the tests allow for consideration of other factors beyond treatment effect, such as regression towards the mean and placebo effects.

Means and standard deviations of the secondary cognitive outcome measures for complete cases at baseline, midpoint and endpoint are presented in Table 5. Within group mean change from baseline to midpoint and from baseline to endpoint are also presented. The statistical significance of the within group change was tested using paired t-tests; p values were adjusted using Bonferroni correction for repeated testing within pairs.

Processing speed

Results of paired sample t-tests indicated that processing speed, as measured by time to complete trail making task A and number of words listed during the verbal fluency task, did not change in the CoQ10 group. Performance on trail making task A improved in the placebo group from baseline to endpoint. Verbal fluency performance did not change in the placebo group by midpoint or endpoint.

Executive Function

Results of paired sample t-tests indicated that executive function, as measured by time to complete trail making task B and the strategy score of the spatial working memory task, did not change in the CoQ10 group. On average, time to complete trail making task B reduced in the placebo group from baseline to endpoint. There was no change on strategy scores of the spatial working memory task at either time point in the placebo group.

Current IQ

There was no change in scores on the WAIS similarities and matrix reasoning subtests in the CoQ10 group at either follow up assessment. Similarly, no change was observed in estimated IQ in the CoQ10 group at 3 month or 6 month follow-up. In the placebo group, scores on the WAIS similarities subtest improved at midpoint and endpoint. Scores on WAIS matrix reasoning subtest improved at 6 months. Estimated full scale IQ improved in the placebo group from baseline to endpoint.
Table 4.5 Descriptive statistics and mean change in scores from baseline to midpoint (3 months) and endpoint (6 months) on secondary cognitive outcome measures for complete cases at endpoint.

| Secondary outcome measure | Placebo | | | | | CoQ10 | | | |
|----------------------------|---------|-----------------|-----------------|-----------------|-----------------|---------|-----------------|-----------------|-----------------|-----------------|---------|-----------------|-----------------|-----------------|-----------------|---------|
|                            | Baseline 0 Months | Midpoint 3 months | Endpoint 6 months | Within group change 0 to 3 months | p | Baseline 0 Months | Midpoint 3 months | Endpoint 6 months | Within group change 0 to 3 months | p | Baseline 0 Months | Midpoint 3 months | Endpoint 6 months | Within group change 0 to 3 months | p |
| Processing speed           |         |                 |                  |                                |    |                     |                     |                  |                                |    |                     |                     |                  |                                |    |
| Trail Making Task A        | 46.33(17.68) | 43.70(16.21) | 42.70(12.49) | -2.63 | .568 | 53.19(17.40) | 46.42(13.01) | 45.20(11.48) | -6.77 | .044 | -7.99 | .034 |
| Verbal Fluency             | 35.96(13.85) | 37.57(13.37) | 38.43(13.94) | 1.61 | .634 | 34.25(11.22) | 37.05(12.31) | 39.00(14.39) | 2.80 | .078 | 4.75 | .140 |
| Executive function         |         |                 |                  |                                |    |                     |                     |                  |                                |    |                     |                     |                  |                                |    |
| Trail Making Task B        | 128.99(71.02) | 118.75(65.44) | 101.48(38.82) | -10.24 | .264 | 112.09(55.81) | 110.51(41.58) | 120.83(69.68) | -14.59 | .184 | -4.26 | 1.00 |
| Spatial Working Memory (Strategy) | -0.69(0.96) | -0.28(1.63) | -0.24(1.61) | 0.41 | .468 | -0.61(1.36) | -1.07(0.92) | -1.04(1.11) | -0.46 | .132 | -0.44 | .326 |
| Current IQ                 |         |                 |                  |                                |    |                     |                     |                  |                                |    |                     |                     |                  |                                |    |
| Similarities               | 8.82(2.81) | 10(2.81) | 10(2.94) | 1.18 | .032 | 9.74(2.7) | 10.16(3.11) | 10.53(3.01) | 0.42 | .720 | 0.79 | .156 |
| Matrix Reasoning           | 8.45(3.14) | 9.23(2.74) | 9.5(3.29) | 0.77 | .270 | 9.2(3.37) | 9.1(3.58) | 9.85(3.5) | 0.10 | 1.00 | 0.65 | .338 |
| Estimated Full scale IQ    | 90.71(16.99) | 97.29(18.3) | 98.57(19.62) | 9.57 | .036 | 96.89(18.35) | 98.63(20.81) | 102.58(20.4) | 1.74 | 1.00 | 5.68 | .070 |

Mean and standard deviation (SD) within group at baseline, midterm, and endpoint assessments. Change within group is mean change in scores from baseline to follow up assessment. P-values for paired t-tests of within group change, Bonferroni adjustment was applied to control for multiple testing within group (n=2), and significance level was set at alpha < .05.
4.3.3 Effect of CoQ10 supplementation on primary cognitive outcome measures at 3 months and 6 months.

4.3.3.1 Principle analysis: Complete cases

Differences in performance on attention and working memory tasks between the CoQ10 and placebo groups were analysed at 3 and 6 months using a series of ANCOVAs, with baseline test performance entered as a covariate. This method adjusts for baseline differences between groups and has multiple advantages in that it reduces bias of estimated treatment effects and is more powerful than repeated measures analysis or analysis of change (Borm et al., 2007; Egbewale et al., 2014; Twisk et al., 2018). Results are presented in Table 4.6.

Attention

Controlling for baseline performance, there were no differences in mean scores between the placebo and CoQ10 treatment groups on any of the three task conditions of the CPT-IP at 3 months and at 6 months. A moderate effect size in favour of placebo for attention on the first task of the CPT-IP (2-digits) may have been present, however this effect was non-significant within the sample, \( F (1, 42) = 2.98, p=.092, \eta^2_p = 0.07 \). Conversely, a small to moderate effect size in favour of CoQ10 for attention was indicated on the second task of the CPT-IP (3-digits), though this effect was non-significant within the sample, \( F (1, 41) = 2.34, p=.134, \eta^2_p = 0.05 \). These results indicate that CoQ10 supplementation has no effect on sustained attention in schizophrenia and schizoaffective disorder (Figure 4.1a-c).
Figure 4.1 a,b,c Means and confidence intervals at baseline, 3 month and 6 month follow up on attention task (CPT-IP). Follow-up values are adjusted for baseline.
Working memory

With baseline task performance entered as a covariate, there were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of working memory performance at 3 months or 6 months.

There was no difference in mean scores between the placebo and CoQ10 treatment groups on the errors score of the spatial working memory task at 3 months, $F(1,47) = 0.25$, $p=0.623$, $\eta^2_p = 0.01$. Similarly, there was no difference in mean scores between the placebo and CoQ10 treatment groups on the errors score of the spatial working memory task at 6 months, $F(1,47) = 0.46$, $p=0.499$, $\eta^2_p = 0.01$.

There was also no difference in mean scores between the treatment groups noted on the letter number sequencing task at 3 months, $F(1,48) = 0.88$, $p=0.352$, $\eta^2_p = 0.02$, or at 6 months, $F(1,48) = 0.00$, $p=0.988$, $\eta^2_p = 0.00$.

These results indicate that CoQ10 supplementation has no effect on working memory in schizophrenia and schizoaffective disorder (Figures 4.2a-b).

Figure 4.2 a,b Means and confidence intervals at baseline, 3 month and 6 month follow up on working memory tasks (CANTAB Spatial working memory, WMS Letter number sequencing). Follow-up values are adjusted for baseline.
4.3.3.2 Sensitivity analysis: Intention to Treat

The sensitivity analysis using multiple imputation did not alter the outcome results for attention or working memory performance at 3 months or 6 months. Again, this indicates that CoQ10 supplementation does not support attention or working memory performance in schizophrenia or schizoaffective disorder.
Table 4.6 Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on primary outcomes.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th></th>
<th></th>
<th></th>
<th>Endpoint (6 months)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
<td>Mean difference</td>
<td>95% CI</td>
<td>Placebo</td>
<td>CoQ10</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>Attention</td>
<td>D’prime: 2 digits</td>
<td>Unadjusted⁷</td>
<td>45 3.09 0.18 2.60 0.22</td>
<td>0.49</td>
<td>-0.08</td>
<td>1.07</td>
<td>40 3.08 0.15 2.83 0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Adjusted⁷</td>
<td>45 3.03 0.15 2.66 0.16</td>
<td>0.38</td>
<td>-0.06</td>
<td>0.82</td>
<td>.092</td>
<td>0.07</td>
<td>40 2.97 0.15 2.95 0.16</td>
</tr>
<tr>
<td></td>
<td>D’prime: 3 digits</td>
<td>Unadjusted⁷</td>
<td>44 1.97 0.17 2.12 0.22</td>
<td>-0.15</td>
<td>-0.71</td>
<td>0.41</td>
<td>40 2.62 0.20 2.14 0.29</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Adjusted⁷</td>
<td>44 1.89 0.15 2.22 0.15</td>
<td>-0.33</td>
<td>-0.76</td>
<td>0.11</td>
<td>.134</td>
<td>0.05</td>
<td>40 2.51 0.17 2.25 0.18</td>
</tr>
<tr>
<td></td>
<td>D’prime: 4 digits</td>
<td>Unadjusted⁷</td>
<td>43 1.21 0.13 1.08 0.16</td>
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<td>-0.27</td>
<td>0.54</td>
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<td>Adjusted⁷</td>
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<td>0.38</td>
<td>.831</td>
<td>0.00</td>
<td>39 1.25 0.15 1.46 0.16</td>
</tr>
<tr>
<td>Working memory</td>
<td>Spatial Working Memory (Errors)</td>
<td>Unadjusted⁷</td>
<td>50 -1.26 0.29 -1.50 0.26</td>
<td>0.24</td>
<td>-0.55</td>
<td>1.03</td>
<td>46 -0.97 0.27 -1.37 0.26</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Adjusted⁷</td>
<td>50 -1.32 0.16 -1.44 0.17</td>
<td>0.14</td>
<td>-0.35</td>
<td>0.58</td>
<td>.623</td>
<td>0.01</td>
<td>46 -1.07 0.17 -1.24 0.18</td>
</tr>
<tr>
<td></td>
<td>Letter number sequencing</td>
<td>Unadjusted⁷</td>
<td>51 9.30 0.69 7.71 0.76</td>
<td>1.59</td>
<td>-0.47</td>
<td>3.64</td>
<td>45 9.00 0.69 8.48 0.85</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Adjusted⁷</td>
<td>51 8.95 0.61 8.10 0.65</td>
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<td>-0.97</td>
<td>2.67</td>
<td>.352</td>
<td>0.02</td>
<td>45 8.76 0.64 8.75 0.68</td>
</tr>
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</table>

For unadjusted values, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
4.3.4  Effect of CoQ10 supplementation on secondary cognitive outcome measures at 3 months and 6 months.

4.3.4.1  Principle analysis: Complete cases

Differences in performance on processing speed, executive function, and estimated current IQ tasks between the CoQ10 and placebo groups were analysed at 3 and 6 months using a series of analysis of covariance models (ANCOVA). In each analysis, baseline task performance was entered as a covariate, to control for potential group imbalances at baseline. This method adjusts for baseline differences between groups and has multiple advantages in that it reduces bias of estimated treatment effects and is more powerful than repeated measures analysis or analysis of change (Borm et al., 2007; Egbewale et al., 2014; Twisk et al., 2018). The statistical significance level of 0.05 was adjusted for multiple testing within families of tests using the Benjamini and Hochberg (1995) method to minimise risk of false positives.

Processing speed and executive function results are presented in Table 4.7a. Current IQ results are presented in Table 4.7b.

Processing speed

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of processing speed at 3 months or 6 months.

There was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form A at 3 months, $F(1,48) = 0.28, p = .597, \eta_p^2 = 0.01$, or at 6 months, $F(1,43) = 0.00, p = .960, \eta_p^2 = 0.00$.

Again, no difference between the treatment groups was noted for mean number of words listed during the verbal fluency task at 3 months, $F(1,48) = 0.02, p = .898, \eta_p^2 = 0.00$, or at 6 months, $F(1,48) = 0.65, p = .425, \eta_p^2 = 0.02$.

These results indicate that CoQ10 supplementation has no effect on processing speed in schizophrenia and schizoaffective disorder.

Executive function

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of executive functioning at 3 months or 6 months, upon adjusting for multiple testing within the family of tests (four statistical tests for differences in executive function).

Controlling for baseline performance, there was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form B at 3 months, $F(1,48) = 0.01, p = .945, \eta_p^2 = 0.00$. There was also no difference between the two groups at 6 months, though
a moderate effect size in favour of placebo may have been present, \( F(1,41) = 3.18, p = .082, \eta_p^2 = 0.072 \).

The placebo group had higher strategy scores on the spatial working memory task compared to the CoQ10 group at 3 months, \( F(1,47) = 5.09, p = .029, \eta_p^2 = 0.10 \). This was a moderate to large effect, however upon adjusting for multiple testing the difference no longer reached statistical significance \( (p > .0125) \). At 6 months, the placebo group had higher strategy scores on the spatial working memory task compared to the CoQ10 group, \( F(1,47) = 5.00, p = .031, \eta_p^2 = 0.10 \). This was a moderate to large effect, though the effect no longer reached statistical significance after adjusting for multiple testing \( (p > .025) \).

These results indicate that CoQ10 supplementation has no effect on executive functioning in schizophrenia and schizoaffective disorder.

**Estimated current IQ**

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of current IQ at 3 months or 6 months.

No difference between the treatment groups was noted for current estimated full scale IQ at 3 months, \( F(1,44) = 1.00, p = .324, \eta_p^2 = 0.02 \), or at 6 months, \( F(1,39) = 0.45, p = .507, \eta_p^2 = 0.01 \). Consistent with this, there was no difference between the placebo and CoQ10 treatment groups on mean scores of the WAIS subtest similarities at 3 months, \( F(1,45) = 1.19, p = .281, \eta_p^2 = 0.03 \), or at 6 months, \( F(1,40) = 0.11, p = .746, \eta_p^2 = 0.00 \). Likewise, there was no difference between the placebo and CoQ10 treatment groups on mean scores of the WAIS subtest matrix reasoning 3 months, \( F(1,45) = 0.52, p = .476, \eta_p^2 = 0.01 \), or at 6 months, \( F(1,40) = 0.15, p = .699, \eta_p^2 = 0.00 \).

These results indicate that CoQ10 supplementation has no effect on general cognitive function or current IQ in schizophrenia and schizoaffective disorder.

### 4.3.4.2 Sensitivity analysis: Intention to Treat

The sensitivity analysis using multiple imputation did not alter the results at 3 months or 6 months on measures for processing speed and current IQ. The sensitivity analysis using multiple imputation did not alter the outcome results on the trail making task form B at 3 months or 6 months. The indication that CoQ10 intervention impaired spatial working memory strategy was also no longer supported by the sensitivity analysis using the multiply imputed dataset at 3 months \( (p = .067) \) and 6 months \( (p = .113) \). Again, these results suggest that CoQ10 supplementation has no effect on processing speed, executive function, or current IQ in schizophrenia and schizoaffective disorder.
Table 4.7 Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary cognitive outcomes

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th></th>
<th>Endpoint (6 months)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Trail Making Task (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>51</td>
<td>43.68</td>
<td>2.96</td>
<td>50.41</td>
</tr>
<tr>
<td>Adjusted</td>
<td>51</td>
<td>45.87</td>
<td>2.64</td>
<td>47.98</td>
</tr>
<tr>
<td>Verbal fluency (FAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>51</td>
<td>36.15</td>
<td>2.58</td>
<td>34.33</td>
</tr>
<tr>
<td>Adjusted</td>
<td>51</td>
<td>35.18</td>
<td>1.34</td>
<td>35.43</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Task (B)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
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<td>117.40</td>
<td>12.18</td>
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<td>Adjusted</td>
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<td>120.86</td>
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<tr>
<td>Spatial Working Memory (Strategy)</td>
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<td></td>
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<tr>
<td>Unadjusted</td>
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<td>0.31</td>
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<tr>
<td>Adjusted</td>
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<td>-0.42</td>
<td>0.24</td>
<td>-1.19</td>
</tr>
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</table>

*For unadjusted values, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. *When adjusted for multiple comparisons (four tests) did not reach adjusted level of statistical significance (p < .025**, p < .0125***). η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
Table 4.7 continued. Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary cognitive outcomes.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Descriptive Statistics</th>
<th>Mean difference between groups</th>
<th>Endpoint (6 months)</th>
<th>Descriptive Statistics</th>
<th>Mean difference between groups</th>
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<td>CoQ10</td>
<td>Placebo</td>
<td>95% CI</td>
<td>p</td>
<td>η²</td>
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<tr>
<td></td>
<td>n  Mean  SE</td>
<td>Mean  SE</td>
<td>Lower   Upper</td>
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<tr>
<td>Current IQ</td>
<td></td>
<td></td>
<td></td>
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<td>Similarities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>48  9.76 0.58 9.52 0.68</td>
<td>0.24</td>
<td>-1.56   2.03</td>
<td></td>
<td></td>
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<tr>
<td>Adjusted</td>
<td>48  9.94 0.39 9.32 0.41</td>
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<td>-0.52   1.77</td>
<td>.281</td>
<td>0.03</td>
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<tr>
<td>Unadjusted</td>
<td>48  9.00 0.54 8.78 0.74</td>
<td>0.22</td>
<td>-1.61   2.04</td>
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<td></td>
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<tr>
<td>Adjusted</td>
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<td>0.48</td>
<td>-0.86   1.81</td>
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<td>0.01</td>
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<td>Estimated IQ</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted</td>
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<td>0.84</td>
<td>-10.78  12.46</td>
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<tr>
<td>Adjusted</td>
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<tr>
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<td>Placebo</td>
<td>95% CI</td>
<td>p</td>
<td>η²</td>
</tr>
<tr>
<td></td>
<td>n  Mean  SE</td>
<td>Mean  SE</td>
<td>Lower   Upper</td>
<td></td>
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<tr>
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<td>Similarities</td>
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<td></td>
<td></td>
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<td>-2.46   1.24</td>
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<tr>
<td>Adjusted</td>
<td>43 10.28 0.41 10.07 0.47</td>
<td>0.21</td>
<td>-1.06   1.47</td>
<td>.746</td>
<td>0.00</td>
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<td>Matrix Reasoning</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
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<td>-2.49   1.66</td>
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<td></td>
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<tr>
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<td>0.24</td>
<td>-0.99   1.46</td>
<td>.699</td>
<td>0.00</td>
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<td>Estimated IQ</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
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<td>-4.49</td>
<td>-16.88  7.90</td>
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<tr>
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<td>2.27</td>
<td>-4.58   9.12</td>
<td>.507</td>
<td>0.01</td>
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For unadjusted values, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented.

η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect.

Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
4.3.5  Post-hoc secondary analyses on primary and secondary cognitive outcomes

Post-hoc secondary (exploratory) analyses were conducted to control for potential confounding by non-adherence to study treatment regime and changes to concomitant medication during the course of the study on the RCT outcomes. Level of significance was adjusted within families of tests.

Post-hoc subgroup analysis was conducted including only participants subjects who completed the study and reported full adherence during the study (defined as >90% adherence to assigned regimen).

Further, it was noted that more participants in the CoQ10 group had remained on the same concomitant medication during the course of the study. Post-hoc analyses were conducted using the subset of participants who remained on the same medication throughout the study in order to eliminate potentially confounding effects of changes to routine treatment regimen.

4.3.6  Effect of CoQ10 supplementation on primary and secondary cognitive outcomes in participants reporting > 90% adherence to treatment

Twenty-eight (61%) of participants (CoQ10=16) reported greater than 90% adherence to assigned study treatment at 6 months. The effect of CoQ10 supplementation on the primary and secondary cognitive outcomes was considered within this subset of adherent participants, using a series of ANCOVAs with baseline task performance entered as a covariate (Table 4.8). At baseline, there were no differences between the CoQ10 and placebo groups on the primary and secondary cognitive outcome variables.

4.3.6.1 Effect of CoQ10 supplementation on primary outcomes in participants reporting > 90% adherence to treatment

Attention

After controlling for baseline task performance, no statistically significant differences in mean scores at 3 months and 6 months were observed between the placebo and CoQ10 treatment groups on the three conditions of the CPT-IP. In adherent participants, a moderate effect in favour of CoQ10 may have been present on the 4-digit condition of the CPT-IP at 6 months, though this was not statistically significant within the small sample, $F(1, 20) = 1.87, p = .187, \eta^2_p = 0.09$. This potential effect was not present at 3 months, $F(1, 20) = 0.49, p = .493, \eta^2_p = 0.02$. The results suggest that CoQ10 supplementation has no effect on sustained attention in schizophrenia and schizoaffective disorder, even in fully adherent patients.
**Working memory**

Adjusting for baseline task performance, no differences in mean scores at 3 months and 6 months were detected between the placebo and CoQ10 treatment groups on either measure of working memory within the adherent sample.

There was no difference in mean scores between the placebo and CoQ10 treatment groups on the errors score of the spatial working memory task at 3 months, \( F(1,25) = 0.04, p=.845, \eta^2_p = 0.00 \), or at 6 months, \( F(1,25) = 0.07, p=.788, \eta^2_p = 0.00 \).

Similarly, no difference in mean scores between the treatment groups was noted on the letter number sequencing task at 3 months, \( F(1,25) = 0.12, p=.737, \eta^2_p = 0.01 \). There was indication that a moderate effect in favour of CoQ10 may have been present on the letter number sequencing task at 6 months, though this was not statistically significant within the small sample, \( F(1, 24) = 1.77, p = .196, \eta^2_p = 0.07 \).

The results indicate that CoQ10 supplementation has no effect on working memory performance in schizophrenia and schizoaffective disorder, even in fully adherent patients.

4.3.6.2 **Effect of CoQ10 supplementation on secondary cognitive outcomes in participants reporting > 90% adherence to treatment**

**Processing speed**

No statistically significant differences in mean scores at 3 months or 6 months were noted between the placebo and CoQ10 treatment groups on the measures of processing speed.

There was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form A at 3 months, \( F(1,25) = 0.90, p=.351, \eta^2_p = 0.04 \), or at 6 months, \( F(1,25) = 0.02, p=.868, \eta^2_p = 0.00 \).

Similarly, no difference between the treatment groups was noted for mean number of words listed during the verbal fluency task at 3 months, \( F(1,25) = 0.11, p=.744, \eta^2_p = 0.00 \), or at 6 months, \( F(1,24) = 0.99, p = .330, \eta^2_p = 0.04 \).

The results suggest that CoQ10 supplementation has no effect on processing speed in schizophrenia and schizoaffective disorder, even in fully adherent patients.

**Executive function**

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of executive functioning at 3 months or 6 months.
There was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form B at 3 months, $F(1,25) = 0.50, p = .486, \eta^2_p = 0.02$. A moderate effect size in favour of placebo at 6 months on trail making task form B may have been present, though this difference was not significant, $F(1,23) = 1.63, p = .215, \eta^2_p = 0.07$.

No difference in strategy scores on the spatial working memory task between the two groups at 3 months was indicated, $F(1,25) = 0.16, p = .694, \eta^2_p = 0.01$, or at 6 months, $F(1,25) = 0.16, p = .695, \eta^2_p = 0.01$.

The results indicate that CoQ10 supplementation has no effect on executive function in schizophrenia and schizoaffective disorder, even in fully adherent patients.

*Estimated current IQ*

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of current IQ at 3 months or 6 months.

No difference between the treatment groups was noted for current estimated full scale IQ at 3 months, $F(1,23) = 0.69, p = .415, \eta^2_p = 0.03$, or at 6 months, $F(1,22) = 0.05, p = .823, \eta^2_p = 0.00$.

Relatedly, there was no difference between the placebo and CoQ10 treatment groups on mean scores of the WAIS subtest similarities at 3 months, $F(1,24) = 0.57, p = .458, \eta^2_p = 0.02$, or at 6 months, $F(1,23) = 0.64, p = .433, \eta^2_p = 0.03$. Likewise, there was no difference between the placebo and CoQ10 treatment groups on mean scores of the WAIS subtest matrix reasoning 3 months, $F(1,23) = 0.03, p = .862, \eta^2_p = 0.00$, or at 6 months, $F(1,22) = 1.18, p = .288, \eta^2_p = 0.05$.

The results indicate that CoQ10 supplementation has no effect on general cognitive function or current IQ in schizophrenia and schizoaffective disorder, even in fully adherent patients.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Mean(SE)</td>
<td>Mean(SE)</td>
</tr>
<tr>
<td>Placebo</td>
<td>CoQ10</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 digits</td>
<td>24  2.97(0.28)</td>
<td>2.74(0.22)</td>
</tr>
<tr>
<td>3 digits</td>
<td>23  2.01(0.25)</td>
<td>2.32(0.20)</td>
</tr>
<tr>
<td>4 digits</td>
<td>23  1.05(0.21)</td>
<td>1.24(0.17)</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWM (Errors)</td>
<td>28 -1.34(0.24)</td>
<td>-1.27(0.21)</td>
</tr>
<tr>
<td>LNS</td>
<td>28  8.30(0.90)</td>
<td>7.90(0.78)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>28  49.03(3.12)</td>
<td>45.09(2.69)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>28  36.01(1.82)</td>
<td>36.81(1.57)</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making B</td>
<td>28  126.47(9.00)</td>
<td>118.04(7.78)</td>
</tr>
<tr>
<td>SWM (Strategy)</td>
<td>28 -0.84(0.23)</td>
<td>-0.96(0.19)</td>
</tr>
<tr>
<td><strong>Current IQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>27  10.56(0.60)</td>
<td>9.95(0.53)</td>
</tr>
<tr>
<td>Matrix Reasoning</td>
<td>26  9.09(0.64)</td>
<td>8.94(0.56)</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>26  100.49(3.98)</td>
<td>96.11(3.39)</td>
</tr>
</tbody>
</table>

Table 4.8: Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on cognitive outcomes, subset of adherent participants. 

Subset analysis of participants who reported >90% adherence to treatment regimen during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval of estimated marginal mean difference between groups. η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10. LNS Letter number sequencing task, SWM Spatial working memory task.
4.3.7  Effect of CoQ10 supplementation on primary and secondary cognitive outcomes in participants with stable concomitant medication over 6 months

Concomitant medication remained unchanged over the course of the study in 26 (57%) of participants (CoQ10 = 16). The effect of CoQ10 supplementation on the primary and secondary outcomes was considered within this subset of medication-stable participants, using a series of ANCOVAs. Again, baseline task performance was entered as a covariate to control for potential bias attributable to chance differences between treatment groups at baseline (Table 4.9). At baseline, there were no differences between the CoQ10 and placebo groups on the secondary cognitive outcome variables.

4.3.7.1  Effect of CoQ10 supplementation on primary outcomes in participants with stable concomitant medication over 6 months

Attention

Within medication-stable participants, no differences in mean scores at 3 months and 6 months were observed between the placebo and CoQ10 treatment groups on the three conditions of the CPT-IP.

There was a moderate to large effect in favour of placebo may have been present on the 2-digit condition of the CPT-IP at 3 months, though this was not statistically significant within the small sample, $F(1,19) = 2.45, p = .133, \eta_p^2 = 0.11$. There was no evidence of this potential effect at 6 months, $F(1,20) = 0.00, p = .997, \eta_p^2 = 0.00$. No other potentially substantive effects were observed between groups on the attention tasks.

The results indicate that CoQ10 supplementation has no effect on sustained attention in clinically stable patients with a diagnosis of schizophrenia and schizoaffective disorder.

Working memory

After co-varying for baseline performance, no differences in mean scores at 3 months and at 6 months were observed between the placebo and CoQ10 treatment groups on either measure of working memory.

There was no statistically significant effect of treatment in medication stable participants on the errors score of the spatial working memory task at 3 months, $F (1,23) = 0.97, p=.335, \eta_p^2 = 0.04$, or at 6 months, $F (1,23) = 0.73, p=.401, \eta_p^2 = 0.03$.

There was no evidence of a substantive treatment effect on letter number sequencing scores at 3 months, $F (1,23) = 0.03, p=.869, \eta_p^2 = 0.00$, or at 6 months, $F (1,22) = 1.14, p=.297, \eta_p^2 = 0.05$. 

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The results suggest that CoQ10 supplementation has no effect on working memory in clinically stable patients with a diagnosis of schizophrenia and schizoaffective disorder.

4.3.7.2  Effect of CoQ10 supplementation on secondary cognitive outcomes in participants with stable medication over 6 months

Processing speed

No statistically significant differences in mean scores at 3 months or 6 months were noted between medication stable participants in the placebo and CoQ10 treatment groups on the measures of processing speed.

There was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form A at 3 months, $F(1,23) = 0.01, p = .920, \eta^2_p = 0.00$, or at 6 months, $F(1,23) = 1.32, p = .263, \eta^2_p = 0.05$.

Similarly, no difference between the treatment groups was noted for mean number of words listed during the verbal fluency task at 3 months, $F(1,23) = 0.04, p = .846, \eta^2_p = 0.00$, or at 6 months, $F(1,22) = 0.01, p = .919, \eta^2_p = 0.00$.

The results indicate that CoQ10 supplementation has no effect on processing speed in clinically stable patients with a diagnosis of schizophrenia and schizoaffective disorder.

Executive function

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of executive functioning at 3 months or 6 months, upon adjusting for multiple testing within the family of tests (four statistical tests for executive function).

There was no difference between the placebo and CoQ10 treatment groups on mean time taken to complete trail making task form B at 3 months, $F(1,23) = 0.03, p = .874, \eta^2_p = 0.00$. Controlling for baseline performance, a moderate effect size may have been present in favour of placebo at 6 months on trail making task form B, though the difference was not significant, $F(1,21) = 1.23, p = .281, \eta^2_p = 0.06$.

On average, the placebo group had better strategy scores on the spatial working memory task compared to the CoQ10 group at 3 and 6 months. The difference in strategy scores on the spatial working memory task was significant at 0.05 level between the two groups at 3 months, $F(1,23) = 5.82, p = .024, \eta^2_p = 0.20$, and at 6 months, $F(1,23) = 5.35, p = .030, \eta^2_p = 0.19$. These were large effect sizes. However, upon adjusting for multiple testing within the family of tests (n=4), the
results no longer reached statistical significance. The adjusted critical values for 3 and 6 months were .0125 and .025 respectively.

The results suggest that CoQ10 supplementation has no beneficial effect on executive function in clinically stable patients with a diagnosis of schizophrenia and schizoaffective disorder.

Estimated current IQ

There were no differences in mean scores between the placebo and CoQ10 treatment groups on the measures of current IQ at 3 months or 6 months, upon adjusting for multiple testing (six statistical tests for differences in estimated current IQ).

No statistically significant difference between the treatment groups was noted for current estimated full scale IQ at 3 months, though a potential large effect in favour of placebo was indicated, $F_{(1,22)} = 3.73$, $p = .066$, $\eta^2_p = 0.15$. This potential effect not indicated at 6 months, and there was no significant difference between group means, $F_{(1,20)} = 0.66$, $p = .426$, $\eta^2_p = 0.03$.

At 3 months, the placebo group had substantially higher WAIS subtest similarities scores than the CoQ10 group, $F_{(1,22)} = 5.49$, $p = .029$, $\eta^2_p = 0.20$. Upon adjusting for testing within the family of tests ($n=6$), the difference no longer reached statistical significance, as the adjusted critical value was .008. This potential substantive effect was also no longer present at 6 months, $F_{(1,20)} = 0.64$, $p = .432$, $\eta^2_p = 0.03$.

No statistically significant difference was noted between the placebo and CoQ10 treatment groups on mean scores of the WAIS subtest matrix reasoning at 3 months, though again a moderate effect in favour of placebo may have been present, $F_{(1,22)} = 1.73$, $p = .201$, $\eta^2_p = 0.07$. This potentially moderate difference in scores was no longer present at 6 months, $F_{(1,21)} = 0.07$, $p = .802$, $\eta^2_p = 0.00$.

The results indicate that CoQ10 supplementation has no effect on current IQ or general cognitive function in clinically stable patients with a diagnosis of schizophrenia and schizoaffective disorder.
Table 4.9 Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on cognitive outcomes, subset of participants with stable concomitant medication.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Mean(SE)</td>
<td>CoQ10 Mean(SE)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean difference</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 digits</td>
<td>3.22(0.25)</td>
<td>2.72(0.18)</td>
</tr>
<tr>
<td>3 digits</td>
<td>2.01(0.27)</td>
<td>2.30(0.20)</td>
</tr>
<tr>
<td>4 digits</td>
<td>1.30(0.20)</td>
<td>1.23(0.15)</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWM (Errors)</td>
<td>-1.17(0.23)</td>
<td>-1.46(0.18)</td>
</tr>
<tr>
<td>LNS</td>
<td>8.30(1.20)</td>
<td>8.56(0.93)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>45.91(3.16)</td>
<td>45.50(2.48)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>38.32(2.02)</td>
<td>37.80(1.58)</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making B</td>
<td>118.15(9.20)</td>
<td>116.27(7.24)</td>
</tr>
<tr>
<td>SWM (Strategy)</td>
<td>-0.39(0.27)</td>
<td>-1.22(0.21)</td>
</tr>
<tr>
<td>Current IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>10.15(0.52)</td>
<td>8.56(0.42)</td>
</tr>
<tr>
<td>Matrix Reasoning</td>
<td>9.63(0.78)</td>
<td>8.31(0.63)</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>99.13(3.92)</td>
<td>89.31(3.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subset analysis of participants with stable concomitant medication during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval of estimated marginal mean difference between groups. ηp² - partial eta squared – the proportion of variability in outcome attributed to treatment group effect. *p-value not significant upon adjustment for multiple testing (4 tests differences in executive function, 6 tests for differences in current IQ). **Direction of effect in favour of placebo. Direction of effect in favour of CoQ10. LNS Letter number sequencing task, SWM Spatial working memory task.
Clinically significant and reliable change on primary and secondary cognitive outcomes at 6 months.

Clinically significant improvement was determined where positive reliable change occurred, and where the participant’s final outcome score was closer to the mean of a healthy control population than the baseline mean of the total participant sample. Participants were judged to have deteriorated if the change in outcome score surpasses the reliable change criteria, but in the direction of poorer task performance. Figure 3 illustrates the proportion of participants in each group who reliably improved or deteriorated on the cognitive measures.

Reliable change indices (RCI), based on estimated measurement error, were calculated for all cognitive variables using the Jacobson & Truax (1991) formula (1).

\[
RCI = \pm 1.96 \times Estimated \, S_{diff}
\]

Where

\[
Estimated \, S_{diff} = \sqrt{2(SE)^2}
\]

And

\[
SE = s_1 \sqrt{1 - r_{xx}}
\]

Standard error of measurement (SE), reliability (r_{xx}) and reference SD (s_1) values were obtained from procedural manuals and published validation studies of the measures, to calculate an estimated standard error to difference. Reliable change was determined when change on the cognitive variable exceeded the RCI.

Number needed to treat (NNT) for CoQ10 was then calculated on each cognitive domain based on the proportion of participants who demonstrated clinically significant change on measures within that domain. NNT is clinically meaningful measure that indicates the number of persons who would need to receive the intervention to achieve a therapeutic goal (Laupacis et al., 1988). NNTs for cognitive response have previously been used in RCTs in schizophrenia (Weickert et al., 2015). NNT is the reciprocal of the absolute risk reduction (ARR). ARR is obtained by subtracting a measure of the post-treatment outcome (e.g. response rate) in the comparison group from the measure of post-treatment outcome in the treatment being studied. The higher the NNT the less effective an intervention.

In the CoQ10 RCT, this goal was improvement within cognitive function domains.
4.3.8.1 Clinically significant and reliable change on primary outcomes at 6 months.

Attention

Two participants in the CoQ10 group exhibited clinically significant improvement on the 2 digit condition of the CPT-IP. No participants improved on this condition in the placebo group, though one person’s performance deteriorated. The difference in proportion of improvements between the two groups was not significant ($p = .219$, two-tailed Fisher’s exact test). Three participants in the placebo group and four participants in the CoQ10 group exhibited clinically significant improvement on the 3 digit condition of the CPT-IP. The difference in proportions between groups was not significant ($p = .689$, two-tailed Fisher’s exact test). One participant in the placebo group and four participants in the CoQ10 group exhibited clinically significant improvement on the 4 digit condition of the CPT-IP. One participant’s performance deteriorated on this task in the CoQ10 group. The difference in proportions between groups was not significant ($p = .148$, two-tailed Fisher’s exact test).

One participant in the placebo group, and two participants in the CoQ10 group demonstrated reliable, clinically significant change on two conditions of the CPT-IP, no participant improved on all conditions of the CPT-IP in either group.

The number need to treat (NNT) was 18; on average 18 patients with schizophrenia or schizoaffective disorder would need to receive CoQ10 supplementation in order for one patient’s performance to improve on two conditions of the attention task. These results indicate that CoQ10 supplementation has little impact on sustained attention in schizophrenia or schizoaffective disorder.

Working memory

Equal numbers of participants (n=2) in the placebo group and in the CoQ10 group demonstrated clinically significant improvement in between error scores of the spatial working memory task, ($p = 1$, two-tailed Fisher’s exact test).

Three participants in the placebo group and four participants in the CoQ10 group exhibited clinically significant improvements in working memory as measured by the letter number sequencing task. The difference between groups was not significant ($p = .689$, two-tailed Fisher’s exact test). One participant’s performance on the LNS deteriorated in the placebo group.

Clinically significant improvements on one working memory measure only were indicated in 5 participants in the placebo group and four participants in CoQ10 group. One participant demonstrated clinically significant improvements on both working memory tasks after 6 months of CoQ10 supplementation. No participant in the placebo group improved on both measures. There
was no significant difference in proportion of responders between groups \((p = 1, \text{ two-tailed Fisher’s exact test})\). The NNT to improve on both working memory tasks was 21. These results indicate that CoQ10 supplementation has minimal impact on working memory in schizophrenia or schizoaffective disorder.

4.3.8.2  Clinically significant and reliable change on secondary cognitive outcomes at 6 months.

Processing speed

Three participants in the placebo group and two participants in the CoQ10 group demonstrated clinically significant improvements in processing speed as measured by verbal fluency \((p = 1, \text{ fisher’s exact test two-tailed})\). Three participants in the placebo group and two participants in the CoQ10 group demonstrated clinically significant improvements in processing speed as measured by trail making task A \((p = 1, \text{ fisher’s exact test two-tailed})\). Two participants in the placebo group and one participant in the CoQ10 group performed worse on this task.

No participant improved on both measures of processing speed in either group. These results indicate that CoQ10 supplementation has minimal impact on processing speed in schizophrenia or schizoaffective disorder.

Executive function

Three participants in the placebo group and no participants in the CoQ10 group demonstrated clinically significant changes in executive function as measured by the strategy score of spatial working memory task \((p = .239, \text{ fisher’s exact test two-tailed})\). In each group, one participant’s strategy score deteriorated.

One participant in the placebo group and two participants in the CoQ10 group demonstrated clinically significant changes in executive function as measured by trail making task B \((p = .570, \text{ fisher’s exact test two-tailed})\). Performance declined for two participants in the CoQ10 group.

No participant improved on both measures of executive function in either group. These results indicate that CoQ10 supplementation has minimal impact on executive function in schizophrenia or schizoaffective disorder.

Current IQ

Five participants in the placebo group exhibited clinically significant improvement on the WAIS subtest Similarities. No participants improved on this subtest in the CoQ10 group. The difference in proportions was not significant \((p = .056, \text{ two-tailed Fisher’s exact test})\). One participant in the CoQ10 group deteriorated.
Four participants in the placebo group and three participants in the CoQ10 group exhibited clinically significant improvement on the WAIS subtest Matrix reasoning. The difference in proportions between groups was not significant \((p = 1, \text{ two-tailed Fisher’s exact test})\). One participant in the placebo group deteriorated.

Nine participants in the placebo group and seven participants in the CoQ10 group demonstrated clinically significant improvement in estimated full scale IQ. Again, this difference between groups was not significant \((p = 1, \text{ two-tailed Fisher’s exact test})\). Two participants in the placebo group and three CoQ10 participants declined.

One participant in the placebo group demonstrated clinically significant change on both WAIS subtests and estimated full scale IQ. These results indicate that CoQ10 supplementation has minimal to no impact on estimated current IQ or general cognitive function in schizophrenia or schizoaffective disorder.

![Figure 4.3 Proportion of participants per group who demonstrated reliable change on cognitive measures from baseline to 6 months.](image-url)
4.4 Interpretation of results: Effect of CoQ10 supplementation on primary and secondary cognitive outcomes

This study tested the hypothesis that CoQ10 supplementation would improve cognitive function in schizophrenia and schizoaffective disorder. In this study, no beneficial effect of CoQ10 was detected on the primary outcome variables for sustained attention and working memory, or on the secondary cognitive outcomes of processing speed, executive function or general cognitive function. The results suggest that adjunctive CoQ10 has no effect on cognitive function in schizophrenia or schizoaffective disorder. No significant differences on measures of cognitive function were found between participants treated with CoQ10 (300mg/day) and participants who received placebo at either 3 months or 6 months post randomisation. As such the study provides no evidence that CoQ10 can improve cognitive function in schizophrenia and schizoaffective disorder. The RCT was concluded without recruiting the planned sample size; however the current data do not justify a further extension of the RCT.

There are few pharmacological or adjunctive agents that induce robust improvements in attention in schizophrenia and schizoaffective disorder, despite attention performance correlating with functional status and recovery (Iwata et al., 2015; Sinkeviciute et al., 2018; Xiang et al., 2017). As such, the identification of novel treatments for impaired attention is important. However, this study provides no evidence that CoQ10 administration improved attention in schizophrenia and schizoaffective disorder. There was no significant difference in sustained attention between the placebo and CoQ10 group at after 3 and 6 months of CoQ10 supplementation in patients with schizophrenia and schizoaffective disorder (Figure 4.1a-c). Within group analyses indicated that sustained attention improved with CoQ10 supplementation over 6 months, but not for the placebo group. This observed change over time most likely reflects regression toward the mean as participants with the highest initial cognitive scores tend to decline with follow up testing, while participants with lower scores tend to improve with repeated testing (Bland & Altman, 2011, 2015; Salthouse, 2012). Further, there was no difference in the proportion of participants demonstrating clinically reliable change on any condition of the attention task. It was estimated that on average 18 patients with schizophrenia or schizoaffective disorder would need to receive CoQ10 supplementation in order for one patient to exhibit reliable improvement in attention.

CoQ10 therapy has previously demonstrated substantial effects on attention in disorders exhibiting mitochondrial dysfunction (Huntington Study Group, 2001). However the absence of statistically significant difference between groups post-treatment and the high NNT suggests that there may be minimal effect of CoQ10 on attention in schizophrenia and schizoaffective disorder; NNT of 18 equates to an effect size of approximately .1 Cohen’s d (Kraemer & Kupfer, 2006).

Working memory impairments are another core feature in schizophrenia and schizoaffective disorder for which there are few therapeutic agents (Lett et al., 2014). Again the CoQ10 RCT
indicated that CoQ10 supplementation at 300mg/day has no effect on this core deficit. There was no significant difference in working memory performance between the placebo and CoQ10 group at after 3 and 6 months of CoQ10 supplementation in patients with schizophrenia and schizoaffective disorder. Within group analyses indicated that spatial working memory improved within the placebo group over 6 months, but not in the CoQ10 treated group. Similar to attention performance, it is most likely that the within group change observed reflects regression-toward-the-mean or placebo effects (Salthouse et al., 2012; Bland & Altman, 2011, 2015). There was also no difference in the proportion of participants who exhibited reliable change on either working memory measure after six months of treatment. Further, the NNT to improve both spatial and verbal working memory is 21, indicative of a minimal or negligible effect, less than .1 Cohen d, of CoQ10 supplementation on working memory performance.

Several animal and case studies suggest neuroprotective and potentially restorative effects of CoQ10 administration on memory (Langsjoen et al., 2005; Monsef et al., 2019; Okeahialam, 2015; Omidi et al., 2019; Sandhir et al., 2014). However, there have been no reported effects of CoQ10 specifically on working memory in RCTs of CoQ10. A recent RCT of adjunct N-acetylcysteine (NAC), a free radical scavenger and precursor to glutathione, induces moderate to large effects on working memory in psychosis after 6 months of treatment (Rapido-Castro et al., 2017). That study indicates the potential of anti-oxidant therapies in improving memory function through reversal of oxidative stress damage in schizophrenia and other psychotic disorders, though the precise mechanism of action is yet to be determined (Rapido-Castro et al., 2017), see Chapter 6 for further discussion. However, there was no indication that CoQ10 supplementation as administered in the CoQ10 RCT induces similar effects.

The potential effect of CoQ10 supplementation on secondary outcomes processing speed, executive function and general cognitive function by proxy of current estimated IQ, was also considered. Again there were no effects of CoQ10 supplementation on these outcomes. Between group analyses indicated no therapeutic benefit on these functions. There was also no difference in the proportions of participants in each group who exhibited reliable change. There was an indication that CoQ10 administration may have been detrimental to executive functioning which was no longer significant upon correction for multiple testing. This potential effect was however surprising, as one RCT in PSP reported a large beneficial effect of CoQ10 on executive functioning (Stamelou et al., 2008).

There were no significant imbalances between the CoQ10 and placebo groups on demographic characteristics, baseline outcome measures, attrition rate or suspected adverse events that may explain the absence of detected effect on cognition. However, post-randomisation, more participants in the CoQ10 remained on the same concomitant medication regime compared to placebo. MATRICS recommend that clinical trials of cognitive interventions be conducted in
patients with stable concomitant medication as changes make it more difficult to isolate the cognitive effect of the target intervention from other variables (Buchanan et al., 2005). Changes in medication may have been indicative of changes in clinical status, which in turn is associated with changes in cognition (Buchanan et al., 2005). The potential confound introduced by medication changes was considered through an exploratory subgroup analysis. However, there continued to be no significant difference between the treatment groups on cognitive measures at either midpoint or endpoint (Table 4.9). The potentially detrimental impact of CoQ10 on executive function after 3 and 6 months of treatment was once again indicated; however, correction through multiple testing removed this effect. A negative effect of CoQ10 was also indicated on the similarities subtest of the WAIS, though again the difference was not significant with multiple testing corrections (Table 4.9). In summary, CoQ10 appears to have no effect on cognition in clinically stable patients with schizophrenia or schizoaffective disorder.

Further, though adherence rates tend to be higher in RCTs compared to normal practice, full adherence in the CoQ10 RCT was only 61%. This is in line with estimates of adherence in routine care (Kane et al., 2013). Thus while allowing for greater generalisability of results; non-adherence to treatment reduces estimates of efficacy in RCTs. However, after excluding non-adherent participants (Chapter 4.2.4), there continued to be no evidence of effect of CoQ10 on any measure of cognition (Table 4.9). Further, the indication that CoQ10 may have had a detrimental effect on executive function was no longer present. The initial trend within the complete cases may have been spurious, potentially as a result of multiple testing or practice effects, or the change may reflect regression towards the mean; within group change with repeated measures can be perceived as real change but is a consequence of natural variation at an individual or group level. However it may also be indicative of patient related factors not attributable to CoQ10 treatment or RCT involvement, including severity of symptoms and cognitive dysfunction associated with prescribed treatment non-adherence (Iasevoli et al., 2017).

While it is possible that there is no effect of CoQ10 on cognitive function within the sample, several alternative explanations related to study design and conduct present.

The CoQ10 RCT hypothesised that CoQ10 supplementation would have a moderate effect on attention and working memory. This effect was anticipated based on effects on attention identified in other non-pharmacological interventions in psychosis (Firth et al., 2016; Wykes et al., 2008). Previously reported cognitive benefits of CoQ10 were large but not maintained, and there a few pharmacological agents that induce positive effects on attention in schizophrenia. Thus a smaller effect was anticipated than those reported in other CoQ10 RCTs. With an initial sample size of 70 and an attrition rate of 34% the CoQ10 RCT was underpowered to detect such an effect. Null hypothesis statistical testing (NHST) is heavily dependent on sample size and homogeneity, however more idiographic approaches including determining responders and NNT give further
insight into treatment effect, even in small samples (Black et al., 2019). However, the NNTs for both primary outcomes were high, indicative of minimal to small effects of CoQ10 on attention and working memory. If this is reflective of a true effect, a sample size of approximately 1,200 patients would have been required to detect a difference at 6 months between the two groups, using the same methods (Kraemer & Kupfar, 2006). Further, the ITT sensitivity analyses supported the principle complete cases analysis, indicating that attrition did not disproportionately bias the results.

It is also possible that the selected cognitive measures were not sensitive enough to detect a treatment effect between groups. However the cognitive measures used in the CoQ10 RCT have demonstrated treatment effects in pharmacological and non-pharmacological trials and observational studies (Donohoe et al., 2017; Keefe et al., 2017; Wagner et al., 2005).

It is possible that the selected dosage was too low to induce an effect on cognition in schizophrenia and schizoaffective disorder. The daily dose of 300mg CoQ10 was selected as it was previously determined as safe to use and well-tolerated in RCTs with cardiac, neurological and neuropsychiatric conditions (Alcocer-Gómez et al., 2017; Lei & Liu, 2017; Sándor et al., 2005; Storch et al., 2007). However, trials that reported significant benefits on cognitive function tended to use higher doses ranging from 600mg to 2,400mg, thus the selected dose in this RCT may have been insufficient to improve ATP production and restore redox balance. On the other hand, 150 and 200mg/day doses were sufficient to improve attention (cognitive effort) in CFS and self-reported cognitive problems in multiple sclerosis (Fukuda et al., 2016; Moccia et al., 2019).

4.5 Conclusion

There appears to be little indication of potential benefits of CoQ10 on improving cognitive function in schizophrenia and schizoaffective disorder. In addition to the absence of a significant difference between groups using complete cases and the ITT sensitivity analysis, there was limited indication of individual cognitive benefit. Thus given the current data, the potential benefits of CoQ10 on cognitive function in schizophrenia or schizoaffective disorder appear minimal, requiring a much larger sample size to demonstrate. It remains plausible however that CoQ10 supplementation is insufficient to repair the mitochondrial dysfunction, in particular impairments in the ETC and damage from oxidative stress, which is thought, to underlie the cognitive impairments in schizophrenia and schizoaffective disorder. Chapter 6 explores the reasons why CoQ10 supplementation may not have had a treatment effect.
5 EFFECT OF COQ10 SUPPLEMENTATION ON SECONDARY PSYCHOLOGICAL, HEALTH AND BIOCHEMICAL OUTCOMES.

This chapter presents and interprets the results of the psychological, health and biochemical outcomes that are energy, depression and anxiety levels, negative symptoms, quality of life, functional status, physical activity levels, blood pressure, CoQ10 status and mitochondrial function. These outcomes were secondary to the primary cognitive outcomes.

5.1 Background

Dysregulated immune-inflammatory pathways, oxidative stress, and mitochondrial dysfunction are implicated in several psychiatric and neurological disorders including bipolar disorder, depression, schizophrenia, and multiple sclerosis (Filler et al., 2014; Kallaur et al., 2017; Morris et al., 2019; Sanoobar et al., 2015; Smaga et al., 2015). Through oxidative phosphorylation (OXPHOS), mitochondria generate adenosine triphosphate (ATP) for cellular function. During the production of ATP, electrons escape the electron transport chain (ETC) to combine with oxygen, generating reactive oxygen species (ROS) (Turunen et al., 2004). These molecules are critical for cell function, survival and apoptosis (Turunen et al., 2004). However, mitochondrial dysfunction, particularly abnormality in the ETC, produces excessive ROS, which disrupt redox balance and damage lipids, proteins and DNA (Valko et al., 2007). Further, pro-inflammatory cytokines (PIC) are activated in response to the chronic elevation of ROS levels, which in turn induce further ROS, increasing oxidative stress and mitochondrial damage (López-Armada et al., 2013; Morris & Berk, 2015; Yubero et al., 2016). Common features of disorders associated with oxidative stress, inflammation and mitochondrial dysfunction include fatigue, psychiatric disturbances and metabolic syndrome (Smaga et al., 2015).

Agents that support mitochondrial function may therefore prove beneficial for the treatment of such symptoms and associated disorders. As an electron carrier, CoQ10 enhances electron flow in the ETC, supporting ATP production (Hargreaves, 2014). Additionally, CoQ10 acts as a mitochondrial anti-oxidant by quenching excessive ROS and promoting the regeneration and activity of other antioxidants such as α-tocopherol, ascorbate, superoxide dismutase and glutathione-peroxidase (Crane, 2007; Duberley et al., 2014; Feher et al., 2007; Sanoobar et al., 2013). A key attribute of CoQ10 is that it prevents the formation of lipid peroxyl radicals before they can damage the cell membrane (Turunen et al., 2004).

Though CoQ10 can be synthesised in the body, and obtained through the diet, CoQ10 levels may be diminished with age, chronic disease, medications, increased demand or primary defects in biosynthesis (Zozina et al., 2018). CoQ10 deficiency was first described by Ogasahara et al. (1989) in siblings with fatigue, progressive muscle weakness, cognitive disturbance, and central nervous system dysfunction. Subsequently, mitochondrial dysfunction and potential CoQ10 deficiency have
been associated with several other disorders and chronic conditions including Huntington’s disease, cardiovascular disease, obesity, CFS, autism and schizophrenia. The extent of CoQ10 deficiency has been positively correlated with the severity of symptoms such as fatigue, depression, pain and neurocognitive deficits and is also predicative of cardiac mortality (Maes et al., 2009; Lei & Liu, 2017). Such detriments may occur as CoQ10 deficiency can disrupt cellular energy metabolism and contribute to oxidative stress; specifically decreasing ATP generation and ETC complex activity, and increasing ROS production (Duberley et al., 2014).

However, cells with elevated CoQ10 display an increased resistance to oxidative stress mediated apoptosis (González et al., 2009; Somayajulu et al., 2005). Further, CoQ10 administration improves ATP production and decreases markers of inflammation such as Tumor Necrosis Factor-alpha, Interleukin 6, matrix metallopeptidase 9 and oxidative stress such as malondialdehyde (Farsi et al., 2019; Sanoobar et al., 2013, 2015; Spindler et al., 2009). Thus while a deficit in CoQ10 is likely to contribute to disease pathology and symptoms of fatigue, pain, affective disturbances, and metabolic syndromes, augmentation with CoQ10 may have protective effects via its ability to restore electron flow to the ETC to improve ATP production as well as its anti-oxidant and anti-inflammatory properties (Hargreaves, 2014).

Unsurprisingly, the effects of CoQ10 supplementation have been examined in a number of disorders associated with CoQ10 deficits or mitochondrial dysfunction (Fan et al., 2017; Lei & Liu, 2017; Mehrabani et al., 2019; Tabrizi et al., 2018). Fatigue or energy levels are frequently studied outcomes in RCTs and open label studies of CoQ10 supplementation, as inadequate cellular ATP is associated with severe fatigue (Myhill et al., 2009). CoQ10 supplementation has improved fatigue levels in fibromyalgia (100-400mg/day), statin associated myopathy (200-240mg/day), multiple sclerosis (500mg/day) and end stage heart failure (60mg/day) (Alcocer-Gómez et al., 2017; Berman et al., 2004; Fedacko et al., 2012; Rosenfeldt et al., 2003; Sanoobar et al., 2016). Conversely in CFS (150mg/day), breast cancer (300mg/day), late-onset sequelae of poliomyelitis (100mg/day), Amyotrophic Lateral Sclerosis (ALS) (2700mg/day), healthy (100-300mg/day) and obese (200mg/day) participants, CoQ10 supplementation conferred no benefit on energy levels (Fukuda et al., 2016; Lee et al., 2011; Lesser et al., 2013; Peel et al., 2015). Others have examined the influence of CoQ10 on psychiatric symptoms, as it has been hypothesised that the antioxidant and anti-inflammatory properties of CoQ10 may reduce excess ROS and consequently modulate PICs and inhibit oxidative stress damage (Maes et al., 2009; Reviewed in Chapter 1). CoQ10 supplementation has improved depression scores in bipolar disorder (200-800mg/day), CFS (150mg/day), fibromyalgia (300mg/day), and multiple sclerosis (500mg/day). In contrast, no treatment effect of CoQ10 on affective symptoms was noted in ALS (2700mg/day), Parkinson’s disease (300-2400mg/day), Progressive Supranuclear Palsy (PSP) (5mg/kg/day) or breast cancer patients (300mg/day). CoQ10 supplementation may be also beneficial for cardiovascular health; its
therapeutic potential may derive from its ability to promote OXPHOS and enhance energy production in cardiac muscle (Lei & Liu, 2017). Meta-analytic evidence demonstrates that CoQ10 supplementation in heart failure lowers mortality and improves exercise capacity, although dose was not taken into account in the analysis (100mg- 400mg/day; Lei & Liu, 2017). Further, in patients with metabolic disease, CoQ10 augmentation (100-150mg/day) may reduce systolic blood pressure levels, though diastolic blood pressure levels are not affected (Tabrizi et al., 2018). However, Ho and colleagues (2016) conclude that the evidence supporting long-term use of CoQ10 in clinical hypertension is modest at best. Similarly, there is highly variable evidence indicating the use of CoQ10 supplementation for psychological and physical health. However, it is worth considering that only patients exhibiting a deficit in CoQ10 status may respond to treatment (Neergheen et al., 2017).

Therefore, considering the role of mitochondrial dysfunction, inflammation, and oxidative stress in the pathophysiology of schizophrenia and indication of a CoQ10 deficit in schizophrenia, CoQ10 presents as a potential treatment. The antioxidant, anti-inflammatory, and mitochondrial regulatory properties of CoQ10 may exert beneficial effects in schizophrenia, particularly in terms of fatigue, affective symptoms, and cardiac health. Further, there is a strong relationship between fatigue and affective symptoms and negative symptoms, physical activity, quality of life and functional status in schizophrenia and severe mental illness. Therefore, the impact of adjuvant CoQ10 on these variables was also assessed in the present study. Finally, the biochemical impact of CoQ10 supplementation was evaluated in terms of CoQ10 status and mitochondrial function. Specifically it was hypothesised that:

1) There would be an increase in CoQ10 levels in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

2) There would be improvement in measures of mitochondrial function between patients who received CoQ10 supplementation and patients who received placebo after 3 months and 6 months supplementation.

3) There would be improvement in levels of energy in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

4) There would be less severity of depression symptoms in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.
5) There would be less severity of anxiety symptoms in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

6) There would be less severity of negative symptoms avolition, asociality, blunted affect and alogia in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

7) There would be improvement in self-reported quality of life in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

8) There would be improvement in physical activity levels in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

9) There would be improvement in functional status in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

10) There would be lower systolic and diastolic blood pressure in patients who received CoQ10 supplementation compared to patients who received placebo after 3 months and 6 months supplementation.

The remainder of this chapter presents and interprets the effects of oral CoQ10 supplementation on the secondary biochemical, psychological and health outcomes (Table 5.1) in schizophrenia and schizoaffective disorder.
Table 5.1 List of secondary outcomes measures and direction of change for improvement.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measure</th>
<th>Direction of scores for improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ10 levels</td>
<td>Plasma CoQ10 levels</td>
<td>Higher</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td>Plasma lactate levels</td>
<td>Lower</td>
</tr>
<tr>
<td>Energy</td>
<td>Functional Assessment of Chronic Illness Therapy</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Fatigue Scale (FACIT-F)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Beck Depression Inventory II (BDI-II)</td>
<td>Lower</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Beck Anxiety Inventory (BAI)</td>
<td>Lower</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Brief negative symptoms scale (BNSS) subscales:</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Asociality, Avolition, Blunted affect, Alogia</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>World Health Organisation Quality of Life-Short Form (WHOQOL-SF) domains:</td>
<td>Higher</td>
</tr>
<tr>
<td></td>
<td>Physical health, Psychological functioning, Social relationships, Environmental opportunities</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td>Social and Occupational Functioning Assessment Scale (SOFAS)</td>
<td>Higher</td>
</tr>
<tr>
<td>Physical activity</td>
<td>International Physical Activity Questionnaire Short Form (MET-min/week)</td>
<td>Higher</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic blood pressure (mmhg)</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure (mmhg)</td>
<td></td>
</tr>
</tbody>
</table>

Improvement on measure is indicated if change occurs in the direction listed above.

5.2 Methods particular to this chapter

Chapter 2 provides a detailed description of the methods used in the CoQ10 RCT. Chapter 3 describes the study sample and methodological issues that influenced the analyses and interpretation of results. Below is a description of some methods that are particular to this chapter.

5.2.1 Analyses used

6. Potential differences in baseline scores of outcome measures between groups for all randomised participants were tested using independent t-tests and Mann-Whitney U tests. Variables are presented in terms of mean and SD or median and IQR.

7. For descriptive purposes, within group change from baseline to 3 and 6 month outcome assessments for complete cases were analysed using paired t-tests with Bonferroni adjustments for multiple pairwise comparisons (baseline to midpoint, baseline to endpoint). Tests were exploratory in nature and were not intended to generate claims of treatment effect.

8. To evaluate the effects of CoQ10 supplementation compared to placebo on the secondary outcomes multiple ANCOVAs were conducted to test the differences in mean scores on the outcome measures between the CoQ10 and placebo groups at 3 and 6 months.
a. Due to the high attrition rate (>20%) the principle analysis was based on complete cases for each outcome variable at each time point. Sensitivity analysis followed an ITT approach and used multiple imputation based on chained equations to impute missing values in SPSS 25.

9. Due to extreme floor effects at baseline the results for blunted affect and alogia are presented in terms of the presence or absence of the symptoms and analysed using a generalized estimating equations approach. Values for blunted affect and alogia were not included in the ITT.

10. Secondary exploratory analyses using complete cases:
   a. Adherent participants – differences in mean scores between CoQ10 and placebo groups at 6 months for those participants who reported 90% treatment adherence at 6 months.
   b. Stable medication - differences in mean scores between CoQ10 and placebo groups at 6 months for those participants whose prescribed medication remained unchanged during the study.

11. Differences in the proportion of clinical responders at 6 months in each group on depression and anxiety measures was determined using established reliable and clinically significant change criteria were tested using Chi Square test of independence. Number needed to treat analysis was conducted.

12. Differences in the proportion of participants who exhibit minimal clinically important change at 6 months in each group on anxiety, depression, quality of life, functional status, physical activity, and blood pressure measurements were tested using Chi Square test of independence.
5.3 Results

5.3.1 Comparison of biochemical, psychological and health-related outcomes at baseline between groups

The results of the between groups comparison at baseline of the psychological, health and biochemical secondary outcomes are presented in Table 5.2. Groups were similar across all secondary outcomes measures. Comparisons between groups at baseline were made using independent t-tests for normally distributed variables and Mann Whitney U tests for variables that did not meet the assumptions of the independent t-test. As discussed in Chapter 2 this information may be superfluous. If randomisation were conducted appropriately, any statistically significant imbalance between groups is due to chance.

The majority of CoQ10 plasma samples at baseline were within the reference range of 0.5 – 1.7 μmol/l (M=1.17, SD=0.50). There were no statistically significant differences in CoQ10 levels between groups at baseline. Three participants had baseline CoQ10 levels lower than the reference range, one of whom was in the CoQ10 group. Three participants in each treatment group had elevated CoQ10 levels (>1.7 μmol/l). The proportion of CoQ10 status classifications between the groups was not statistically significant (p = 1.00, Fisher’s exact test, 2-tailed). Baseline plasma CoQ10 level was not correlated with any other outcome variable.

The majority of lactate samples at baseline were within the reference range of 0.5 - 2.2 mmol/l (Mdn=1.3, IQR=0.7). There were no statistically significant differences in mitochondrial function, as measured by plasma lactate levels (mmol/l) between groups at baseline; eight participants had baseline lactate levels higher than the reference range, three of whom were in the CoQ10 group. This difference was not statistically significant (p = 1.00, Fisher’s exact test, 2-tailed). Baseline lactate levels within the whole sample were weakly correlated with avolition (Spearman’s ρ = .264, p= .045), indicating that worse mitochondrial function was related to worse avolition. There was also a weak but negative correlation between baseline lactate levels and energy levels (Spearman’s ρ = -.292, p= .025), indicating that worse mitochondrial function was related to lower energy levels. Lactate was not correlated with any other outcome variable, including plasma CoQ10.

There were no statistically significant differences between groups on the energy measure, or on the psychological symptom measures for anxiety, depression, or negative symptoms: asociality, avolition, blunted affect and alogia. The blunted affect (Mdn=2, IQR=4) and alogia (Mdn=0, IQR=2) subscales of the brief negative symptoms scales exhibited floor effects and were highly skewed. These variables were transformed into new binary variables indicating the presence or absence of the symptoms. A chi-square test of independence indicated that there was no statistically significant difference in the proportion of participants exhibiting blunted affect between the two groups, χ² (1, N=70) = 0.03, p= .874. There was also no statistically significant
difference in the proportion of participants exhibiting alogia between the two groups, $\chi^2(1, N=70) = 0.03, p= .872$. There were no statistically significant results between groups on measures of quality of life, functional status, or physical activity levels. There were no statistically significant differences in systolic or diastolic blood pressure between groups at baseline.

5.3.1.1 Summary

The results of these tests indicate that the treatment groups in the CoQ10 RCT were well-matched, with no significant imbalances in outcomes variables noted at baseline. As expected, lower energy levels and higher avolition were related to poor mitochondrial function.

Table 5.2 Descriptive statistics and comparison of psychological, health and biochemical secondary outcome measures between placebo and CoQ10 groups for randomised sample at baseline.

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
<th>Placebo Mean/Mdn</th>
<th>SD/IQR</th>
<th>CoQ10 Mean/Mdn</th>
<th>SD/IQR</th>
<th>t/U</th>
<th>p</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>35.85</td>
<td>10.55</td>
<td>35.13</td>
<td>10.78</td>
<td>0.28</td>
<td>.781</td>
<td>68</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI II</td>
<td>15.00</td>
<td>16.00</td>
<td>12.00</td>
<td>15.25</td>
<td>519.00</td>
<td>.424</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI</td>
<td>9.00</td>
<td>10.00</td>
<td>15.00</td>
<td>28.00</td>
<td>469.50</td>
<td>.161</td>
<td></td>
</tr>
<tr>
<td><strong>Negative symptoms(BNSS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asociality</td>
<td>3.00</td>
<td>4.00</td>
<td>2.50</td>
<td>4.25</td>
<td>557.50</td>
<td>.735</td>
<td></td>
</tr>
<tr>
<td>Avolition</td>
<td>3.00</td>
<td>5.00</td>
<td>3.00</td>
<td>5.00</td>
<td>515.00</td>
<td>.392</td>
<td></td>
</tr>
<tr>
<td>Blunted Affect</td>
<td>1.00</td>
<td>5.00</td>
<td>1.00</td>
<td>4.00</td>
<td>566.00</td>
<td>.632</td>
<td></td>
</tr>
<tr>
<td>Alogia</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
<td>2.00</td>
<td>572.00</td>
<td>.645</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of life (WHOQOL-SF)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>63.72</td>
<td>15.90</td>
<td>63.82</td>
<td>17.67</td>
<td>-0.02</td>
<td>.982</td>
<td>64</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>56.36</td>
<td>18.95</td>
<td>56.85</td>
<td>20.08</td>
<td>-0.10</td>
<td>.920</td>
<td>64</td>
</tr>
<tr>
<td>Social relationships</td>
<td>60.31</td>
<td>18.53</td>
<td>58.63</td>
<td>19.83</td>
<td>0.35</td>
<td>.726</td>
<td>64</td>
</tr>
<tr>
<td>Environmental opportunities</td>
<td>67.11</td>
<td>16.19</td>
<td>67.86</td>
<td>15.47</td>
<td>-0.19</td>
<td>.850</td>
<td>64</td>
</tr>
<tr>
<td><strong>Functional status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>66.20</td>
<td>13.86</td>
<td>61.42</td>
<td>12.15</td>
<td>1.37</td>
<td>.177</td>
<td>57</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET-min/week</td>
<td>1024.50</td>
<td>1634</td>
<td>906.00</td>
<td>2529</td>
<td>579.00</td>
<td>.904</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123.00</td>
<td>21.00</td>
<td>124.00</td>
<td>16.00</td>
<td>578.00</td>
<td>.754</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.00</td>
<td>10.00</td>
<td>83.00</td>
<td>10.00</td>
<td>540.00</td>
<td>.445</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoQ10 levels</td>
<td>1.18</td>
<td>0.50</td>
<td>1.17</td>
<td>0.50</td>
<td>0.09</td>
<td>.928</td>
<td>58</td>
</tr>
<tr>
<td>Lactate levels</td>
<td>1.20</td>
<td>0.90</td>
<td>1.30</td>
<td>0.50</td>
<td>410.00</td>
<td>.818</td>
<td></td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) within group at baseline for all randomised participants. Independent t-tests (equal variances assumed) or non-parametric equivalent Mann Whitney U and associated p-values.
5.3.2 Within group change from baseline at 3 and 6 months.

Means and SD of biochemical outcomes for complete cases are presented in Table 5.3. Means and standard deviations (SD) of the secondary outcomes of energy and psychological measures for complete cases at baseline, midpoint and endpoint are presented in Table 5.4. Means and SD of the secondary outcomes of quality of life, functional status, physical activity, and blood pressure for complete cases at baseline, midpoint (3 months) and endpoint (6 months) are presented in Table 5.5.

Within group mean changes from baseline to midpoint and from baseline to endpoint are also presented within the tables. The results of these statistical tests were not intended as the primary analysis results or to distort interpretations of treatment effects. The statistical significance of the within group change on continuous measures was tested using paired t-tests. McNemar test was used to assess changes in symptom status on the blunted affect and alogia subscales. P values were only adjusted using Bonferroni correction for repeated testing within pairs (two statistical tests per variable pair: baseline to 3 months, baseline to 6 months). Tests were not intended to establish claims of effect, rather to provide a more comprehensive picture of the data. The tests may have been unnecessary.

Biochemical concentration:

CoQ10 status

Plasma CoQ10 levels (μmol/l) did not change from baseline to midpoint or baseline to endpoint in the placebo group. Plasma CoQ10 levels increased significantly from baseline to midpoint in the CoQ10 group by on average 2.93 μmol/l, but not from baseline to endpoint.

Mitochondrial function

No significant changes from baseline in mitochondrial function, as indicated by plasma lactate (mmol/l), occurred in either group at either midpoint or endpoint.

Energy and psychological symptoms:

Energy

Results of the paired t-test indicated that energy levels, measured using the FACIT-F, on average, did not change in either treatment group from baseline to midpoint or from baseline to endpoint.

Depression

Depression scores, measured using BDI-II, did not change significantly from baseline to midpoint and from baseline to endpoint in the CoQ10 group. In the placebo group, depression scores reduced significantly by 3.63 points from baseline to midpoint on average. This significant reduction was
maintained at endpoint; depression scores had reduced on average by 4.5 point from baseline to endpoint in the placebo group.

Anxiety

A significant reduction in anxiety scores, as measured with BAI, from baseline was evident in the CoQ10 group at both midpoint and endpoint. Average change from baseline at both time points was 7.5 points. Symptoms of anxiety did not change significantly in the placebo group from baseline to either follow-up assessment.

Negative symptoms

Negative symptoms were assessed using the relevant subscale scores of the Brief Negative Symptoms Scale (BNSS).

Asociality symptoms significantly decreased in both the CoQ10 and the placebo groups from baseline at both midpoint and endpoint assessments. In the CoQ10 group, scores reduced on average by 0.71 points from baseline to midpoint, and by 1.14 points from baseline to endpoint. In the placebo group, asociality symptoms reduced by an average of 1.04 points at midpoint and 1.33 points at endpoint from baseline.

Avolition symptoms decreased significantly from baseline levels in the CoQ10 group at midpoint by 0.76 point and this significant change was maintained at endpoint (0.95 mean point reduction from baseline). In the placebo group, avolition symptoms significantly decreased from baseline to midpoint by 0.96, but change from baseline was not evident at endpoint (0.71 mean point reduction from baseline).

McNemar test indicated that the number of participants classified as exhibiting symptoms of blunted affect changed significantly from baseline to endpoint in the CoQ10 group. Ten participants in the CoQ10 group initially presented with the symptom at baseline, of whom three continued to exhibit blunted affect at endpoint. There was no statistically significant change in reclassification from baseline to midpoint in the CoQ10 group. No statistically significant change regarding the number of participants reclassified as exhibiting or not exhibiting symptoms of blunted affect at midpoint or endpoint occurred in the placebo group.

No statistically significant change regarding the number of participants reclassified as exhibiting or not exhibiting symptoms of alogia at midpoint or endpoint occurred in either group.
Health-related outcomes:

Quality of life

Changes in quality of life were assessed on each of the WHOQOL-SF domains. No significant changes from baseline occurred in either group on the quality of life domain of physical health, psychological functioning, social relationships and environmental opportunity at either midpoint or endpoint. However, there was indication that self-reported physical health improved within the CoQ10 group at 6 months, with participants on average reporting improvements of 5.16 points in physical health scores. However this was not statistically significant ($p=0.058$).

Functional status

No significant changes from baseline occurred in either group in terms of functional status (SOFAS) at midpoint and endpoint.

Physical activity

Level of physical activity was expressed in weekly metabolic minutes (MET-min/week) according to the International Physical Activity Questionnaire (IPAQ) scoring guidelines. No significant change in MET-min/week expended from baseline to midpoint or baseline to endpoint was detected in either group.

Blood pressure

No significant changes in systolic or diastolic blood pressure occurred in either group from baseline to midpoint and from baseline to endpoint.

5.3.2.1 Summary of within group change results

Levels of anxiety, asociality and avolition symptoms improved from baseline to midpoint and from baseline to endpoint in the CoQ10 group. Blunted affect symptoms also improved from baseline to endpoint in those randomised to CoQ10. CoQ10 status increased from baseline with 3 months of CoQ10 supplementation, but not after 6 months of supplementation. No other changes in psychological, health or biochemical outcomes occurred in the CoQ10 group. In the placebo group, levels of depression and asociality symptoms improved from baseline to midpoint and endpoint. Levels of avolition symptoms also improved from baseline to midpoint. No other changes in psychological, health or biochemical outcomes occurred in the placebo group. The results tentatively indicate that CoQ10 supplementation may improve psychological symptoms, but is unlikely to affect energy or other health-related outcomes. Between groups analyses is necessary to determine whether a treatment effect of CoQ10 exists.
Table 5.3 Descriptive statistics and mean change in scores from baseline to midpoint (3 months) and endpoint (6 months) on secondary biochemical outcome measures for complete cases at endpoint.

<table>
<thead>
<tr>
<th>Secondary outcome measure</th>
<th>Placebo</th>
<th>CoQ10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 0 Months</td>
<td>Midpoint 3 months</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CoQ10 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CoQ10</td>
<td>1.20(0.53)</td>
<td>1.41(0.71)</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Lactate</td>
<td>1.27(0.6)</td>
<td>1.21(0.42)</td>
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</tbody>
</table>

Mean and standard deviation (SD) within group at baseline, midpoint, and endpoint assessments. Change within group is mean change in scores from baseline to follow up assessment. P-values for paired t-tests of within group change, Bonferroni adjustment was applied to control for repeated multiple testing of variable within group (n=2) and significance level was set at alpha < .05. *Wilcoxon signed rank test: 3 months $Mdn = 1.11$, $IQR = 0.46$; 6 months $Mdn = 1.53$, $IQR = 2.25$.
Table 5.4 Descriptive statistics and mean change in scores from baseline to midpoint (3 months) and endpoint (6 months) on energy and psychological outcome measures for complete cases at endpoint.

<table>
<thead>
<tr>
<th>Secondary outcome measure</th>
<th>Placebo</th>
<th>CoQ10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 0 Months</td>
<td>Midpoint 3 months</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Energy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>37.67(9.31)</td>
<td>39.92(9.87)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.58(11.27)</td>
<td>9.29(8.78)</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asociality</td>
<td>2.67(2.24)</td>
<td>1.63(2.00)</td>
</tr>
<tr>
<td>Avolition</td>
<td>2.54(2.40)</td>
<td>1.58(1.64)</td>
</tr>
<tr>
<td>Blunted affect*</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Alogia*</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) within group at baseline, midpoint, and endpoint assessments. Change within group is mean change in scores from baseline to follow up assessment. P-values for paired t-tests of within group change, Bonferroni adjustment was applied to control for repeated multiple testing of variable within group (n=2) and significance level was set at alpha < .05. * Number of cases presenting with symptoms and McNemar test of significance. FACIT-F Functional Assessment of Chronic Illness Therapy- Fatigue Scale, BDI-II Beck Depression Inventory II, BAI Beck Anxiety Inventory.
Table 5.5 Descriptive statistics and mean change in scores from baseline to midpoint (3 months) and endpoint (6 months) on secondary health-related outcome measures for complete cases at endpoint.

<table>
<thead>
<tr>
<th>Secondary outcome measure</th>
<th>Placebo</th>
<th>CoQ10</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 0 Months</td>
<td>Midpoint 3 months</td>
<td>Endpoint 6 months</td>
<td>Baseline 0 Months</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>63.82(17.51)</td>
<td>66.15(15.89)</td>
<td>65.92(16.43)</td>
<td>59.52(17.54)</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>57.97(20.45)</td>
<td>59.53(19.78)</td>
<td>59.42(19.23)</td>
<td>54.63(19.54)</td>
</tr>
<tr>
<td>Social relationships</td>
<td>63.77(18.22)</td>
<td>60.87(20.79)</td>
<td>58.51(18.57)</td>
<td>58.33(20.81)</td>
</tr>
<tr>
<td>Environmental opportunities</td>
<td>69.29(14.4)</td>
<td>70.52(17.77)</td>
<td>68.07(16.7)</td>
<td>66.84(16.01)</td>
</tr>
<tr>
<td><strong>Functional status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>66.75(14.14)</td>
<td>69.19(13.41)</td>
<td>70.81(13.82)</td>
<td>64.06(11.87)</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET-min/week</td>
<td>1508(1161)</td>
<td>1933(1642)</td>
<td>1421(1001)</td>
<td>2450(3467)</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127.04(21.17)</td>
<td>119.87(15.88)</td>
<td>126.7(17.26)</td>
<td>120.82(14.71)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.09(10.22)</td>
<td>80.48(11.48)</td>
<td>82.65(10.12)</td>
<td>78.76(9.44)</td>
</tr>
</tbody>
</table>

Mean and standard deviation (SD) within group at baseline, midpoint, and endpoint assessments. Change within group is mean change in scores from baseline to follow up assessment. P-values for paired t-tests of within group change. Bonferroni adjustment was applied to control for repeated multiple testing of variable within group (n=2) and significance level was set at alpha < .05. SOFAS Social and occupational functioning assessment scale. MET-min/week, weekly metabolic minutes expended.
5.3.3 Effect of CoQ10 supplementation on secondary psychological, health and biochemical outcome measures at 3 and 6 months.

5.3.3.1 Principle analysis: Complete cases

Differences in CoQ10 concentration, lactate concentration, energy, depression, anxiety, asociality, and avolition, quality of life, functional status, physical activity levels, and blood pressure between the CoQ10 and placebo groups were analysed at 3 and 6 months using a series of analysis of covariance models (ANCOVA), with baseline levels entered as a covariate. This method adjusts for baseline differences between groups and has multiple advantages in that it reduces bias of estimated treatment effects and is more powerful than repeated measures analysis or analysis of change (Borm et al., 2007; Egbewale et al., 2014; Twisk et al., 2018). Generalized estimating equation approach was applied to tests for change over time between groups for the presence of blunted affect and alogia symptoms. The statistical significance level of 0.05 was adjusted for multiple testing within families of measures using the Benjamini and Hochberg (1995) method to minimise risk of false positives.

Biochemical results for CoQ10 status and mitochondrial function (lactate concentration) are presented in Table 5.6. Results for energy and psychological symptoms are presented in Table 5.7. Quality of life and functional status results are presented in Table 5.8. Physical activity and blood pressure results are presented in Table 5.9. Each table presents the group adjusted means and estimated mean difference (with 95% confidence interval) between groups at 3 months and 6 months.

5.3.3.1.1 CoQ10 status

CoQ10 values were approximately normally distributed with the exception of one case at 3 months and one case at 6 months (different participants). These values were extreme outliers (greater than three times the interquartile range above the third quartile range). To improve fit of the general linear model accounting for baseline CoQ10 status, these values were windsorised for the remaining analyses, that is they were recoded to the 95th percentile of the whole sample values at the given time point.

At 3 months, there was a significant, large effect of CoQ10 supplementation on plasma CoQ10 levels (μmol/l) after controlling for baseline values, $F (1,28) = 16.06, p < .001, \eta^2_p = 0.37$. However there was no difference in plasma CoQ10 levels between the placebo and CoQ10 treatment groups at 6 months. $F (1,29) = 2.77, p = .107, \eta^2_p = 0.09$. The increased CoQ10 concentration within the CoQ10 treated group at 3 months was expected and indicative that participants were taking the CoQ10 supplement. The absence of statistically significant difference
between the two groups at 6 months was not anticipated, multiple factors may have influenced this and will be discussed later.

At midpoint (3 months) one participant in the placebo group had a plasma CoQ10 level below the reference range (0.5-1.7 μmol/l) while five had plasma CoQ10 levels above the reference range. In the CoQ10 group, 12 participants had plasma CoQ10 levels above the reference range. The difference was significant \( p = .003 \), Fisher’s exact test, two-tailed).

After 6 months of CoQ10 supplementation, three participants in the CoQ10 group had plasma CoQ10 values below the reference range, while six participants had values above the range. Of those receiving placebo for 6 months, three had CoQ10 levels above the reference range. The difference in categorization between the two groups was statistically significant \( p = .003 \), Fisher’s exact test, two-tailed).

Change in plasma CoQ10 concentration was negatively correlated with change in CPT-IP 2-digit condition at 3 months; increase in plasma CoQ10 was associated with poorer sustained attention (Spearman’s rho =-.498, \( p = .044 \)). Change in plasma CoQ10 was moderately correlated with change in WAIS subtest matrix reasoning scores at 3 months; increase in plasma CoQ10 was associated with improved problem solving (Spearman’s rho =.432, \( p = .017 \)). An increase in CoQ10 status from baseline to 6 months was moderately correlated with a reduction in systolic blood pressure (Spearman’s rho =-.444, \( p = .011 \)) and a reduction in blunted affect symptoms (Spearman’s rho =-.396, \( p = .025 \)). Change in CoQ10 status was not correlated with change on any other outcome variable.

5.3.3.1.2 Mitochondrial function
There was no difference in mitochondrial function between the placebo and CoQ10 treatment groups as determined by plasma lactate levels (mmol/l) at 3 months and 6 months.

Controlling for baseline lactate levels, there was no difference between the placebo and CoQ10 treatment groups on mean lactate at 3 months, \( F (1,28) = 1.20 \), \( p = .284 \), \( \eta^2_p = 0.04 \), or at 6 months, \( F (1,29) = 0.15 \), \( p = .701 \), \( \eta^2_p = 0.01 \).

No participant in either group had a plasma lactate level outside the reference range (0.5-2.2mmol/l) at 3 months or 6 months. Change in plasma lactate was moderately correlated with change in spatial working memory between error scores at 6 months, such that increase in lactate was associated with improved spatial working memory performance (Spearman’s rho =.450, \( p = .010 \)). Change in lactate was not correlated with change on any other variable at 3 months or 6 months.
Table 5.6 Descriptive statistics and mean difference between groups at midpoint (3 months) on secondary biochemical outcomes.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td>CoQ10 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CoQ10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>31</td>
<td>1.33</td>
</tr>
<tr>
<td>Adjusted</td>
<td>31</td>
<td>1.34</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Lactate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>31</td>
<td>1.19</td>
</tr>
<tr>
<td>Adjusted</td>
<td>31</td>
<td>1.20</td>
</tr>
</tbody>
</table>

For unadjusted, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented.

95% CI – 95% confidence interval  $\eta^2$ – partial eta squared – the proportion of variability in outcome attributed to treatment group effect.

Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
5.3.3.1.3 Energy

After controlling for baselines energy level, there were no statistically significant difference in mean energy levels between the placebo and CoQ10 treatment groups at 3 months, $F(1,48) = 0.79$, $p = .379$, $\eta^2_p = 0.02$. Likewise, there was no difference between the placebo and CoQ10 treatment groups on mean energy levels at 6 months, $F(1,43) = 0.25$, $p = .618$, $\eta^2_p = 0.01$.

The results indicate that CoQ10 supplementation has no impact energy levels in schizophrenia or schizoaffective disorder.

5.3.3.1.4 Psychological symptoms

With baseline scores entered as a covariate, there were no statistically significant differences in mean scores between the placebo and CoQ10 treatment groups on the continuous measures of psychological symptoms (BDI-II, BAI, BNSS Asociality, BNSS Avolition) at 3 months or 6 months. There was also no statistically significant group effect on the presence or absence of blunted affect and alogia.

**Depression**

There were no statistically significant differences in mean depression scores between the placebo and CoQ10 treatment groups at 3 months, $F(1,48) = 0.00$, $p = .949$, $\eta^2_p = 0.00$, or at 6 months, $F(1,43) = 0.51$, $p = .481$, $\eta^2_p = 0.01$. These results indicate that CoQ10 supplementation has no effect on depression levels in schizophrenia or schizoaffective disorder.

**Anxiety**

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean BAI scores at 3 months, $F(1,48) = 0.20$, $p = .660$, $\eta^2_p = 0.00$, or at 6 months, $F(1,43) = 0.16$, $p = .691$, $\eta^2_p = 0.00$. These results indicate that CoQ10 supplementation has no effect on anxiety levels in schizophrenia or schizoaffective disorder.

**Negative symptoms**

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean asociality levels at 3 months, $F(1,48) = 0.04$, $p = .835$, $\eta^2_p = 0.00$, or at 6 months, $F(1,43) = 0.16$, $p = .695$, $\eta^2_p = 0.00$.

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean avolition levels at 3 months, $F(1,48) = 0.00$, $p = .959$, $\eta^2_p = 0.00$, or at 6 months, $F(1,43) = 0.00$, $p = .983$, $\eta^2_p = 0.00$. 

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There was no significant group effect on presence of blunted affect over time from baseline to 3 months, Wald’s $\chi^2=0.04$, beta = 0.08, 95% confidence interval = −0.71 to 0.87, $p = .845$. Comparably, there was no significant group effect on presence of blunted affect over time from baseline to 6 months Wald’s $\chi^2=0.74$, beta = 0.38, 95% confidence interval = −0.49 to 1.26, $p = .390$.

There was no significant group effect on presence of alogia over time from baseline to 3 months, Wald’s $\chi^2=0.85$, beta = −0.45, 95% confidence interval = −0.51 to 1.41, $p = .357$. There was no significant group effect on presence of alogia over time from baseline to 6 months Wald’s $\chi^2=0.03$, beta = 0.79, 95% confidence interval = −0.86 to 1.02, $p = .869$.

These results suggest that CoQ10 supplementation has no effect on negative symptoms in schizophrenia or schizoaffective disorder.
Table 5.7 Descriptive statistics and mean difference between groups at midpoint (3 months) on secondary energy and psychological outcomes.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Energy</td>
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</tr>
<tr>
<td>Unadjusted</td>
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</tr>
<tr>
<td>Placebo</td>
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<td>CoQ10</td>
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<td>Negative symptoms</td>
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<td>Alogia</td>
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<td></td>
</tr>
</tbody>
</table>

*For unadjusted, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval.

η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
5.3.3.1.5 Quality of life

Controlling for baseline scores, there were no statistically significant differences in self-reported quality of life between the placebo and CoQ10 treatment groups on the physical health, psychological functioning, social relationships, or environmental opportunities domains of the WHOQOL-SF at 3 months or 6 months.

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean physical health at 3 months, $F (1,40) = 1.47, p = .232, \eta^2_p = 0.03$, or at 6 months, $F (1,40) = 1.36, p = .250, \eta^2_p = 0.03$.

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean psychological functioning at 3 months, $F (1,45) = 0.61, p = .440, \eta^2_p = 0.01$, or at 6 months, $F (1,40) = 1.20, p = .279, \eta^2_p = 0.03$.

Similarly, there was no statistically significant difference between the placebo and CoQ10 treatment groups on mean social relationships score at 3 months, $F (1,45) = 1.67, p = .202, \eta^2_p = 0.04$, or at 6 months, $F (1,40) = 0.67, p = .271, \eta^2_p = 0.02$.

Likewise, there was no statistically significant difference between the placebo and CoQ10 treatment groups on mean environmental opportunities score at 3 months, $F (1,45) = 0.00, p = .980, \eta^2_p = 0.00$, or at 6 months, $F (1,40) = 1.25, p = .271, \eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on quality of life in schizophrenia or schizoaffective disorder.

5.3.3.1.6 Functional status

After adjusting for baseline values, there was no statistically significant difference in functional status between the placebo and CoQ10 treatment groups on the SOFAS at 3 months, $F (1,36) = 0.00, p = .986, \eta^2_p = 0.00$, or at 6 months, $F (1,34) = 0.18, p = .673, \eta^2_p = 0.01$.

These results suggest that CoQ10 supplementation has no effect on functional status in schizophrenia or schizoaffective disorder.
5.3.3.1.7 Physical activity

There was no statistically significant difference in overall physical activity levels (MET-min/week) between the placebo and CoQ10 treatment groups at 3 months or at 6 months after controlling for baseline activity.

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean metabolic minutes at 3 months, $F(1,47) = 0.00, p = .965, \eta^2_p = 0.00$. There was however, a trend towards a small to moderate effect size in favour of placebo at 6 months, though this difference was not significant within the sample, $F(1,42) = 1.99, p = .165, \eta^2_p = 0.05$.

These results indicate that CoQ10 supplementation has no effect on physical activity levels in schizophrenia or schizoaffective disorder.

5.3.3.1.8 Blood pressure

Controlling for baseline values, no difference was recorded in systolic or diastolic blood pressure between the placebo and CoQ10 treatment groups at 3 months or 6 months.

There was no statistically significant difference between the treatment groups on mean systolic blood pressure at 3 months, $F(1,44) = 2.37, p = .131, \eta^2_p = 0.05$. There was also no significant difference or evidence of treatment effect between treatment groups at 6 months, $F(1,41) = 0.82, p = .776, \eta^2_p = 0.00$.

No statistically significant difference between treatment groups was noted on mean diastolic blood pressure at 3 months, $F(1,44) = 0.34, p = .564, \eta^2_p = 0.01$, or at 6 months, $F(1,41) = 0.02, p = .883, \eta^2_p = 0.00$.

These results indicate that CoQ10 supplementation has no effect on blood pressure levels in schizophrenia or schizoaffective disorder.

5.3.3.1.9 Summary of between group difference results

These results indicate that CoQ10 supplementation has no effect on energy, psychological symptoms, quality of life, functional status, physical activity, blood pressure and mitochondrial function after 3 months and 6 months of treatment. CoQ10 treatment for 3 months increased plasma CoQ10 levels; however the effect was not maintained with 6 months of treatment.
Table 5.8 Descriptive statistics and mean difference between groups at midpoint (3 months) on quality of life and functional status.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Physical health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted²</td>
<td>48</td>
<td>65.81</td>
</tr>
<tr>
<td>Adjusted²</td>
<td>48</td>
<td>65.05</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted²</td>
<td>48</td>
<td>59.27</td>
</tr>
<tr>
<td>Adjusted²</td>
<td>48</td>
<td>58.63</td>
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<tr>
<td>Social Relationships</td>
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</tr>
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<td>Unadjusted²</td>
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<td>61.00</td>
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<tr>
<td>Adjusted²</td>
<td>48</td>
<td>59.51</td>
</tr>
<tr>
<td>Environmental opportunities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted²</td>
<td>48</td>
<td>70.13</td>
</tr>
<tr>
<td>Adjusted²</td>
<td>48</td>
<td>69.25</td>
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<tr>
<td>Functional status</td>
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</tr>
<tr>
<td>SOFAS</td>
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<td></td>
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<tr>
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<td>39</td>
<td>67.74</td>
</tr>
<tr>
<td>Adjusted²</td>
<td>39</td>
<td>66.31</td>
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</tbody>
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*For unadjusted, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval. \( \eta_p^2 \) partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
Table 5.9 Descriptive statistics and mean difference between groups at midpoint (3 months) on physical activity and blood pressure.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Descriptive Statistics</td>
<td>Mean difference between groups</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET-min/Week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted⁴</td>
<td>50</td>
<td>1776</td>
</tr>
<tr>
<td>Adjusted⁴</td>
<td>50</td>
<td>2002</td>
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<tr>
<td>Blood pressure</td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted⁴</td>
<td>47</td>
<td>119.08</td>
</tr>
<tr>
<td>Adjusted⁴</td>
<td>47</td>
<td>118.08</td>
</tr>
<tr>
<td>Diastolic</td>
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</tr>
<tr>
<td>Unadjusted⁴</td>
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<td>80.58</td>
</tr>
<tr>
<td>Adjusted⁴</td>
<td>47</td>
<td>80.03</td>
</tr>
</tbody>
</table>

⁴For unadjusted, the values for follow-up mean, standard error (SE), mean difference and 95% confidence interval of mean difference between groups are presented. For adjusted models, the estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval ηp² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
5.3.3.2 Sensitivity analysis

5.3.3.2.1 Sensitivity analysis: Intention to Treat

The sensitivity analysis using multiple imputations did not alter the results at 3 months or 6 months on the energy, psychological, quality of life, functional status, or blood pressure outcomes. Thus it is remains unlikely that CoQ10 supplementation has a beneficial effect on these outcomes.

5.3.3.2.2 Influence of extreme cases

Physical activity was not imputed during multiple imputations for intention to treat due to the presence of two extreme outliers and the absence of correlated variables. Including physical activity prevented convergence of the multiply imputed dataset. Extreme outliers were defined as values greater than three times the interquartile range above the third quartile range. Two extreme outliers in the CoQ10 groups were identified at baseline, 3 and 6 months.

The influence of these two outliers on the physical activity results was considered first via square root transformation of all cases, and second by excluding the two cases from the untransformed analysis. Both cases were considered exceptional due to age and personal circumstances.

Transforming all cases improved model fit due to the residuals’ closer approximation to a normal distribution. There was no treatment effect on physical activity at 3 months, \( F(1,47) = 0.01, p = .925, \eta^2_p = 0.00 \), or at 6 months, \( F(1,42) = 1.24, p = .272, \eta^2_p = 0.03 \).

Excluding the two cases also improved model fit at 3 and 6 months. Again, there was no treatment effect on physical activity at 3 months, \( F(1,45) = 0.02, p = .896, \eta^2_p = 0.00 \), or at 6 months, \( F(1,40) = 1.92, p = .174, \eta^2_p = 0.05 \).

Thus, conclusions regarding the absence of CoQ10 treatment effect on levels of physical activity remain the same, despite the presence of two extreme cases.
5.3.4 Post-hoc (exploratory) analyses on secondary psychological and health outcomes

Post-hoc secondary (exploratory) analyses were conducted to control for potential confounding by non-adherence to study treatment regime and changes to concomitant medication during the course of the study on the RCT outcomes. Critical values for level of significance were adjusted using the Benjamini and Hochberg (1995) method to minimise risk of false positives.

Post-hoc subgroup analysis was conducted including only participants who completed the study and reported full adherence during the study (defined as >90% adherence to assigned regimen).

Further, it was noted that more participants in the CoQ10 group had remained on the same concomitant medication during the course of the study. Post-hoc analyses were conducted using the subset of participants who remained on the same medication throughout the study in order to eliminate potentially confounding effects of changes to routine treatment regimen.

5.3.5 Effect of CoQ10 supplementation on secondary psychological and health outcomes in participants reporting >90% adherence to treatment

Twenty-eight (61%) of participants (CoQ10=16) reported greater than 90% adherence to assigned study treatment at 6 months. The effect of CoQ10 supplementation on the secondary psychological and health related outcomes was considered within this subset of adherent participants, using a series of ANCOVAs with baseline task performance entered as a covariate (Table 5.9). At baseline, there were no differences between the CoQ10 and placebo groups on the psychological and health outcome variables.

Mitochondrial function

There was no difference in mitochondrial function, as measured by plasma lactate level, between the placebo and CoQ10 treatment groups at 3 months or 6 months.

Controlling for baseline lactate levels, there was no difference between treatment groups at 3 months, $F(1,14) = 3.56$, $p = .080$, $\eta^2_p = 0.20$, or at 6 months, $F(1,15) = 1.25$, $p = .282$, $\eta^2_p = 0.08$.

CoQ10 status

There was no difference in plasma CoQ10 concentration between the placebo and CoQ10 treatment groups at 3 months or 6 months.

At 3 months, CoQ10 levels appeared higher in the CoQ10 group, however upon adjusting for multiple testing within families of tests ($n=2$, $p < 0.025$), the effect was no longer significant, $F(1,14) = 6.25$, $p = .026$, $\eta^2_p = 0.31$. Surprisingly, even in patients indicating full adherence there was no evidence the CoQ10 concentration was higher in patients who received CoQ10 for 6 months compared to placebo, $F(1,15) = 0.72$, $p = .409$. 
Energy

Controlling for baseline energy levels, there was no difference between the placebo and CoQ10 treatment groups on mean FACIT-F scores at 3 months, $F(1, 25) = 0.17, p = .684, \eta^2_p = 0.01$, or at 6 months, $F(1, 25) = 0.83, p = .372, \eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on energy levels in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

Depression

Controlling for baseline symptoms of depression, there was no difference between the placebo and CoQ10 treatment groups on mean BDI-II scores at 3 months, $F(1, 25) = 0.35, p = .560, \eta^2_p = 0.01$, or at 6 months, $F(1, 25) = 0.07, p = .799, \eta^2_p = 0.00$.

These results suggest that CoQ10 supplementation has no effect on depression levels in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

Anxiety

Upon adjusting for baseline anxiety scores, there appeared to be no statistically significant differences in mean BAI scores between the placebo and CoQ10 treatment groups at 3 months, $F(1, 25) = 0.56, p = .815, \eta^2_p = 0.00$, or at 6 months, $F(1, 25) = 0.67, p = .421, \eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on levels of anxiety in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

Negative symptoms

Controlling for baseline values, there appeared to be no statistically significant differences in mean symptoms levels of asociality and avolition between the placebo and CoQ10 treatment groups on their respective subscales of the Brief Negative Symptom Scale at 3 months or 6 months.

There was no difference between the placebo and CoQ10 treatment groups on mean asociality levels at 3 months, $F(1, 25) = 0.32, p = .576, \eta^2_p = 0.01$, or at 6 months, $F(1, 25) = 0.03, p = .858, \eta^2_p = 0.00$.

There was no statistically significant difference between the placebo and CoQ10 treatment groups on mean avolition levels at 3 months, though there appeared to be a moderate effect in favour of placebo, $F(1, 25) = 2.04, p = .165, \eta^2_p = 0.08$. There was no difference between groups at 6 months, $F(1, 25) = 0.15, p = .703, \eta^2_p = 0.01$. 

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There was also no effect of CoQ10 treatment on blunted affect at 3 months, Wald’s $\chi^2=0.38$, beta = $-0.40$, 95% confidence interval = $-1.67$ to $0.87$, $p = .538$, or at 6 months, Wald’s $\chi^2=0.19$, beta = $-0.33$, 95% confidence interval = $-1.79$ to $1.14$, $p = .661$. At six months, three participants in the CoQ10 group and three participants in the placebo group exhibited blunted affect.

Further, there was no effect of CoQ10 on alogia at 3 months, Wald’s $\chi^2=0.24$, beta = $-0.37$, 95% confidence interval = $-1.88$ to $1.14$, $p = .628$ or at 6 months, Wald’s $\chi^2=0.38$, beta = $0.45$, 95% confidence interval = $-0.98$ to $1.89$, $p = .536$. Four participants in the placebo group and one participant in the CoQ10 groups exhibited alogia at 6 months.

These results indicate that CoQ10 supplementation has no effect on negative symptoms in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

**Quality of life**

Adjusting for baseline values, no statistically significant evidence of treatment effect was identified on the psychological functioning, social relationships, or environmental opportunities domains of the WHOQOL-SF at 3 months or 6 months. There was no evidence of effect on physical health at 3 months, but there was indication that CoQ10 may have a beneficial effect of physical health at 6 months.

There was no difference between the placebo and CoQ10 treatment groups on mean physical health at 3 months, though there was a trend towards a moderate effect in favour of the CoQ10 group, $F(1,23) = 3.37$, $p = .080$, $\eta^2_p = 0.13$. At 6 months, the CoQ10 group reported higher levels of self-reported physical health at 6 months, $F(1,23) = 7.00$, $p = .014$, $\eta^2_p = 0.23$. On average the CoQ10 group had 9.23 point higher physical health. This was significant at 0.05 alpha level, but no longer significant after correcting for multiple tests within family of measures (n=8, four related domains tested at midpoint and endpoint) where the adjusted alpha level was 0.006. The potential change in physical health was not correlated with change in CoQ10 status (Spearman’s $\rho = -.078$, $p = .760$).

There was no difference between the placebo and CoQ10 treatment groups on mean psychological functioning at 3 months, $F(1,23) = 0.02$, $p = .891$, $\eta^2_p = 0.00$, or at 6 months, $F(1,23) = 0.29$, $p = .596$, $\eta^2_p = 0.01$.

Similarly, there was no difference between the placebo and CoQ10 treatment groups on mean social relationships score at 6 months, $F(1,23) = 0.02$, $p = .961$, $\eta^2_p = 0.00$, or at 3 months, $F(1,23) = 0.18$, $p = .678$, $\eta^2_p = 0.01$. 


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Again, there was no difference between the placebo and CoQ10 treatment groups on mean environmental opportunities score at 3 months, $F(1,23) = 0.11, p = .749, \eta^2_p = 0.01$, or at 6 months, $F(1,23) = 0.81, p = .379, \eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on psychological functioning, social relationships, or environmental opportunity in schizophrenia or schizoaffective disorder, even in patients who report full adherence. However, CoQ10 may have beneficial effects on self-reported physical health in patients who fully adhere to the treatment regimen.

**Functional status**

There was no evidence of a treatment effect on functional status at 3 months or 6 months. Controlling for baseline functional status, there was no difference between the placebo and CoQ10 treatment groups on mean SOFAS scores at 3 months, $F(1,36) = 0.03, p = .858, \eta^2_p = 0.00$, or at 6 months, $F(1,21) = 0.14, p = .708, \eta^2_p = 0.01$.

These results suggest that CoQ10 supplementation has no effect on functional status in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

**Physical activity**

There was no difference in weekly physical activity levels (MET-min/week) between the placebo and CoQ10 treatment groups at 3 months or 6 months. Controlling for baseline MET-min/week, there was no difference between the placebo and CoQ10 treatment groups on MET-min/week at 3 months, $F(1,24) = 0.76, p = .391, \eta^2_p = 0.03$, or at 6 months, $F(1,24) = 0.86, p = .772, \eta^2_p = 0.00$.

These results indicate that CoQ10 supplementation has no effect physical activity levels in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

**Blood pressure**

There was no difference in systolic or diastolic blood pressure between the placebo and CoQ10 treatment groups at 3 months or 6 months.

Controlling for baseline systolic blood pressure, there was no difference between treatment groups at 3 months, $F(1,22) = 1.09, p = .308, \eta^2_p = 0.05$, or at 6 months, $F(1,24) = 0.29, p = .597, \eta^2_p = 0.01$.

Controlling for baseline diastolic blood pressure, there was no difference between treatment groups on mean diastolic blood pressure at 3 months, $F(1,22) = 1.22, p = .282, \eta^2_p = 0.05$, or at 6 months, $F(1,24) = 0.33, p = .572, \eta^2_p = 0.01$. 

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These results suggest that CoQ10 supplementation has no effect on blood pressure levels in schizophrenia or schizoaffective disorder, even in patients who report full adherence.

5.3.5.1 Summary

Unexpectedly, CoQ10 concentration within the CoQ10 group was not significantly different from the placebo group at either time point upon correction for multiple testing. Even in patients who indicate fully adherence to the treatment regimen, there is no indication that CoQ10 has a beneficial effect on energy, psychological or health-related outcomes in schizophrenia or schizoaffective disorder. There is also no evidence that CoQ10 supplementation improves mitochondrial function. However, potential beneficial or protective effects of CoQ10 supplementation for self-report physical health may exist.
Table 5.9 Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary outcomes, subset of adherent participants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>n Mean(SE)</td>
<td>Mean(SE)</td>
</tr>
<tr>
<td>Energy/FACIT-F</td>
<td>28 38.54(2.36)</td>
<td>39.85(2.04)</td>
</tr>
<tr>
<td>Depression/BDI-II</td>
<td>28 11.21(2.42)</td>
<td>13.10(2.09)</td>
</tr>
<tr>
<td>Anxiety/BAI</td>
<td>28 12.61(2.88)</td>
<td>13.54(2.46)</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avolition</td>
<td>28 1.36(0.39)</td>
<td>2.10(0.34)</td>
</tr>
<tr>
<td>Asociality</td>
<td>28 1.83(0.48)</td>
<td>2.19(0.41)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>26 64.25(3.31)</td>
<td>72.65(2.78)</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>26 58.05(3.58)</td>
<td>58.71(3.07)</td>
</tr>
<tr>
<td>Social relationships</td>
<td>26 62.90(4.27)</td>
<td>60.54(3.65)</td>
</tr>
<tr>
<td>Environmental opportunity</td>
<td>26 70.74(2.71)</td>
<td>69.58(2.32)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>22 67.47(2.94)</td>
<td>68.16(2.19)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>27 2482(502)</td>
<td>1911(416)</td>
</tr>
</tbody>
</table>

Subset analysis of participants who reported >90% adherence to treatment regimen during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. *p-value not significant upon adjustment for multiple testing (n=8, p < .006. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
Table 5.9 continued. Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary outcomes, subset of adherent participants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>CoQ10</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>F</th>
<th>p</th>
<th>η²p</th>
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<tr>
<td><strong>Midpoint (3 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blood pressure</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115.88(4.29)</td>
<td>122.11(4.12)</td>
<td>-6.24</td>
<td>18.64</td>
<td>6.17</td>
<td>1.09</td>
<td>.308</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.76(2.51)</td>
<td>81.60(2.41)</td>
<td>-3.84</td>
<td>-11.06</td>
<td>3.38</td>
<td>1.22</td>
<td>.282</td>
</tr>
<tr>
<td>CoQ10 status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CoQ10</td>
<td>1.65(0.55)</td>
<td>3.54(0.52)</td>
<td>-1.89</td>
<td>-3.51</td>
<td>0.27</td>
<td>6.25</td>
<td>.026</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Lactate</td>
<td>1.09(0.14)</td>
<td>1.45(0.13)</td>
<td>-0.36</td>
<td>-0.77</td>
<td>0.05</td>
<td>3.56</td>
<td>.080</td>
</tr>
<tr>
<td><strong>Endpoint (6 months)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.42(3.54)</td>
<td>121.87(3.16)</td>
<td>2.55</td>
<td>-7.27</td>
<td>12.38</td>
<td>0.29</td>
<td>.597</td>
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<tr>
<td>Diastolic</td>
<td>79.30(2.06)</td>
<td>80.89(1.85)</td>
<td>-1.59</td>
<td>-7.30</td>
<td>4.13</td>
<td>0.33</td>
<td>.572</td>
</tr>
<tr>
<td>CoQ10 status</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CoQ10</td>
<td>1.35(0.56)</td>
<td>1.99(0.50)</td>
<td>-0.64</td>
<td>-2.24</td>
<td>0.97</td>
<td>0.72</td>
<td>.409</td>
</tr>
</tbody>
</table>

Subset analysis of participants who reported >90% adherence to treatment regimen during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. η²p partial eta squared – the proportion of variability in outcome attributed to treatment group effect. *p-value not significant upon adjustment for multiple testing within families of measures (n=2), adjusted alpha = 0.025. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
5.3.6  Effect of CoQ10 supplementation on secondary outcomes in participants with stable medication over 6 months

Concomitant medication remained unchanged over the course of the study in 26 (57%) of participants (CoQ10=16). The effect of CoQ10 supplementation on the secondary psychological and health outcomes was considered within this subset of medication-stable participants, using a series of ANCOVAs. Again, baseline measure value was entered as a covariate to control for potential bias attributable to chance differences between treatment groups at baseline (Table 5.10). At baseline, there were no differences between the CoQ10 and placebo groups on the psychological and health outcome variables.

CoQ10 status

There was no difference in plasma CoQ10 concentration between the placebo and CoQ10 treatment groups at 3 months, $F(1,10) = 3.85, p = .078, \eta_p^2 = 0.28$, or at 6 months, $F(1,11) = 0.06, p = .806, \eta_p^2 = 0.01$.

Mitochondrial function

There was no difference in mitochondrial function, as measured by plasma lactate level, between the placebo and CoQ10 treatment groups at 3 months or 6 months.

Controlling for baseline lactate levels, there was no difference between treatment groups at 3 months, $F(1,10) = 2.27, p = .163, \eta_p^2 = 0.19$, or at 6 months, $F(1,11) = 0.79, p = .394, \eta_p^2 = 0.07$.

Energy

There were no differences in mean energy levels between the placebo and CoQ10 treatment groups on the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) at 3 months or 6 months.

Controlling for baseline energy levels, there was no difference between the placebo and CoQ10 treatment groups on mean energy levels at 3 months, $F(1,23) = 0.05, p = .827, \eta_p^2 = 0.00$, or at 6 months, $F(1,23) = 0.09, p = .768, \eta_p^2 = 0.00$.

These results indicate that CoQ10 supplementation has no effect on energy levels in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.
**Depression**

There were no differences in mean symptoms of depression between the placebo and CoQ10 treatment groups on the Beck Depression Inventory II (BDI-II) at 3 months or 6 months.

Controlling for baseline symptoms of depression, there was no difference between the placebo and CoQ10 treatment groups on mean BDI-II scores at 3 months, $F (1,23) = 0.35, p = .559, \eta^2_p = 0.02$, or at 6 months, $F (1,23) = 0.949, p = .340, \eta^2_p = 0.04$.

These results indicate that CoQ10 supplementation has no effect on levels of depression in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

**Anxiety**

There were no differences in mean symptoms of anxiety between the placebo and CoQ10 treatment groups on the Beck Anxiety Inventory (BAI) at 3 months or 6 months.

Controlling for baseline symptoms of anxiety, there was no difference between the placebo and CoQ10 treatment groups on mean BAI scores at 3 months, $F (1,23) = 0.27, p = .607, \eta^2_p = 0.01$, or at 6 months, $F (1,23) = 0.01, p = .909, \eta^2_p = 0.00$.

These results suggest that CoQ10 supplementation has no effect on anxiety levels in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

**Negative symptoms**

There were no differences in mean symptoms levels of asociality and avolition between the placebo and CoQ10 treatment groups on their respective subscales of the Brief Negative Symptom Scale at 3 months or 6 months.

Controlling for baseline symptoms of asociality, there was no difference between the placebo and CoQ10 treatment groups on mean asociality levels at 3 months, $F (1,23) = 0.42, p = .524, \eta^2_p = 0.02$, or at 6 months, $F (1,23) = 0.89, p = .355, \eta^2_p = 0.04$.

Controlling for baseline symptoms of avolition, there was no statistically significant difference between the placebo and CoQ10 treatment groups on mean avolition levels at 3 months, though there appeared to be a moderate effect in favour of placebo, $F (1,23) = 1.87, p = .184, \eta^2_p = 0.08$. There was no difference between groups at 6 months, $F (1,23) = 0.15, p = .699, \eta^2_p = 0.01$.

There was also no effect of CoQ10 treatment on blunted affect at 3 months, Wald’s $\chi^2 = 0.05$, beta = 0.16, 95% confidence interval = −1.28 to 1.61, $p = .825$, or at 6 months, Wald’s $\chi^2 = 0.01$, beta = −0.07, 95% confidence interval = −1.51 to 1.64, $p = .934$. At six months three participants in the CoQ10 group and four participants in the placebo group exhibited blunted affect.
Further, there was no effect of CoQ10 on alogia at 3 months, Wald’s $\chi^2=0.31$, beta = -0.47, 95% confidence interval = -2.13 to 1.19, $p = .579$ or at 6 months, Wald’s $\chi^2=0.49$, beta = 0.54, 95% confidence interval = -0.98 to 2.07, $p = .486$. Four participants in the placebo group and one participant in the CoQ10 groups exhibited alogia at 6 months.

These results indicate that CoQ10 supplementation has no effect on negative symptoms in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

**Quality of life**

Adjusting for baseline scores, no statistically significant treatment effect on in self-reported quality of life domains were noted at 3 months or 6 months.

No statistically significant difference between the placebo and CoQ10 treatment groups was noted on mean physical health at 3 months, $F (1,22) = 0.14$, $p = .710$, $\eta^2_p = 0.01$, or at 6 months, $F (1,20) = 2.49$, $p =.131$, $\eta^2_p = 0.11$.

Similarly, there was no difference between the placebo and CoQ10 treatment groups on mean psychological functioning at 3 months, $F (1,22) = 2.36$, $p =.139$, $\eta^2_p = 0.10$, or at 6 months, $F (1,20) = 2.49$, $p =.131$, $\eta^2_p = 0.11$.

Likewise, there was no difference between the placebo and CoQ10 treatment groups on mean social relationships score at 3 months, $F (1,22) = 3.21$, $p =.087$, $\eta^2_p = 0.13$, and at 6 months, $F (1,20) = 0.45$, $p =.511$, $\eta^2_p = 0.02$.

There was also no difference between the placebo and CoQ10 treatment groups on mean environmental opportunities score at 3 months, $F (1,22) = 0.49$, $p =.493$, $\eta^2_p = 0.02$, or at 6 months, $F (1,20) = 0.51$, $p =.483$, $\eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on quality of life domains in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

**Functional status**

Controlling for baseline functional status, there was no difference between the placebo and CoQ10 treatment groups on mean SOFAS scores at 3 months, $F (1,20) = 0.08$, $p =.780$, $\eta^2_p = 0.00$, or at 6 months, $F (1,20) = 0.52$, $p =.480$, $\eta^2_p = 0.03$.

These results indicate that CoQ10 supplementation has no effect on functional status in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.
Physical activity

Controlling for baseline metabolic minutes, there was no difference between the placebo and CoQ10 treatment groups on mean metabolic minutes at 3 months, $F (1,22) = 0.60$, $p = .449$, $\eta^2_p = 0.03$, or at 6 months, $F (1,22) = 2.39$, $p = .137$, $\eta^2_p = 0.10$.

These results suggest that CoQ10 supplementation has no effect on physical activity levels in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

Blood pressure

Adjusting for baseline values, there appeared to be no statistically significant treatment effect on systolic or diastolic blood pressure values.

There was no difference between treatment groups on mean systolic blood pressure at 3 months, $F (1,21) = 0.68$, $p = .420$, $\eta^2_p = 0.03$, or at 6 months, $F (1,21) = 0.06$, $p = .817$, $\eta^2_p = 0.00$.

Again, there was no difference between treatment groups on mean diastolic blood pressure at 3 months, $F (1,21) = 0.46$, $p = .506$, $\eta^2_p = 0.02$, or at 6 months, $F (1,21) = 0.00$, $p = .968$, $\eta^2_p = 0.00$.

These results indicate that CoQ10 supplementation has no effect on blood pressure levels in clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder.

5.3.6.1 Summary

The results combined indicate that CoQ10 supplementation has no effect on energy, psychological or health-related outcomes in clinically stable patients with schizophrenia and schizoaffective disorder. It also appears to have no effect on mitochondrial function or CoQ10 status in clinically stable patients.
Table 5.10 Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary outcomes, subset of clinically stable participants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midpoint (3 months)</th>
<th>Endpoint (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>n  Mean(SE)</td>
<td>Mean(SE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ηp²</td>
</tr>
<tr>
<td>Energy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>26</td>
<td>38.34(2.93)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-II</td>
<td>26</td>
<td>10.54(2.63)</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI</td>
<td>26</td>
<td>13.95(3.45)</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avolition</td>
<td>26</td>
<td>1.61(0.44)</td>
</tr>
<tr>
<td>Asociality</td>
<td>26</td>
<td>1.58(0.53)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>25</td>
<td>67.84(3.99)</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>25</td>
<td>57.63(3.05)</td>
</tr>
<tr>
<td>Social relationships</td>
<td>25</td>
<td>55.57(4.38)</td>
</tr>
<tr>
<td>Environmental opportunity</td>
<td>25</td>
<td>68.14(2.73)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>23</td>
<td>67.57(2.64)</td>
</tr>
<tr>
<td>Physical activity</td>
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<td></td>
</tr>
<tr>
<td>MET-min/week</td>
<td>25</td>
<td>2642(452)</td>
</tr>
</tbody>
</table>

Subset analyses of participants with stable concomitant medication during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. 95% CI – 95% confidence interval. ηp² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. *p-value not significant upon adjustment for multiple testing. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
Table 5.10 continued. Descriptive statistics and mean difference between groups at midpoint (3 months) and endpoint (6 months) on secondary outcomes, subset of clinically stable patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>CoQ10</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>24</td>
<td>117.21(5.37)</td>
<td>123.00(4.54)</td>
<td>-5.79</td>
<td>-20.43</td>
<td>8.85</td>
<td>0.68</td>
</tr>
<tr>
<td>Diastolic</td>
<td>24</td>
<td>79.22(3.12)</td>
<td>81.99(2.62)</td>
<td>-2.77</td>
<td>-11.27</td>
<td>5.74</td>
<td>0.46</td>
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<tr>
<td><strong>CoQ10 status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CoQ10</td>
<td>13</td>
<td>1.37(1.47)</td>
<td>5.06(1.16)</td>
<td>-3.69</td>
<td>-7.88</td>
<td>0.50</td>
<td>3.85</td>
</tr>
<tr>
<td><strong>Mitochondrial function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Lactate</td>
<td>13</td>
<td>1.10(0.18)</td>
<td>1.44(0.14)</td>
<td>-0.34</td>
<td>-0.84</td>
<td>0.16</td>
<td>2.27</td>
</tr>
</tbody>
</table>

Subset analysis of participants with stable concomitant medication during study. Estimated marginal mean and associated values from the ANCOVA with baseline score as covariate are presented. η² partial eta squared – the proportion of variability in outcome attributed to treatment group effect. *p-value not significant upon adjustment for multiple testing. Direction of effect in favour of placebo. Direction of effect in favour of CoQ10.
5.3.7 Determining responders on psychological and health-related outcomes

Minimum clinically important difference (MCID) is a threshold value for a change on patient reported outcomes that is perceived as meaningful and worthwhile by the patient (Jaeschke, Singer & Guyatt, 1989). MCID is also referred to as minimal clinically important or meaningful change (Revicki, Hays, Cella & Sloan, 2008). MCID is typically population and measure specific (Revicki et al., 2008). Where MCID has not been established for an outcome measure, MCID can be approximated as 0.5SD of the baseline cohort scores (Norman, Sloan & Wyrwich, 2003). The proportion of participants in each group who exhibited MCID from baseline on individual psychological and health-related measures is depicted in Figure 1.

In addition to determining responders in terms of MCID, reliable and clinically significant changes in depression and anxiety symptoms were also considered. Criteria for both reliable change indices and clinically significant change have been established in the literature for the BDI-II and BAI for a number of populations in various settings. These indices were used to determine whether there was a difference in the number of participants who “recovered” from depression and anxiety symptoms during the 6 months of the study (Seggar et al., 2002; Westbrook & Kirk, 2005).

5.3.8 Minimally important, reliable, and clinically significant changes on depression and anxiety symptom levels

Depression

The MCID for the BDI-II has been determined as 17.5% change from baseline total score (Button et al., 2015). Within the current sample this equates to an average change of 3 points in total BDI-II score from baseline. In the placebo group, the scores of 15 participants improved and the scores of three participants deteriorated by 17.5% on the baseline-endpoint measure of depression. In the CoQ10 group, the scores of 14 participants improved and the scores of four participants deteriorated by 17.5% from the baseline measure of depression. Fisher’s exact test did not indicate a significant difference in MCID frequency between the groups ($p = .531$, two-tailed). The NNT to achieve MCID on depression scores is 15.

Within participants who demonstrated MCID, five participants in each group reliably improved (total BDI-II scores decreased by more than 8.46 points from baseline), while two participants in the CoQ10 group reported reliable deterioration of symptoms (total BDI-II scores increased by more than 8.46 points from baseline). The difference of frequency in participants who reliably improved or deteriorated was not significant between groups ($p = .304$, two-tailed Fisher’s exact test). Three participants in the placebo group and four participants in CoQ10 group met the criteria for clinically significant change, again this was not significant ($p = .686$, two-tailed Fisher’s exact test). The NNT for clinically significant change on depression scores is 15.
Anxiety

There is no established criterion for MCID on the BAI; as such MCID was determined as 0.5SD of the total sample baseline scores.

Of the 21 participants who completed 6 months of CoQ10 supplementation, seven demonstrated MCID (endpoint BAI total scores were more than 6.5 points lower than baseline scores) compared to four out of 25 participants in the placebo group. One participant in the CoQ10 group deteriorated by the MCID. The frequency MCID on anxiety levels was not statistically significant between groups (\( p = .124 \), two-tailed Fisher's exact test). The NNT to achieve MCID on anxiety scores is 6.

One participant in the placebo group exhibited an improvement in anxiety that reached MCID, but was below the threshold for reliable change (10 point decrease from baseline BAI score). In the placebo group, three participants demonstrated reliable improvements from baseline anxiety. In the CoQ10 group, seven participants improved reliably while one participant reliably deteriorated. The Fisher’s exact test of reliable change from baseline anxiety between the placebo and CoQ10 groups was not significant (\( p = .054 \)). In terms of clinically significant change, two participants in the placebo group and three participants in the CoQ10 group showed clinical improvement on anxiety symptoms, the difference in response frequency was not statistically significant (\( p = .648 \), two-tailed Fisher’s exact test). The NNT for clinically significant change on anxiety scores is 16.
5.3.9 Minimal clinically important differences on energy, negative symptoms, quality of life, functional status, physical activity and blood pressure.

The MCID has not been previously established in psychiatric populations for the FACIT-F, WHOQOL-SF, or the SOFAS. As suggested in the literature, the MCIDs for schizophrenia and schizoaffective disorder on these measures were calculated as one-half of the SD at baseline scores (Norman et al., 2003). MCID for blood pressure has previously been set at a reduction ≥2mmhg; such a reduction in systolic and diastolic blood pressure could reduce coronary heart disease and stroke risk (Baddeley-White et al., 2019; Collaboration, 2003). Meaningful change on physical activity was considered to have occurred when a participant moved from one level of health enhancing physical activity category to another.

**Energy**

In the placebo group, nine participants improved and two participants deteriorated by 5.3 points (MCID) from baseline scores of the FACIT-F, which indicated that meaningful change in energy levels from baseline had occurred. In the CoQ10 group, the scores of seven participants improved and the scores of three participants deteriorated by the estimated MCID. There was no statistically significant differences in MCID response frequencies from baseline to endpoint on the energy measure (\( p = .832 \), two-tailed Fisher’s exact test). The NNT to achieve meaningful improvement in energy levels is -38.

**Negative symptoms**

One participant in the CoQ10 group demonstrated improvement on all negative symptom subscales. The NNT to achieve minimal clinically important difference across negative symptoms is 21. Breakdown of MCID within each negative symptom category is described below.

Ten participants in the placebo group and eight participants in the CoQ10 group demonstrated MCID in asociality symptoms (endpoint scores 1.4 points lower than baseline scores). The frequency of MCID in asociality symptoms was not statistically significant between groups, \( \chi^2(1, N = 46) = 0.02, p = .895 \).

Nine participants in the placebo group and eight participants in the CoQ10 group demonstrated MCID in avolition symptoms (endpoint scores 1.3 points lower than baseline scores). Four participants in the placebo group and one participant in the CoQ10 group declined by the MCID. The frequency of MCID in avolition symptoms was not statistically significant between groups \( p = .491, \) two-tailed Fisher’s exact test).

Six participants in the placebo group and seven participants in the CoQ10 group demonstrated MCID in blunted affect symptoms (endpoint scores 1.9 points lower than baseline scores). One
participant in the placebo group deteriorated by the MCID. The frequency of MCID was not statistically significant between groups ($p = .860$, two-tailed Fisher’s exact test).

Two participants in the placebo group and five participants in the CoQ10 group demonstrated MCID in alogia symptoms (endpoint scores 1.3 points lower than baseline scores). Three participants in the placebo group deteriorated by the MCID. The frequency of MCID was not statistically significant between groups ($p = .123$, two-tailed Fisher’s exact test).

Functional status

In the placebo group, SOFAS ratings increased in seven participants and decreased in two participants by more than 6 points (MCID). In the CoQ10 group, SOFAS ratings for 8 participants increased and the ratings for two participants decreased by the MCID. There was no statistically significant difference between the frequencies of change in functional status from baseline ($p = .894$, two-tailed Fisher’s exact test). The NNT to achieve meaningful improvement on functional status is 10.

Quality of life

Only one participant in the sample demonstrated meaningful improvement on all four domains of the WHOQOL-SF from baseline to endpoint. This participant was in the CoQ10 treatment group. The NNT for global improvement in self-reported quality of life is 21.

One participant in the placebo group exhibited meaningful deterioration across the four WHOQOL-SF domains. Breakdown of minimally clinically important responses across the four quality of life domains are described below.

Physical health domain

Six participants in the placebo group and four participants in the CoQ10 group demonstrated meaningful improvement on the physical health domain of the WHOQOL-SF (endpoint scores 8 points higher than baseline scores). Six participants in the placebo group and one participant in CoQ10 group exhibited meaningful decline on the domain. The frequency of MCID on self-reported physical health was not statistically significant between groups ($p = .289$, two-tailed Fisher’s exact test). The NNT to achieve a meaningful improvement on self-reported physical health is -21.

Psychological functioning

Three participants in the placebo group and five participants in the CoQ10 group demonstrated meaningful improvement on the psychological functioning domain of the WHOQOL-SF (endpoint scores 9.6 points higher than baseline scores). Six participants in the placebo group and two participants in CoQ10 group exhibited meaningful decline on the domain. The frequency of MCID on self-reported psychological functioning was not statistically significant between groups ($p =$
.372, two-tailed Fisher’s exact test). The NNT to achieve a meaningful improvement on self-reported psychological functioning is 9.

**Social relationships**

In the placebo group, social relationships improved meaningfully for four participants and deteriorated in 10 participants by more than 9.5 points (MCID). In the CoQ10 group, three participants reported meaningful improvement and five reported meaningful deterioration in social relationships. The frequency of MCID on the social relationships domain was not statistically significant between treatment groups ($p = .775$, two-tailed Fisher’s exact test). The NNT to achieve meaningful improvement on self-reported QoL related to social relationships is 59.

**Environmental opportunity**

Five participants in the placebo group and six participants in the CoQ10 group demonstrated meaningful improvement on the environmental opportunity domain of the WHOQOL-SF (endpoint scores 7.9 points higher than baseline scores). Six participants in the placebo group and four participants in CoQ10 group exhibited meaningful decline on the domain. The frequency of MCID on self-reported environmental opportunity was not statistically significant between groups ($p = .659$, two-tailed Fisher’s exact test). The NNT to achieve a meaningful improvement on environmental opportunity is 12.

**Physical activity**

Physical activity levels as reported on the IPAQ were categorised into low, moderate and high, according to IPAQ guidelines. Meaningful change was deemed to have occurred when a participant moved from one physical activity category to another over 6 months. In the placebo group, four participants increased their level of physical activity, while two reduced their activity level. In the CoQ10 group, two participants increased their physical activity while four reduced their activity. There was no statistically significant difference in frequency of change between groups ($p = .505$, Fisher’s exact test). The NNT to meaningfully increase physical activity level is 16.

**Blood pressure**

MCID reduction in systolic blood pressure levels occurred in 12 participants in the placebo group and 10 participants in the CoQ10 group, $\chi^2(1, N = 44) = 0.09, p = .761$. MCID in diastolic blood pressure levels occurred in seven participants in the placebo group and eight participants in the CoQ10 group, $\chi^2(1, N = 44) = 0.96, p = .328$. Both systolic and diastolic blood pressure decreased for seven participants in each treatment group, the NNT to decrease both diastolic and systolic blood pressure is 19.
Figure 5.1 Proportion of participants per group who demonstrated minimal clinically important change on psychological and health measures from baseline to 6 months.
5.4 Interpretation of results: Effect of CoQ10 supplementation on secondary biochemical, psychological, and health-related outcomes

This study tested several hypotheses that CoQ10 supplementation would have beneficial effects on a selection of psychological and health outcomes. These hypotheses were not supported. There was no indication that CoQ10 supplementation (300mg/day) affected symptoms of fatigue, depression, anxiety, avolition, asociality, blunted affect or alogia. Additionally, there appeared to be no effect of CoQ10 on the self-reported quality of life domains of physical health, psychological functioning, social relationships and environmental opportunity or functional status. Further, CoQ10 supplementation had no effect on physical activity levels and blood pressure. Finally, the RCT also tested the hypotheses that CoQ10 supplementation would improve mitochondrial function and increase CoQ10 status in patients with schizophrenia and schizoaffective disorder. There was no evidence that CoQ10 supplementation improved mitochondrial function. CoQ10 status did increase with CoQ10 supplementation by 3 months; however the difference in CoQ10 concentration between the CoQ10 and placebo groups was no longer evident at 6 months. As such, despite plasma CoQ10 levels increasing with supplementation initially, the study provides no evidence that CoQ10 can improve psychological or health outcomes or mitochondrial function in patients with schizophrenia and schizoaffective disorder.

Fatigue is a common symptom of mitochondrial dysfunction and CoQ10 deficits, thought to arise from an inability to meet energy demands (Filler et al., 2014; Hargreaves, 2014). Fatigue frequently presents in schizophrenia spectrum disorders and is associated with poorer physical, mental and overall health, cognitive impairment, negative symptoms, and reduced physical activity (Water et al., 2003; Kanchanatawan et al., 2017; Hedlund et al., 2014). It was hypothesised that patients with schizophrenia and schizoaffective disorder who received CoQ10 supplementation would have higher energy levels post-treatment than patients who received placebo. However, there was no significant difference in energy between the placebo and CoQ10 groups after 3 and 6 months of CoQ10 supplementation. Further, there was no difference in the proportion of participants demonstrating minimal clinically important change in energy levels. It was estimated that on average 38 patients with schizophrenia or schizoaffective disorder would need to receive CoQ10 supplementation in order for one patient to exhibit meaningful improvement in energy levels. Thus, the absence of statistically significant difference between groups post-treatment and the high NNT indicate that it is unlikely CoQ10 supplementation improves energy levels in schizophrenia and schizoaffective disorder. These findings are in contrast with those reported in other disorders associated with oxidative stress and immune-inflammatory pathways such as fibromyalgia and multiple sclerosis (Alcocer-Gómez et al., 2017; Sanoobar et al., 2016). Rather, the results are similar to other studies’ findings in CFS, breast cancer, late-onset sequelae of poliomyelitis, ALS, and obesity (Fukuda et al., 2016; Kaufmann et al., 2009; Lee et al., 2011; Lesser et al., 2013; Peel et al., 2015).
Affective symptoms such as depression and anxiety frequently also present in schizophrenia spectrum disorders (Emsley et al., 1999). Recent conceptualizations of depression, anxiety and schizophrenia have centred on the dysregulation of the inflammatory pathways, oxidative stress, and mitochondrial dysfunction (Do et al., 2009; Kanchanatawan et al., 2018; Smaga et al., 2015). By modulating mitochondrial function via its antioxidant and anti-inflammatory properties, CoQ10 supplementation was hypothesized to improve symptoms of depression and anxiety in patients with schizophrenia and schizoaffective disorder. However, the RCT results indicate that CoQ10 supplementation at 300mg/day has no effect on these symptoms. Critically, the results of the RCT indicate that CoQ10 had no effect on mitochondrial function either. There was no significant difference in depression or anxiety scores between the placebo and CoQ10 group at 3 and 6 months. Within group analyses indicated that depression scores improved from baseline to 3 and 6 months in the placebo group, but not in the CoQ10 treated group. Anxiety levels improved within the CoQ10 group but not the placebo group after 3 and 6 months of treatment. These within group changes may reflect placebo effects or regression towards the mean as there appeared to be no effect of CoQ10 on mitochondrial function. Participants with more severe symptoms are likely to improve over time while others may naturally deteriorate or improve with or without intervention (Bland & Altman, 2011).

There was also no difference in the proportion of participants who exhibited MCID, reliable or clinically significant change on the depression and anxiety measures after six months of treatment. For one patient to experience clinically significant improvement of symptoms of depression, on average 15 patients would need to receive CoQ10. For the same clinically significant effect on anxiety symptoms, on average 16 patients would need to receive CoQ10 treatment. It is therefore unlikely that CoQ10 supplementation has a large treatment effect on affective symptoms in schizophrenia, though other trials have reported large effects of CoQ10 supplementation on symptoms of depression in bipolar disorder and multiple sclerosis (Mehrhooya et al., 2018; Sanoobar et al., 2016). To the author’s knowledge no published RCT has examined the effect of CoQ10 on symptoms of anxiety. In order to improve anxiety symptoms by the MCID in one patient, on average six patients require treatment with CoQ10. This indicates that there may be a small treatment effect of CoQ10 on anxiety levels (Kraemer & Kupfer, 2006). Nonetheless, as the estimated MCID for anxiety was determined by a distribution based calculation, it may not be clinically meaningful to patients (McGlothlin & Lewis, 2014). Further, it is likely that the observed improvements over time reflect an expectancy bias or placebo effect, result from participation in the trial, as well as natural changes in symptom severity (Morton & Torgerson, 2005; Rief et al., 2009).

Negative symptoms are a core feature of schizophrenia and a predictor of functional recovery (Schaefer et al., 2013). Mitochondrial abnormalities, in particular abnormal antioxidant capacity and decreased complex 1 activity in the ECT, have been associated with the severity of negative
symptoms (Ben-Shacher, 2017; Park & Park, 2012). Thus it was hypothesised that CoQ10 supplementation may improve negative symptoms by enhancing ETC function and anti-oxidant capacity. However, adjuvant CoQ10 at 300mg/day had no effect on the negative symptoms of avolition, asociality, blunted affect or alogia at 3 months or 6 months. There was no difference between groups in the proportions of participants displaying MCID on each of the symptom scales. Further only one participant in the CoQ10 improved across all symptom scales. However, patients who enrolled and remained on the RCT had low baseline levels of negative symptoms; the majority of participants exhibited no symptoms of blunted affect or alogia. As discussed in Chapter 3, participants who remained on the RCT had lower levels of avolition compared to participants who withdrew. Thus though there is no indication that CoQ10 affects negative symptom severity, it is also possible that average baseline symptom severity in the sample was too low to detect a treatment effect.

The extent of negative and affective symptoms of schizophrenia spectrum disorders are associated with poorer long term functional outcomes and quality of life and increased use of mental health services (Conley et al., 2007; Priebe et al., 2011; Ritsner et al., 2012). Further, the impact of a treatment on patients’ quality of life can often be neglected in RCTs, despite patients’ expressing most concern about symptoms and adverse effects that impact on their ability to “live a normal lifestyle” (Keefe et al., 2013). Quality of life outcomes are typically most meaningful and understandable to patients (Keefe et al., 2013). As such the impact of CoQ10 supplementation on functional status and self-reported quality of life was also examined. However, adjuvant CoQ10 had no effect on functional status or the quality of life domains of physical health, psychological, functioning, social relationships and environmental opportunity in terms of between group differences or MCID proportions between groups. The lowest NNT for minimal improvement on a quality of life domain was 9; this indicates that there may be a small effect on subjective psychological functioning. However again as the MCID was calculated using distribution based method, consultation with patients regarding the value of such a difference to their daily life is warranted (McGlothin & Lewis, 2014).

Patients with schizophrenia are at increased risk of metabolic syndromes and cardiovascular disease (De Hert et al., 2010; Hansen et al., 2016; Stubbs et al., 2018). While antipsychotic medication and genetic risk factors contribute to this increased risk, sedentary behaviour and lower levels of physical activity are associated worse metabolic profiles in patients with schizophrenia (Stubbs et al., 2018; Vancampfort et al., 2016). Depression, fatigue, and avolition are barriers to exercise in schizophrenia (Firth et al., 2016; Matthews et al., 2018). I considered whether physical activity levels would be affected with CoQ10 supplementation given the relationship between low energy and low activity levels in schizophrenia. However, unsurprisingly, given the absence of effect on energy levels, CoQ10 supplementation had no effect on physical activity levels in schizophrenia.
Hypertension is frequently observed in patients with schizophrenia spectrum disorders (Liao et al., 2011). It was hypothesised CoQ10 supplementation affect blood pressure levels in schizophrenia and schizoaffective disorder. CoQ10’s potential therapeutic benefits for cardiovascular health may be due to its ability to promote OXPHOS and enhance energy production in cardiac muscle (Lei & Liu, 2017). However no effect of CoQ10 supplementation on either systolic or diastolic blood pressure was observed. There was also no statistically significant difference between the CoQ10 and placebo group in the proportion of participants whose blood pressure meaningfully reduced over 6 months. Other studies have indicated that adjuvant CoQ10 may reduce blood pressure (Tabrizi et al., 2018; Rosenfeldt et al., 2007). However this effect may be restricted to those with primary clinical hypertension, rather than in patients with multiple metabolic conditions such as Type 2 diabetes mellitus, dyslipidaemia, and obesity (Zozina et al., 2018).

Chronic schizophrenia is associated with mitochondrial dysfunction including impaired complex I activity in the ETC and elevated lactate (Ben-Shachar, 2017; Rowland et al., 2016). It has previously been reported that CoQ10 supplementation decreased blood lactate and lactate/pyruvate concentrations; though the treatment effect was inversely related to baseline levels suggesting that CoQ10 treatment may be most effective in patients with worse mitochondrial dysfunction (Koroshetz et al., 1997; Remes et al., 2002). It was hypothesised that patients treated with CoQ10 would have lower plasma lactate levels at 3 and 6 months compared to those receiving placebo (Nattagh-Eshivani et al., 2018). However there was no evidence to support this hypothesis. Furthermore, it is likely that the single significant correlation between change in lactate and spatial working memory performance at 6 months may be spurious given the absence of other significant correlations with change in lactate. It is possible that the absence of effect may be because the majority of study participants did not possess mitochondrial dysfunction. On average the sample did not exhibit elevated plasma lactate at baseline. Further, while 16% of the sample possessed plasma levels beyond the laboratory reference range at baseline, no participant showed mitochondrial dysfunction at follow-up regardless of treatment group. This finding was not expected; it was hypothesised, that patients with schizophrenia would exhibit elevated lactate levels, particularly as all participants were receiving antipsychotics which are associated with increasing lactate levels (Elmorsy et al., 2016; Herberth et al., 2011; Regenold et al., 2009; Rowland et al., 2016). It is also possible that the elevated lactate levels at baseline were artefacts due do sample acquisition and processing. For example, lactate levels increase as a result of continued constriction of the blood vessel and clenching of the fist during venepuncture (Chen et al., 1993).

Interestingly, baseline plasma CoQ10 concentration was at the centre of the CoQ10 reference range ($M$=1.17, $SD$=0.50; reference range: 0.5-1.7 $\mu$mol/L). This was unexpected given prior, but inconsistent, reports of ETC abnormalities and lower CoQ10 levels in patients with schizophrenia compared to controls (Ben-Shachar, 2017; Holper et al., 2019; Imagawa, 1989; Kumar & Kurup,
Kumar and Kurup (2001) reported that serum CoQ10 concentration was lower in patients compared to age-match controls. However, Imagawa (1989) observed that while CoQ10 concentration in erythrocytes was lower in schizophrenia, plasma CoQ10 level in schizophrenia was similar to controls. As expected plasma CoQ10 concentration was higher in the CoQ10 group than the placebo group at 3 months. However this effect was not maintained at 6 months. The non-significant difference between groups may reflect a number of factors including reduced adherence to assigned intervention, interaction with concomitant medications including statins, dietary changes, or saturation of lipophilic carriers (Bhagavan & Chopra, 2006; Neergheen et al., 2017). However, plasma CoQ10 concentration is only a surrogate marker for tissue CoQ10 status and the plasma CoQ10 concentration may be more reflective of peaks and troughs of CoQ10 release into the blood stream than overall CoQ10 status (Duncan, 2005). Further, change in plasma CoQ10 status was expected to correlate with change in cognitive performance in schizophrenia and schizoaffective disorder; however the negative association between increase in CoQ10 concentration and cognitive performance as seen in the small to moderate negative correlation with decline in attention performance at 3 months was not anticipated. At the same time point, a similar sized but positive correlation was noted with problem solving. However in light of the number of correlation analyses conducted and conflicting directions of the relationship with cognitive function, it is highly probably that these correlations are due to chance.

There were no significant imbalances between the CoQ10 and placebo groups on demographic characteristics, baseline outcome measures, attrition rate or suspected adverse events that may explain the absence of detected effect on psychological or health related outcomes. As detailed in Chapter 3, confounding introduced by changes to concomitant medication or poor adherence to treatment reduce estimates of efficacy in RCTs. The potential confound introduced by medication changes was considered through an exploratory subgroup analysis. However, there continued to be no significant difference between the treatment groups on psychological, health related, or mitochondrial function measures at either midpoint or endpoint (Table 5.10). Thus, it is unlikely that changes to medication during the RCT influenced the results. However, when the analysis was restricted to adherent participants (Table 5.9), there was indication that self-reported physical health may have been higher with CoQ10 treatment. The effect was non-significant after correcting for multiple testing. Interestingly, the estimated mean difference was 9.23, which was close to the estimated MCID for physical health. Future consultation with patients with schizophrenia and schizoaffective disorder may be warranted to determine the personal benefit of such a potential difference, particularly if the prospect of the potential difference may influence adherence behaviour (Adams & Scott, 2000; McGlothlin & Lewis, 2014). However as this was the only potentially significant difference between the CoQ10 and placebo group after treatment, it remains probable that the potential difference was a spurious finding.
5.5 Conclusion

There has been inconsistent and highly variable support for the use of CoQ10 supplementation on psychological and health related outcomes in neurological and neuropsychiatric disorders in the literature. The current data indicate that adjuvant CoQ10 has no effect on psychological, health related or mitochondrial function outcomes in schizophrenia and schizoaffective disorder. In addition to the absence of a significant difference between groups using complete cases and the ITT sensitivity analysis, there was no indication of individual psychological or health related improvements. Any potential individual benefits in terms of anxiety and quality of life appear minimal and the clinical value of these benefits requires further determination. Further, there is no indication that CoQ10 supplementation enhances mitochondrial function, or that change in mitochondrial function relates to change in other outcomes. As such, it is likely that CoQ10 supplementation may be insufficient to enhance mitochondrial function and thereby improve energy, psychological symptoms, and general health related outcomes in schizophrenia and schizoaffective disorder.
OVERALL DISCUSSION AND CONCLUSIONS

The primary aim of this thesis was to examine the potential effect of CoQ10 supplementation on 1) cognitive function and 2) psychological and physical health in schizophrenia. To this end, a double-blind, randomised, placebo-controlled trial of CoQ10 supplementation in patients with a diagnosis of schizophrenia and schizoaffective disorder was conducted. Chapter 4 details the effects of CoQ10 supplementation on primary and secondary cognitive outcomes. Chapter 5 details the effects of CoQ10 on secondary psychological and health related outcomes. Finally, the effects of CoQ10 supplementation on CoQ10 status and mitochondrial function were considered (Chapter 5). Methodological issues that presented during the conduct of the RCT and influenced subsequent analyses and interpretation of findings are discussed in Chapter 3. This discussion chapter provides an overall summary of the findings and considers potential reasons why CoQ10 had no effect on the symptoms and features of schizophrenia. It addresses study limitations and contributions.

6.1 CoQ10 supplementation as a potential treatment in schizophrenia and schizoaffective disorder: Summary of findings

Observational and interventional evidence (detailed in Chapter 1) support an association between CoQ10 status and cognitive function, energy, psychological symptoms, cardiovascular health, and mitochondrial function in an array of disorders from diabetes to Parkinson’s disease. However, findings from this RCT of CoQ10 in patients with schizophrenia and schizoaffective disorder demonstrate no beneficial effects of CoQ10 supplementation on these features. This is despite observing an increase in plasma CoQ10 concentration at 3 months in the CoQ10 group compared to placebo, demonstrating treatment adherence – a comparative plasma increase which subsequently disappeared at 6 month analysis.

CoQ10 (300mg/day) had no effect on the primary outcomes. There was no difference between treatment groups at 3 months or 6 months on tasks of sustained attention or working memory. This remained true even when secondary subgroup analyses of adherent and clinically stable participants were conducted. There was also no difference between the treatment groups in the proportion of individual change that occurred on each condition of the attention task or on the working memory measures at the end of the treatment period. Furthermore, the NNT to improve attention was 18; patients who receive CoQ10 have a 5.6% chance of improving sustained attention performance or alternatively if 18 patients receive CoQ10 there is a 64% chance that one person will benefit. The NNT was even higher for working memory; on average 21 patients would need to receive CoQ10 for one to potentially experience improvement in verbal and spatial working memory. It is therefore concluded that CoQ10 has no effect on attention or working memory performance in patients with schizophrenia.
No beneficial effect of CoQ10 was demonstrated on secondary cognitive functions of processing speed, executive function, or general cognitive function. Rather, prior to adjusting for multiple testing within families of measures, it appeared that 3 and 6 months of CoQ10 supplementation had a negative effect on executive function as measured by the spatial working memory strategy score. This was unexpected as protective effects of CoQ10 on executive function have previously been reported in PSP (Stamelou et al., 2008). The potentially negative effect was also present in post-hoc analyses including only patients who remained on the same medication throughout the study, though again the difference was no longer significant with adjustment for number of tests. Interestingly, patients who indicated full adherence to the treatment regimen did not exhibit any trend toward decline in executive function at 3 months ($p = .694$) and 6 months ($p = .695$). Further change in strategy score was not correlated with change in plasma CoQ10 levels at either time point from baseline. The potential negative effect may be a spurious finding resulting from practice effects, regression towards the mean, or repeated multiple testing, and for which correcting for family wise error was justified. However, it is also plausible that the apparent decline in executive function in the CoQ10 group may be attributable to factors associated with broader treatment non-adherence such as severity of symptoms, general cognitive dysfunction, or number of medications (Iasevoli et al., 2017). At baseline, participants in the CoQ10 group tended to be prescribed more psychiatric medications than the placebo group. It is known that treatment non-adherence increases with complexity of medication routine (Iasevoli et al., 2017). Thus whether or not participants were adherent to their existing medication regimen prior to entry into the study, the addition of a trice daily regimen may have influenced overall adherence behaviour. Poor adherence to medication is likely to exacerbate psychiatric symptoms, which in turn are associated with impairments in cognitive function, particularly executive functions such as planning, initiation, and flexibility (Zogg et al., 2011). Nonetheless, whether the single trend towards decline in executive function is an artefact due to multiple testing, patient adherence, or natural variation within the data reflecting regression towards the mean, the CoQ10 RCT demonstrated no beneficial effect on cognitive function in schizophrenia and schizoaffective disorder relative to placebo.

There was also no evidence of CoQ10 treatment effect on energy, psychological symptoms, or health related outcomes including functional status, quality of life, physical activity levels, and systolic blood pressure at either 3 months or 6 months. Again these results were generally supported by the secondary subgroup and individual change analyses, with one exception. Physical health appeared to improve in patients who adhered fully to CoQ10 supplementation over 6 months, though whether this potential effect was due to CoQ10 supplementation is unclear as change in CoQ10 concentration was not correlated with change in physical health rating ($p = .760$). CoQ10 treatment also had no effect on lactate levels, nor was there an association between change from baseline in CoQ10 and lactate concentration at 3 or 6 months. Thus it is unlikely that CoQ10 supplementation improves mitochondrial function in schizophrenia and schizoaffective disorder.
As detailed in Chapters 3-5, there were no significant imbalances between the CoQ10 and placebo groups on demographic characteristics, baseline outcome measures, attrition rate or suspected adverse events that may explain the absence of detected effect on the primary and secondary outcomes. As described in Chapters 3-5 confounding introduced by changes to concomitant medication or low adherence to treatment may have reduced estimates of CoQ10 efficacy. However, as outlined above the exploratory subgroup analyses to reduce variability and confounding were generally consistent with principal complete case analyses. It is therefore concluded that CoQ10 supplementation has no effect on cognitive function, energy and psychological symptoms, functional status, quality of life, physical activity, blood pressure, and mitochondrial function.

The following section details potential reasons as to why CoQ10 appears to have no beneficial effect in schizophrenia.

6.2 Potential reasons as to why CoQ10 has no effect in schizophrenia

6.2.1 No evidence of CoQ10 deficit in schizophrenia

Deficiencies in CoQ10 are associated with multiple mitochondrial disorders including Kearns Sayre Syndrome and MELAS, and disorders more broadly associated with mitochondrial or metabolic impairment such as Parkinson’s disease, Huntington’s disease, depression, and cardiovascular disease (Maes et al., 2009; Pieczenik & Neustadt, 2007). In light of this association, the effects of CoQ10 supplementation have been considered in these disorders, as well as other conditions associated with other mitochondrial abnormalities including ALS and bipolar disorder (Kaufmann et al., 2009; Mehrpooya et al., 2018). Some similarities in mitochondrial abnormalities exist between schizophrenia and the aforementioned disorders, in particular ETC complex activity impairments and associated ATP depletion, and elevated oxidative stress, though findings are highly heterogeneous (Dror et al., 2002; Gubert et al., 2013; Holper et al., 2019; Rowland et al., 2016; Somerville et al., 2011). Additionally, mitochondrial disorders such a Kearns Sayre Syndrome and MELAS also present with cognitive impairments, mood disturbances and psychosis, similar to schizophrenia (Anglin et al., 2012; Kraya et al., 2018; Fattal et al., 2006).

Mitochondrial abnormalities have been reported in schizophrenia, particularly dysfunction within the mitochondrial ETC and increased oxidative stress, though the extent to which the abnormalities are present in all individuals, attenuated or exacerbated by medication, or state-dependent remains to be determined (Ben-Shachar, 2017; Do et al., 2009; Dror et al., 2002; Hjelm et al., 2015; Holper et al., 2019; Maas et al., 2017; Rollins et al., 2017; Scaini et al., 2018; Whatley et al., 1996). For example, while complex I activity in the mitochondrial ETC appears to be dysregulated in
schizophrenia, the direction of the dysregulation is highly heterogeneous (Holper et al., 2019). Complex I activity is decreased in patients with residual schizophrenia, but is increased in patients who exhibit active psychosis (Ben-Shachar et al., 2007; Dror et al., 2002; Rosenfeld et al., 2011). Reduced complex I activity may contribute to the manifestation of the cognitive impairments present in schizophrenia, particularly attention, working memory and executive function (Haghighatfard et al., 2018). Notably, a reduction in the function of Disrupted-in-Schizophrenia 1 (DISC1), schizophrenia-susceptibility gene associated with mitochondrial dysfunction including decreased cellular ATP and mitochondrial complex I activity, has also been associated with cognitive symptoms in schizophrenia (Callicott et al., 2005; Park & Park, 2012; Vassos et al., 2010; Zai et al., 2017). Schizophrenia is associated with abnormal markers of oxidative stress in red blood cells, serum, and plasma and disrupted OXPHOS may contribute to this redox imbalance or oxidative stress evident in schizophrenia (Flatow et al., 2013; Maas et al., 2017). For example, in schizophrenia, markers of oxidative damage including thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) are elevated, and increased levels are associated with a decreased complex I activity (Gubert et al., 2013). However, as with complex activity within the ETC, it appears that changes in oxidative stress markers are dependent on clinical status and medication use (Flatow et al., 2013). For example, while patients experiencing acute relapse exhibited significantly decreased red blood cell glutathione peroxidase (an antioxidant enzyme) levels, stable medicated outpatients did not (Flatow et al., 2013). Nonetheless, there is a reasonably substantial evidence base documenting mitochondrial dysfunction in schizophrenia, though more research is required to ascertain the sources and consequences of this dysfunction.

Given the similarities between schizophrenia and mitochondrial disorders, evidence of mitochondrial dysfunction in schizophrenia, and two papers reporting lower CoQ10 concentration in either erythrocytes or serum of patients with schizophrenia compared to controls, low CoQ10 levels in those with a diagnosis of schizophrenia/schizoaffective disorder were anticipated (Imagawa, 1989; Kumar & Karup, 2001). It was hypothesised that CoQ10 supplementation would increase plasma CoQ10 concentration, restore ETC complex activity and ATP generation and reduce oxidative stress, and thereby present as a potential means to improve symptoms.

The results of the CoQ10 RCT suggest the CoQ10 at 300mg/day had no effect on cognitive functions, psychological symptoms or other health related outcomes. This is intriguing as CoQ10 is essential for cellular function, primarily as an electron carrier in the synthesis of ATP energy by the ETC, but also as an antioxidant protecting cellular membranes and plasma lipoproteins against oxidative stress induced damage (Duberley et al., 2014; Hargreaves, 2014; Turenen et al., 2003). Low levels of CoQ10 are likely to contribute to mitochondrial dysfunction and associated disease pathology through reduced antioxidant capacity and impaired ATP generation (Spindler et al., 2009; Duberley et al., 2014). Though CoQ10 can be synthesised in the body, and obtained through the diet, CoQ10 status may decline with age, chronic disease, medications, increased demand or
primary defects in biosynthesis (Zozina et al., 2018). The specific mechanisms that induce such acquired or secondary CoQ10 deficiency are yet to be fully determined (Neergheen et al., 2017; Quinzii et al., 2010). However, it is likely that mitochondrial dysfunction and CoQ10 deficiency hold a reciprocal relationship in which the two are inextricably interlinked (Quinzii et al., 2010). CoQ10 is synthesised in the mitochondrial membrane and oxidative damage to this membrane may impair CoQ10 synthesis (Turunen et al., 2004). Further, CoQ10 deficits increase mitochondrial oxidative stress and reduce activity of complexes I, II + III and IV in the ETC within neuronal cells, thereby impairing ATP generation and further exacerbating oxidative stress and decreasing cellular antioxidant capacity (Duberley et al., 2013; Turunen et al., 2004). Regardless of the absolute mechanisms behind acquired CoQ10 deficiency, lower concentration of CoQ10 likely reflects impaired bioenergetics and increased oxidative stress and may thus be a marker of general mitochondrial impairment (Neergheen et al., 2017). Thus, treatment with CoQ10 may help to preserve mitochondrial function by restoring electron flow to the ETC, increasing complex activity, and improving antioxidant capacity (Chan et al., 2002; Duberley et al., 2013; Duberley et al., 2014; Hargreaves, 2014).

It was hypothesised that CoQ10 supplementation would have beneficial cognitive and clinical effects in patients with schizophrenia through improving mitochondrial function via the restoration of ATP generation and increasing anti-oxidant capacity. Yet this study found no benefit of CoQ10 supplementation. One possible reason for this is that a deficit in CoQ10 was not present in the participants who took part in the study; baseline plasma CoQ10 concentration was at the centre of the CoQ10 reference range ($M$=1.17, $SD$=0.50; reference range: 0.5-1.7 µmol/L). Three patients (5%) exhibited plasma CoQ10 levels below the lower bound of the plasma CoQ10 reference range (< 0.5 µmol/L), only one of whom had been randomised to receive CoQ10. Unfortunately these participants withdrew from the study prior to any follow-up assessment, so it is not possible to determine their outcomes. Interestingly, six participants exhibited elevated plasma CoQ10 concentration prior to treatment (>1.7 µmol/L). This finding was slightly surprising, given prior, but inconsistent, findings of lower CoQ10 levels in patients with schizophrenia compared to healthy controls (Imagawa, 1989; Kumar & Kurup, 2001). However, though CoQ10 levels in erythrocytes (Imagawa, 1989) and serum (Kumar & Karup, 2001) may have been lower in the patient participants of the aforementioned studies, on average serum and plasma levels were within the normal range in both studies. As such though one group may have statistically significant lower levels of CoQ10 than another, the clinical value of the average difference may not be clinically relevant, given inter-individual variability (12%), intra-individual variability (29%) and the wide reference range attached to CoQ10 (Molyneux et al., 2005). Further, baseline plasma CoQ10 concentration was not correlated with any other variable at baseline, including plasma lactate concentration, which was used as a marker of mitochondrial dysfunction. To the author’s knowledge there are no other investigations of the relationship between CoQ10 status and mitochondrial function in schizophrenia. It is possible that CoQ10 supplementation had no
treatment effect, because of the absence of CoQ10 deficiency at baseline in the sample. CoQ10 treatment response may be dependent upon a clear deficit or reliable decrease in CoQ10, rather than mitochondrial impairments such as reduced complex I activity or elevated ROS, and potentially lower, but normal, levels of CoQ10. The mitochondrial impairments noted in schizophrenia likely derive from sources such as changes in the expression of encoding genes or oxidative stress induced by environmental insults antipsychotic medication, rather than definitive CoQ10 deficiency (Ben-Shachar, 2017; Maas et al., 2017). This may also account for the variable treatment effects observed in other patient cohorts (as reviewed in Chapter 1).

Critically, there is a lack of clarity in the literature surrounding CoQ10 status in schizophrenia. For example, though Imagawa (1989) identified lower CoQ10 concentration in erythrocytes of patients compared to controls, there was no difference in plasma levels. However, the utility of erythrocytes for clinical assessment is uncertain (Molyneux, Young et al., 2008). Erythrocytes are highly susceptible to oxidative damage due to their absence of mitochondria and reliance on glycolysis for energy (Di Pierro et al., 2020). It is possible that the difference between patients’ and controls’ CoQ10 levels in the erythrocytes reported by Imagawa (1989) reflects oxidative damage to the cells’ lipid membranes due to increased oxidative stress in patients, as CoQ10 plasma levels were equivalent for patients and controls. Alternatively, while erythrocyte CoQ10 level is entirely dependent on de novo synthesis, plasma CoQ10 level is influenced by dietary intake and lipoprotein concentration (Duncan et al., 2005; Nicklowitz et al., 2004). It is possible that such factors masked a potential deficit in endogenous CoQ10 supply in the patient sample (Duncan et al., 2005). A subsequent study did observe lower serum CoQ10 concentration in patients compared to controls, however as outlined above, on average patient samples were within the normal reference range (Kumar & Kurup, 2001). Importantly, there appear to be no studies investigating associations between CoQ10 levels and cognitive, clinical and functional measures in schizophrenia. As such, conducting an RCT of CoQ10 supplementation in schizophrenia in the absence of consistent, robust evidence of CoQ10 status in the disorder may have been premature. Further research investigating CoQ10 status in schizophrenia and its relationship to meaningful outcomes is warranted, given the limited number of studies and inconsistent findings and methods on the topic (Imagawa, 1989; Kumar & Kurup, 2001).

In primary CoQ10 deficiency, high-dose CoQ10 therapy can be clinically beneficial if administered early in the disease course (Molyneux, Young, et al., 2008). The clinical effects of CoQ10 therapy in secondary CoQ10 deficiency and mitochondrial disorders on the other hand are inconsistent. One potential reason for this is that response to CoQ10 may be dependent on pre-therapy CoQ10 status (Chan et al., 1998; Montero et al., 2013; Sacconi et al., 2010). It is possible that only patients who exhibit CoQ10 deficiency will benefit clinically, as CoQ10 supplementation may compensate for deficit CoQ10 in tissues and restore ETC complex activity (Neergheen et al., 2017). This argument derives from both in vitro and clinical evidence. When treated with CoQ10, fibroblasts
from a CoQ10 deficient patient grew four times more than fibroblasts from non-CoQ10 deficient healthy controls (Montero et al., 2009). The increased growth in CoQ10 deficit fibroblasts is likely due to normalising ETC activity and bioenergetics status, which are normal within healthy individuals (López et al., 2010; Montero et al., 2009). Clinically, though mitochondrial patients with CoQ10 deficiency tend to benefit from CoQ10 supplementation, mitochondrial patients with normal CoQ10 status tend not to respond to CoQ10 intervention (Sacconi et al., 2010).

Likewise, in non-mitochondrial disorders, CoQ10 deficiency appears to predict clinical response to CoQ10 supplementation. For example, there is meta-analytical evidence that CoQ10 supplementation reduces mortality and increases exercise capacity in patients with cardiac failure (Lei & Liu, 2017). Plasma CoQ10 concentration is a predictor of death in cardiac failure, and the deficiency is likely the result of aging; myocardium production of CoQ10 is more than halved by the age of 80 (Kalén et al., 1989; Molyneux, Florkowski, et al., 2008). Further, decreases in CoQ10 concentration are relative to the severity of disease status (Kumar et al., 2009). It is likely that CoQ10 supplementation replenishes CoQ10 supply, thereby improving myocardium energy generation and preventing further ROS induced hypertrophy (Zozina et al., 2018). Recent work also supports the use of adjuvant CoQ10 in relapsing-remitting multiple sclerosis to alleviate fatigue and depression (Sanoober et al., 2015; Moccia et al., 2019). The clinical response co-occurred with a reduction in markers of inflammation and oxidative stress, potentially in response to the restoration of depleted CoQ10 (Gironi et al., 2014).

However, in other disorders associated with CoQ10 deficits the results are less robust, again supporting the premise that response to supplementation is dependent on baseline CoQ10 status. Initially promising findings that CoQ10 supplementation may have protective effects against functional decline in Parkinson’s disease and Huntington’s disease were subsequently refuted by larger RCTs (Beal et al., 2014; McGarry et al., 2017; Müller et al., 2003; Storch et al., 2007). The discrepancy in results may be related to initial CoQ10 status in treated patients; average baseline plasma CoQ10 concentrations were within a normal range in the larger RCTs. However it is also possible that the oxidative damage and previously reported CoQ10 deficiency observed in these disorders is secondary to degenerative pathways in the diseases rather than the primary source of impairment (Beal et al., 2014). In populations with no known CoQ10 deficit, there appear to be minimal if any therapeutic effects of CoQ10 supplementation. For example, in an adaptive, two-stage RCT in ALS, though the initial dose escalation phase reported potentially protective effects of high-dose CoQ10 (2,700mg/day) against functional decline, the subsequent efficacy phase II RCT found no effect of CoQ10 on functional outcomes, fatigue or quality of life (Kaufmann et al., 2009). There was no evidence of CoQ10 deficiency at baseline in the study sample, and the potential superiority of high-dose CoQ10 was likely driven by outliers for deceased patients (Kaufmann et al., 2009). In another RCT, of breast-cancer related fatigue, no effect of CoQ10 (300mg/day) was observed on fatigue severity, depression or quality of life, despite increases in
plasma CoQ10 over 24 weeks (Lesser et al., 2013). Though a subgroup of the sample exhibited lower levels of CoQ10 concentration, on average the CoQ10 concentration was within normal limits, and the absence of treatment effect may reflect this. Further, the majority of studies of CoQ10 supplementation on exercise performance in healthy adults found no performance enhancing or post-exercise fatigue reducing effects, despite some reductions in plasma lactate and pyruvate concentration post-exercise (Cooke et al., 2008; Östman et al., 2012; Sarmiento et al., 2016). Cells with sufficient CoQ10 cannot absorb exogenous CoQ10 due to normal saturation in the inner mitochondrial membrane (Turunen et al., 2003). It is therefore unlikely that CoQ10 supplementation will induce robust clinical effects in subjects with no pre-existing CoQ10 deficit.

However, beneficial effects of CoQ10 supplementation on severity of depression have been reported in bipolar disorder, which has no established CoQ10 deficit (Forester et al., 2012; Mehrpooya et al., 2018). To the author’s knowledge there has been no published work documenting CoQ10 status in bipolar disorder. Despite the absence of evidence for CoQ10 deficiency in the disorder, CoQ10 may have conferred therapeutic benefit by enhancing antioxidant capacity and subsequently reducing lipid peroxidation and the expression of pro-inflammatory cytokines (Jahangard et al., 2019). Unfortunately, neither the RCT nor the open-label study reported measuring CoQ10 status in their sample prior to or during treatment. As such it is not possible to entirely dismiss the absence of baseline CoQ10 deficiency within the samples. It was noted that the bipolar study samples exhibited high levels of depression at baseline. Plasma CoQ10 deficit has previously been detected in treatment resistant major depressive disorder and the severity of depression was directly correlated with extent of CoQ10 deficit (Maes et al., 2009). Further, decreased ETC activity in blood mononuclear cells is correlated with severity of depression, and it is hypothesised that the decline in ETC activity originates from reduced availability of coenzymes (Fišar et al., 2019; Hroudová et al., 2013; Karabatsiakis et al., 2014; Maes et al., 2009). As such, given evidence of CoQ10 deficit in major depressive disorder it remains plausible that a CoQ10 deficit was present in both samples. The beneficial effect of CoQ10 supplementation on depression may have been in response to restored CoQ10 status.

The patients within this study however, on average, did not present low levels of CoQ10 at baseline. Further, CoQ10 status was not correlated with any outcome variable at baseline. Thus it remains highly probable that the absence of treatment effect in the current study was due to normal CoQ10 status at baseline. This CoQ10 supplementation may be more effective in patients with CoQ10 deficiency.
6.2.2 Neuroprotective properties of CoQ10

Given the multifaceted role CoQ10 plays in supporting mitochondrial bioenergetics and enhancing mitochondrial and cellular anti-oxidant capacity, it was hypothesised that adjuvant CoQ10 would have therapeutic effects in schizophrenia. However there was no evidence of cognitive, clinical or mitochondrial benefit. While it is possible that the absence of effect may be the result of an absence of CoQ10 deficiency, an alternative explanation is that the extent of neural damage induced by oxidative stress is simply too severe to repair with adjuvant CoQ10 (Ammal Kaidery & Thomas, 2018; Murphy & Hartley, 2018). While there is limited in vitro evidence that CoQ10 administration can enhance myelination, to the author’s knowledge this effect has yet to be demonstrated in human cells (Hyung et al., 2015). It is probable that the therapeutic effects seen with CoQ10 supplementation are restricted to neuroprotection by inhibiting the formation of lipid-peroxyl radicals and inhibiting further oxidative damage and restoring mitochondrial energy supply, rather than stimulating neuronal growth and repair (Ammal Kaidery & Thomas, 2018; Długosz et al., 2005).

Most reported cases of CoQ10 deficiency in childhood have been fatal when untreated (Kwong et al., 2019; Rahman et al., 2012). However, CoQ10 therapy can fundamentally influence disease outcomes and progression in primary CoQ10 deficiency (Artuch et al., 2006; Eroglu et al., 2018; Haas, 2007). Unfortunately, the extent of clinical response is largely dependent on the genetic mutation causing deficiency, the location of deficiency and severity of symptoms (Emmanuelle et al., 2012; Eroglu et al., 2018). Generally, muscular symptoms and renal dysfunction are most responsive to treatment while neurological symptoms tend to be refractory (Artuch et al., 2006; Emmanuelle et al., 2012; Hargreaves, 2014; Neergheen et al., 2017). One possible explanation for the variability in symptom response to treatment is that irreversible neurological damage may occur prior to treatment (Auré et al., 2004; Eroglu et al., 2018; Quinzii et al., 2007; Sacconi et al., 2010). Neuronal cells may be more sensitive to CoQ10 deficiency than those in muscular tissues (Eroglu et al., 2018). Small deficits of CoQ10 induce reductions in ETC activity, increase oxidative stress and damage mitochondrial DNA within neuronal cells (Duberley et al., 2014). Thus while CoQ10 supplementation inhibits subsequent oxidative damage and supports ETC activity, it is unlikely to have a reparative effect on damage within the central nervous system. This may also account for the absence of effect in the current study, particularly on cognition.

Schizophrenia is a neurodevelopmental disorder in which cognitive impairments are a reliable and enduring feature, and are associated with reduced white matter integrity (Maas et al., 2017). Oligodendrocytes are particularly vulnerable to oxidative stress due to their increased metabolic rate and decreased antioxidant status (Do et al., 2015; Maas et al., 2017). Cognitive impairments in schizophrenia are associated with the consequential hypomyelination and reduced brain connectivity (Griffa et al., 2019; Maas et al., 2017). Such abnormalities may occur prior to onset of schizophrenia, and are likely exacerbated with illness course (Maas et al., 2017; Do et al., 2015).
CoQ10 may protect against further oxidative stress, and long-term administration early in the illness course may have beneficial protective effects. However, there was no evidence that CoQ10 supplementation restores cognitive function or ameliorates fatigue or psychological symptoms in chronic schizophrenia. It is likely that the damage induced by chronic oxidative stress and related inflammation is too severe to be treated with CoQ10 (Murphy & Hartley, 2018). Nonetheless, the absence of CoQ10 deficit within the sample remains the most plausible explanation for the non-significant findings across both clinical and cognitive symptoms. However there are several alternative explanations for the non-significant findings that relate to limitations within the study which must be addressed. The following section will discuss these.

6.3 Limitations within the study

6.3.1 Sample size

A major limitation of the CoQ10 RCT is the limited sample size as a result of recruitment and retention difficulties. As detailed in Chapter 3, though the recruitment target was 300 participants, only 70 participants were randomised. As a result, the CoQ10 RCT did not have sufficient power to detect the anticipated small to moderate effect of CoQ10 on the primary outcomes of attention and working memory (Chapter 4). As is traditional with clinical trials, sample size was not calculated for the secondary outcomes (Mariano et al., 2007). Additionally, there was a large attrition rate of 34% from the study by 6 months; further reducing power to detect an effect of CoQ10. The potential consequences that the recruitment and retention challenges hold for interpretation of results are further discussed in Section 6.3.2. Despite the final sample size, post-hoc (observed) power analyses were not conducted. Observed power is conditional upon the effect size present within the collected data, and may not reflect the true effect (if one exists) within the population (Hoenig & Heisey, 2001; Lenth, 2007). Nonetheless, a larger study may have provided increased certainty surrounding the effects of CoQ10 in schizophrenia.

However, null hypothesis statistical testing (NHST) is heavily dependent on sample size and homogeneity within that sample. Large trials may detect statistically significant treatment effects, but the clinical significance of that effect may be negligible and generally restricted to the average patient with similar characteristics to those enrolled in the trial (Barlow & Nock, 2009; Black et al., 2019). However more idiographic approaches including determining responders give further insight into treatment effect and its clinical meaning, even in small samples (Barlow & Nock, 2009; Black et al., 2019). Within the current study the between group differences at 3 and 6 months were small and confidence intervals were large (Chapters 4 & 5). Increasing the sample size would have reduced the standard error and thereby confidence intervals and likelihood of determining whether the between group difference noted in each analysis was statistically significant. However the clinical relevance of the non-significant between group differences for patients was unknown.
As such, despite the overall non-significant results within the CoQ10 RCT, individual response to CoQ10/placebo was determined on each cognitive, psychological and health-related outcome variable. This allowed this study to consider whether the absence of detected effect was primarily due to low power for which a larger trial may still be justified, if sufficient meaningful changes occurred. However, though clinically significant, reliable and minimal clinically important changes from baseline to endpoint across the variables in individuals were identified, the number needed to treat for each outcome was high. As responders were present in both groups across the variables it is more likely that the individual changes are a reflection of practice and placebo effects than a treatment effect of CoQ10 (Keefe et al., 2017). Thus, within the current sample, with the current study design, despite the limitation of sample size it appears that CoQ10 had no meaningful clinical effect. Though, as is the case with all RCTs a different sample may have yielded different results.

6.3.2 Representativeness of sample

Self-selection of patients to the study may have influenced both recruitment and limit the generalisability of the results. Illness severity, problems with concentration, low self-efficacy and low motivation have frequently been reported as barriers to recruitment in mental health trials (Hughes-Morley et al., 2015; Kaminsky et al., 2003; Roberts et al., 2005). Patients who enrolled in CoQ10 RCT had generally mild to moderate psychological and clinical symptoms at baseline. Less well patients with more severe negative symptoms may have been less motivated to participate in the study. As a consequence, patients who enrolled may not have been the most clinically representative of the patient population.

Therefore, a proportion of patients who could have responded differently to CoQ10 supplementation may have been missed; given the low levels of negative symptoms within the randomised sample. As detailed in Chapter 5, there was a small trend in the data at baseline between higher lactate concentration (indicating poorer mitochondrial function) and increased avolition. This relationship is consistent with previous work in schizophrenia (Rowland et al., 2016; Sullivan et al., 2018). Others have observed that impairments in mitochondrial energetics, specifically elevated lactate, may only be present within a portion of patients, highlighting the considerable heterogeneity in the pathophysiology of schizophrenia (Regenold et al., 2016). Such variation may also relate to the substantial variation in the range and severity of cognitive impairments and symptoms in schizophrenia; some patients exhibit no to minimal cognitive difficulties whereas others exhibit global deficits (Bosia et al., 2019). Thus despite the non-significant findings of the RCT, a subgroup of patients with schizophrenia who exhibit greater mitochondrial impairment may have responded differently to CoQ10. Unfortunately, participants who withdrew from the study tended to have increased lactate concentration compared to controls, and four out of eight patients with elevated lactate at baseline withdrew from the study. In the CoQ10 group, only one participant with elevated lactate at baseline remained on the study. The selective nature of both enrolment and attrition during CoQ10 RCT will have influenced the
generalisability of the results, as it is not possible to determine whether CoQ10 may have affected this sub-cohort differently to the final sample (Karlson & Rapoff, 2009).

6.3.3 Determining CoQ10 status

A further limitation of the study relates to measurement of CoQ10 status. Plasma CoQ10 concentration is usually used to assess CoQ10 deficiency and monitor absorption and bioavailability of CoQ10 during treatment (Yubero et al., 2014). However, there is considerable intra-individual variation in plasma CoQ10 concentration. CoQ10 is a lipid soluble compound that is mainly absorbed slowly in the small intestine, and absorption is aided when ingested with a fatty meal (Bhavagan & Chopra, 2006). Six hours after administration plasma CoQ10 concentration reaches its maximum peak, with a second, smaller, peak occurring 18 hours later after enterohepatic recycling (Yubero et al., 2014; Neergheen et al., 2017). Thus plasma CoQ10 concentration is heavily influenced by diet and gastrointestinal and liver functioning (Yubero et al., 2014; Bhavagan & Chopra, 2006). There can therefore be considerable intra-individual variation in plasma CoQ10 status which may account for the large standard errors within the CoQ10 analyses. A more accurate measure of CoQ10 plasma concentration may also have been obtained from fasting plasma samples (Bhavagan & Chopra, 2006), though this was unreasonable given the duration of cognitive and neuropsychological assessment. A related limitation is that outcome assessment visits were not timed to account for optimum peaks in plasma CoQ10 with supplementation. Dietary intake of CoQ10 rich foods such as meat and fish in the preceding 24 hours was also not recorded. Such variations are likely to have influenced the plasma concentrations recorded during the study and may account for some of the intra-individual fluctuations in CoQ10 status that were even observed within participants in the placebo group. The most reliable measure of CoQ10 status is via muscle biopsy however blood mononuclear cells (BMCs) may provide a better approximation to muscle CoQ10 concentration (Duncan et al, 2005). Future studies may consider evaluating BMCs for a more accurate determination of CoQ10 status in patients with a diagnosis of schizophrenia or schizoaffective disorder.

6.3.4 Adherence to CoQ10

Finally, there was no difference in plasma CoQ10 status at 6 months between the two treatment groups. While intra-individual variability may account for some discrepancies, it is also possible that participants became less treatment adherent as the study progressed, despite 61% indicating full adherence at 6 months. However, pill count and patient self-report can be inaccurate indications of adherence; they are both subject to social desirability and response biases (McCann et al., 2015). Further, deviations from the treatment regime, such as taking more than one capsule at a time or without food, which would influence CoQ10 absorption, were not recorded or accounted for. Thus, in some cases adherence to assigned intervention may have been over-estimated. Immediacy of treatment response and belief in medication effects are predictors of adherence behaviour in schizophrenia and enduring mental illness (García et al., 2016; Higashi et al., 2013).
Thus the absence of statistically significant treatment effect within the sample may be both a cause and consequence of adherence behaviour. Nonetheless, non-adherence to treatment is frequent occurrence in outpatient populations with schizophrenia and other enduring mental illnesses. As such, though power to detect a significant effect may be reduced due to increased and artificial variability, the overall findings may be more generalizable to routine care.

6.4 Contributions of this research

To the author’s knowledge this is the third and largest study to examine CoQ10 status in schizophrenia and the first intervention study of CoQ10 supplementation in the disorder. Though Imagawa (1989) reported lower levels of CoQ10 concentration in erythrocytes in patients compared to healthy controls, there was no between group difference in plasma concentration. A subsequent smaller study reported that patients with a diagnosis of schizophrenia had lower plasma CoQ10 levels than aged matched controls (Kumar & Kurup, 2001). Further in both studies CoQ10 plasma levels appeared on average to be within the normal expected range (Molyneux, Young et al., 2008). As such though the aforementioned limitations to determining CoQ10 concentration via plasma exist, it does appear that on average CoQ10 status in patients with schizophrenia and schizoaffective disorder is within normal limits.

Despite the multiple limitations and methodological events that occurred during this RCT, the study demonstrated that CoQ10 supplementation at 300mg/day is safe and well-tolerated in patients with schizophrenia and schizoaffective disorder. However, it also demonstrated that while CoQ10 supplementation over 3 months does increase plasma CoQ10 concentration, this increase in CoQ10 status did not translate to clinical and cognitive effects. It is likely that the non-significant findings are due to the absence of baseline CoQ10 deficit within the sample. I therefore postulate that CoQ10 supplementation may only be beneficial in patients (regardless of clinical diagnosis) that exhibit CoQ10 deficiency.

While it may be argued that the use of multiple outcomes increases the risk of Type 2 error, as a first investigation of the effects of CoQ10 in schizophrenia it was highly valuable to consider its effects on a variety of clinically and functionally relevant outcomes in the disorder. Each of the cognitive, psychological and health-related outcomes has been deemed clinically important to patients (Chapter 1). Had a trend of effect in favour of CoQ10 been observed, subsequent studies may then have focused on specific outcomes that appeared responsive to adjuvant CoQ10. However, there was generally no trend towards cognitive or clinical benefit of CoQ10 across outcomes. It is not possible to discount that CoQ10 may have a positive, supportive effect for the quality of life domains of physical health and psychological functioning (Chapter 5). However, the value of the potential effect on physical health and psychological functioning would require investigation prior to conducting any additional trials of CoQ10. While the estimated cost for 6
months of CoQ10 supplementation (300mg) for one person is approximately €170 (BNF-C, 2018),
the remaining costs attached to conducting and monitoring a RCT are immense. As such, the
feasibility of conducting a larger, double-blind, randomised, placebo-controlled trial is unlikely
given “over the counter availability” of CoQ10 (Haas, 2007). Therefore, though obtained from a
limited sample, the findings are sufficiently comprehensive to suggest that CoQ10 is unlikely to be
beneficial for many patients living with schizophrenia and schizoaffective disorder.

6.5 Implications for research, practice, and policy

6.5.1 Implications for research

Overall the findings in this thesis demonstrate that CoQ10 supplementation has no effect on
cognitive function, psychological symptoms, health-related outcomes or mitochondrial function in
schizophrenia and schizoaffective disorder. The absence of treatment effect was most likely due to
the normal CoQ10 levels within the sample. Determining CoQ10 levels within the target
population prior to examining the effects of CoQ10 supplementation is recommended to prevent
ineffective supplementation. Those planning intervention studies of other nutritional supplements
including vitamins and minerals could also consider this finding in the context of the
investigational supplement.

The findings suggest that on average CoQ10 status in patients with schizophrenia and
schizoaffective disorder is within normal limits. This is consistent with the only two other
published studies on the topic (Imagawa, 1989; Kumar & Kurup, 2001). No relationship between
CoQ10 levels and cognitive, psychological symptom, or health-related outcomes was found.
Critically there was no association between CoQ10 levels and mitochondrial function within the
sample. Establishing a stronger evidence base between CoQ10 status, mitochondrial function and
relevant clinical or functional outcomes in schizophrenia with the use of cross-sectional and
longitudinal study designs is required prior to conducting further intervention studies of CoQ10 in
schizophrenia.

The CoQ10 RCT used 20 outcome measure tasks and scales, some of which contained more than
one outcome score. These outcome measures were selected due to their relevance within the
research literature. However, the large assessment battery appeared to act as a barrier to recruitment
and retention; the outcomes may have been considered relevant in the literature, but in practice may
have been burdensome or irrelevant to research candidates and participants. Selecting outcomes
relevant to key stakeholders is important for the successful conduct of an intervention trial, and the
subsequent implications of the findings. If a trial’s findings are to inform clinical practice and
policy, the outcomes must be relevant to all stakeholders, including care commissioners, and easily
synthesised into the existing evidence base (Williamson et al., 2012). However, a survey of 10,000
controlled trials in schizophrenia recorded that 2,194 different outcome measure scales were used,
many of which were developed by researchers for research (Miyar & Adams, 2013). Such scales often have little meaning or relevance for stakeholders such as people with schizophrenia, their personal support networks and clinicians (Miyar & Adam, 2013). Further, this degree of heterogeneity makes evidence synthesis a challenge (Williamson et al., 2012). However, currently there is little guidance in the literature surrounding the most relevant and credible outcomes for use in RCTs in schizophrenia research. Core outcome sets are developed in collaboration with key stakeholders including patients, care givers, healthcare professionals and commissioners, and establish the minimum outcomes that must be measured and reported in trials within a research area (Williamson et al., 2012). These outcomes are necessary, meaningful and relevant to stakeholders. One such outcome set is currently being developed for effectiveness trials involving patients with schizophrenia, managed in a community setting (Keeley et al., 2015).

The estimated sample population size was obtained based on point-prevalence estimates of schizophrenia and the catchment area population for each mental health service. Obtaining more accurate appraisals for the number of potentially eligible research candidates within each clinical team/site will be important for future trials to accurately determine the number recruitment sites required a-priori. Active monitoring of the recruitment rate during the study allowed the research team to make informed decisions about the recruitment period and available or required resources. Maintaining accurate records of weekly and monthly recruitment highlighted that the recruitment window and recruitment sites would need to have been considerably extended in order to meet the required sample size.

Increased clinician involvement in the research process is likely to positively facilitate recruitment during RCTs. Recognising difficulties in engaging clinical teams during study design may identify issues with clinical equipoise, study design, or ethical concerns in advance which may be addressed prior to finalising the protocol.

Research has begun to identify enablers to successful recruitment to clinical trials, though more work is required in mental health, particularly severe mental illness. The literature remains limited with regard to identifying barriers to recruitment to trials involving people with mental illness. More research is required to identify and test interventions to improve recruitment to trials in schizophrenia and other enduring mental illnesses. One avenue of increasing focus is the impact that service-user involvement in trial design and conduct may hold for recruitment (Ennis & Wykes, 2013). Interventions to test the impact may include explicit communication of service user involvement in trial design and conduct, and engaging service users to directly recruit to the study (Crocker et al., 2018; Vat et al., 2017). Knowing other service users enrolled on the CoQ10 RCT appeared to help others choose to enrol on the study. However in efforts to examine such interventions it will also be critical to mindful of “role confusion” and avoid “tokenistic participatory efforts” (Friesen et al., 2019).
6.5.2 Implications for practice

One barrier to recruitment to the CoQ10 RCT appears to have occurred at the level of identification of potential research candidates. While the number of potentially eligible research candidates within the three mental health services may have been overestimated, it also likely that a large proportion were never approached to participate in the research. Both organisational and clinical factors including staff shortages, restricted access to current case lists containing diagnostic information, and selective referral may have contributed to this element of ascertainment. Directly or indirectly excluding people from choosing to participate however has consequences for the representativeness of the findings and risks research waste. Services could consider introducing a “consent to be contacted” system for research. This may help reduce the burden of ascertainment on clinical teams during periods of high caseload intensity and complexity (Pinfold et al., 2019).

Despite potentially missing a proportion of eligible research candidate, the positive-research culture within the majority of clinical sites positively facilitated recruitment to the RCT. Clinical team leads within the services were agreeable to researchers attending clinics for recruitment, meeting service staff, and service staff expressed an interest in study progress, outcomes and outputs. The pro-research environment was likely advantageous, as others frequently cite poor knowledge surrounding research methods and trials within clinical teams as a barrier to recruitment for RCTs (Borschmann et al., 2014; Briel et al., 2016; Patterson et al., 2014). Providing relevant materials and information sessions to clinical teams to increase awareness of and knowledge surrounding clinical research methods and findings may help facilitate research within clinical sites.

Service users appeared to be more willing to discuss the CoQ10 RCT and enrol on the study when referred by supportive and trusted clinicians. Engaging specific clinical team members to champion the trial within the services may help to integrate clinical research into clinical practice, potentially leading to more representative samples (Peckham et al., 2018).

6.5.3 Implications for policy

Recruitment to clinical trials requires clinician referral of potential participants. However, this approach is time consuming and resources intense. In mental health services experiencing increasing caseloads and limited resources, allocating time to discuss research with service users may be a low priority. Providing protected time within mental health services to engage in research activity will enhance trial recruitment. Resource allocation will be necessary to support this and changes at an overall policy level will be required prior to service or culture change.

One key insight from the CoQ10 RCT is that taking CoQ10 may be largely unnecessary in the absence of clinical deficiency, regardless of clinical diagnosis (for example schizophrenia or schizoaffective disorder). Dietary supplementation may hold benefits in those with reduced ability to synthesise or absorb the antioxidant, however within the general population the use of supplementation should be rationalised and reviewed.
6.6 Summary and final remarks

There is considerable evidence that mitochondrial dysfunction is present in patients with schizophrenia and schizoaffective disorder, and this dysfunction is implicated in the manifestation of cognitive impairment and clinical symptoms. CoQ10 can be taken as a nutritional supplement with minimal side effects to target mitochondrial dysfunction via promoting ATP generation and increasing anti-oxidant capacity. However there was no effect of CoQ10 supplementation (300mg/day) on cognition, energy, psychological symptoms, quality of life, functional status, physical activity and blood pressure. Importantly there was no effect on mitochondrial function. However, there may be a subgroup of participants who exhibit greater mitochondrial dysfunction, CoQ10 deficits, and more severe symptoms. A larger investigation of CoQ10 status in schizophrenia may be warranted to consider whether a subgroup of patients exhibiting CoQ10 deficits does exist, who may respond differently to CoQ10 augmentation. The potential of CoQ10 supplementation as a protective agent against exacerbated oxidative stress in clinical high risk populations may also warrant consideration. Finally, though challenges such as changes to concomitant outpatient medication and treatment non-adherence occurred during the study, these are routine events in outpatient populations with enduring mental illness. Thus, the results of the RCT are ecologically valid, and translatable to a community setting.
REFERENCES


Bland, J. M., & Altman, D. G. (2011). Comparisons against baseline within randomised groups are often used and can be highly misleading. *Trials*, 12(1), 264.


Herken, H., Uz, E., Özyurt, H., Söğüt, S., Virit, O., & Akyol, Ö. (2001). Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia. *Molecular Psychiatry, 6*(1), 66–73.


Neuropsychopharmacology, 33(11), 2551–2565. https://doi.org/10.1038/sj.npp.1301671


Appendix A: Ethics approval letters

Dr. April Hargreaves
Research Fellow
Dept. of Psychiatry
St James’s Hospital
James’s Gate
Dublin 8

11th April 2016

Re: A randomised controlled trial of CoQ10 in patients with schizophrenia

REC Reference: 2016-04 List 15 (2)
(Please quote reference on all correspondence)

Dear Dr. Hargreaves,

Thank you for your recent correspondence in which you responded to the conditions as requested by SJH/AMNCH Research Ethics Committee.

The Chairman of the Committee, Dr. Peter Lavin, has reviewed this correspondence, is satisfied with the responses and supporting documentation therein and advises that full ethical approval is now in place for this study.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is conducted in accordance with the European Community (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.
To Dr April Hargreaves TCD

23 March 2018

Research project: 2. A randomised controlled trial of CoQ10 in patients with schizophrenia
Dr April Hargreaves TCD

Dear Dr Hargreaves,

The Ethics Committee at Newcastle Hospital liaised today to consider your proposal subsequent to your responses to various queries.

We are now pleased to approve the study.

I will post you a written copy of this decision.

Best wishes

Yours Sincerely

Marjorie Stokes

Coordinator Ethics Committee

Marjorie Stokes MCRN 09126 MB MPH MRCPsych
COQ10 in the amelioration of cognitive deficits and symptoms in schizophrenia and schizoaffective disorder

Research participant information

Principal Investigator: Prof Michael Gill
Researcher: Aine Maguire  afmaguir@tcd.ie  085 7885147

COQ10 is an enzyme (similar to a vitamin) that is important for making energy in our bodies. It is found in all cells in our bodies called the mitochondria. Mitochondria make energy for the cell. There is some evidence that COQ10 helps certain people with fatigue, depression, anxiety, memory and attention. We want to see if it will do the same for people with schizophrenia and schizoaffective disorder.

To test this, we are conducting a study in which we compare people who take COQ10 with people who do not. We hope it helps with these deficits and symptoms. COQ10 is very safe, but it can cause some side effects such as skin rash, nausea and low blood pressure. It is also not suitable for people who are taking warfarin or have thyroid problems.

As you have come to our service because of concerns about your mental health, you may be a person who could benefit from COQ10. We would like to invite you to participate in our study. This would mean taking COQ10 supplements, in the form of 3 capsules every day for 6 months. Some of these supplements would contain COQ10 and some would not. At the end of the study we would compare how people did with or without COQ10. The COQ10 supplements are provided by a pharmaceutical company called Pharma Nord, who is externally supporting this study.

The study would involve an interview and questionnaires, which could take a couple of hours. This is done at three separate times: at the beginning of the study, at 3 months and at 6 months.

We would also wish to take a blood sample, in a bottle that contains between 6 and 7 teaspoons of blood, or 6-7 ml. This would be done at the same times as the interview and questionnaires: at the beginning of the study, at 3 months and at 6 months. The blood test, like any blood test, may cause some bruising at the site of the vein puncture, inflammation of the vein and possibly infection. Care will be taken to avoid these complications. We would like to keep the blood sample after the trial so we can run genetics testing to see if some people might benefit more from taking COQ10 than others based on differences in their genes. We would also like to use the genetic data to test for the genetic cause of schizophrenia. Allow your blood to be used for genetic testing is entirely optional. You can still take part in the study without giving consent to this.

The information we receive from you and your blood results will be encoded and anonymised so that it is kept confidential, and added to information we receive from other people in the study. We will use this to see if there are differences overall between those who receive COQ10 and those who do not. If the study finds that COQ10 is good at helping to reduce mental illness, then it would be something we could give to people in the future.

CoQ10 Study – Patient information leaflet – [V1.1 / 14/08/2018]
CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH PROTOCOL

Section A

Title of Protocol: CoQ10 in the amelioration of cognitive deficits and symptoms in schizophrenia and schizoaffective disorders.

Principal Investigator: Prof Michael Gill
Researcher: Aine Maguire
Email: aimaguir@tcd.ie

You are being asked to participate in a research study. The doctors at Trinity College Dublin study the nature of disease and attempt to develop improved methods of diagnosis and treatment. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form (yes) to agree to participate.

Section B

1. NATURE AND DURATION OF PROCEDURE:
Co-enzyme Q10 (CoQ10) is an enzyme (like a vitamin) that is important for energy production in our bodies. There is some evidence that it may also help to improve the memory and attentional deficits, fatigue, and depressive and anxiety symptoms experienced by many patients with schizophrenia and schizoaffective disorder. However, there is not enough research to prove that this is true. We are conducting a study in which we compare people who take CoQ10 with people who do not, to see if it helps with these deficits and symptoms.

We would like to invite you to be involved in our study. This would mean taking a 120 capsule 60mg supplement (which we would supply) 3 times a day for 12 months. Some of these capsules would contain CoQ10 and some would not. As the capsules all look identical you would not be aware of which one you were taking. At the end of the study we would compare how people did with or without the CoQ10.

The study would involve an interview, a psychological assessment, questionnaires, a measurement of your blood pressure and a blood sample. All of which could take a couple of hours. We would meet you at three time points in the start of the study, at 3 months and at 6 months.

II. POTENTIAL RISKS AND BENEFITS:
CoQ10 has potential health benefits for the cardiovascular system (the heart and blood system), headaches and fatigue. It has also been linked to benefits for depressive symptoms. If the study finds that CoQ10 is good at reducing the symptoms associated with schizophrenia and schizoaffective disorder than it would be something we could give to people in the future. CoQ10 is very safe, but it can cause some side effects such as skin rash, nausea and low blood pressure. It is also unreliable for people who are taking warfarin or have thyroid problems.

The information we receive from you will be anonymised and added to information we receive from other people in the study. We will then use this to see if there are differences overall between those who receive CoQ10 and those who do not.

Participation in this study is entirely voluntary and will not prevent you from receiving other kinds of treatment such as talking therapies or occupational support. If you become unwell and require medication, you will leave the trial and receive the necessary treatment.

Section C

1. REQUEST FOR BLOOD SPECIMEN:
As part of this study, we would also like to take a blood sample, in two bottles that contain between 7 and 10 teaspoons of blood, at three time points: beginning of the study, at 3 months and at 6 months. We would keep the blood sample after the trial to enable us to compare the amounts of CoQ10 (and similar substances) in the blood of people who receive CoQ10 supplements with those who do not.

II. POTENTIAL RISKS AND BENEFITS:
The blood test may carry some risk, such as bleeding at the site of the vein puncture, infection of the vein, and possibly infection. Care will be taken to avoid these complications.

Any information we receive from you or your blood specimen will be anonymised and added to information we receive from other people in the study. We will then use this to see if there are differences overall between those who receive CoQ10 and those who do not.

Participation in this study is entirely voluntary and will not prevent you from receiving other kinds of treatment such as talking therapies or occupational support.

Section D

Access to Medical records

As part of this study we would like to gain access to your medical records to ensure that there are no medical reasons preventing you from taking CoQ10. To agree to access of your medical records please tick the box below.

I give permission for Aine Maguire, or a person acting on her behalf, to gain access to my medical records for the purpose of this study.

Section E

AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. All experimental procedures have been identified and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning any all aspects of the project and any procedure involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies or sponsors of the research.

I hereby declare, hereby consent to participate as a subject in the above described project conducted at St James’s Hospital Clinical Research Facility. I understand that if I have any questions concerning this research, I can contact the person(s) listed above. If I have further questions concerning my rights in connection with the research, I can contact the Research Ethics Committee of the AMHCP and St James’s Hospital.

After reading the entire consent form, if you have no further questions about giving consent, please sign where indicated.

Signature of Subject Parent or Guardian

Date

Signature of Researcher

Date

CoQ10 Study – Letter of consent – [V1.1] 14/08/2018
Appendix C: Recruitment: Study within a trial documentation

Dr. Peter Louis
Tallaght St. James’s Ethics committee
Tallaght Hospital
Dublin 24


A randomized controlled trial of CBT10 in patients with schizophrenia

Dear Dr Louis

With regard to the above study which received full ethical approval from the LH/MNCH Research Ethics Committee on 1/04/2016, and subsequent approval for minor alterations on 27/01/2016 and 23/03/2017, we wish to request Clar’s approval for two minor alterations and the consequential amending of sections C.1.2 and C.2.1 and alteration to section C.2.16.

1) To improve recruitment to the CBT10 study we request permission to send a pre-information letter to potentially eligible participants who have already been identified by their treating team. This letter will explain the study to voluntary (see attachment). This letter will be signed by a member of the treating team. The letter will not replace the existing information sheet. As a Study Within a Trial (SWAT) we propose to randomise potentially eligible participants to receive the letter or no letter (1:1 ratio) in order to evaluate the effect of the letter on participant recruitment rates.

To reflect this change in recruitment approach we request permission to amend the scoring of questions C.1.2 and C.2.1 as follows:

C.1.2 How will participants to the study be recruited?

Approved text:
Participants will be initially approached by a member of their treating team. On demonstration of interest in the study, permission will be sought to allow the researchers to contact the patient directly.

Proposed amendment:

Participants will be initially approached by a member of their treating team. On demonstration of interest in the study, permission will be sought to allow the researchers to contact the patient directly.

C.2.16 Consent (c) If yes, please outline the consent process in full. (How will consent be obtained, when, by whom and from whom etc.)

Approved text:
Consent for the research team to contact the participant will be obtained verbally from the participant’s treating team, after the study has been briefly explained.

On contact by the research team the study will be explained either over the phone prior to arranging a face-to-face meeting, or in person at the clinic. Consent will be obtained by writing by the researcher on first meeting, after the study has been explained in full and the information sheet and consent form read by the participant. Estimated time between asking a patient to participate and having them sign the consent form is between one week and one month. Consent will be obtained before any assessments are conducted.

There will be a time interval between the study explanation offered by the treating team and the consent sought by the research team. There will also be a time delay between the information provided by the research team via phone and first face-to-face meeting, when formal written consent will be sought.

Proposed amendment:
On contact by the research team the study will be explained either in person or over the phone prior to arranging a face-to-face meeting. Consent will be obtained by writing by the researcher on first meeting, after the study has been explained in full and the information sheet and consent form read by the participant. Estimated time between asking a patient to participate and having them sign the consent form is between one week and one month. Consent will be obtained before any assessments are conducted.

There will be a time interval between the study explanation offered by the treating team and the consent sought by the research team. There will also be a time delay between the information provided by the research team in person or via phone and first face-to-face meeting, when formal written consent will be sought.

2) We request permission to include brief telephone interviews with participants to document their qualitative experience of participating in the study. We wish to take audio recordings of these interviews using a Digtahome and manually transcribe them to ensure accurate coding of the participants’ reports.

To reflect this addition we request permission to amend section E.2.10 as follows:

E.2.10 (a) Will any of the interviews data collected consist of audio recordings / video recordings? Yes

E.2.10 (b) If yes, will participants be given the opportunity to review and amend transcriptions of the tape? Yes
Dear [Service User/Patient Name],

I am writing to let you know that a team in Trinity College Dublin are doing a study to see if taking a health supplement called Coenzyme Q10 (CoQ10) can help improve tiredness, mood, and memory and attention in people who have mental health difficulties.

CoQ10 is a coenzyme (like a vitamin) that is important for making energy in our bodies. Sometimes our bodies do not have enough CoQ10 and we may have problems with tiredness, mood, memory and attention as a result. There is some evidence that taking CoQ10 helps certain people with these problems. The team at Trinity want to see if it will help people with a diagnosis of schizophrenia. To test this, they are doing a study in which they compare people who take CoQ10 with people who do not.

To raise awareness of the study we are sending this letter to individuals who are attending the service.

The research team will be attending the outpatient services over the coming weeks to talk to you about the study, and see if you might be suitable and interested in taking part in the study. You do not have to take part; it is your choice to do the study if you want to. If you would like to take part, or wish to know more about the study you can speak to Áine Maguire or Christina Mooney before the day of your outpatient appointment by telephoning 085-7883147. Áine or Christina can then arrange to meet you on the day you come for your appointment. Alternatively, Áine or Christina may approach you on the day of your appointment and you can speak to them then.

Thank you for considering this research study,

(treating clinician)
18th January 2018

Re: A randomised controlled trial of CoQ10 in patients with schizophrenia

REC Reference: 2018-01 List 1 (11)
(Please quote reference on all correspondence)

Dear Prof. Gill,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you requested an amendment in relation to the above referenced study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this request and grants permission for this amendment.

Yours sincerely,

[Signature]

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.