Feasibility of a Dietary Intervention Using Coconut Oil on Cognition and Quality of Life in Older Adults: Randomised Controlled Pilot study

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Abstract:

Background: With no effective treatments for dementia, research has addressed the efficacy of multi-dimensional interventions against dementia, mostly based on lifestyle modifications, to reduce the progression of the disease. The positive influence of adopting specific diet and nutrition-related habits on the cognitive trajectory throughout the life span has been increasingly investigated. Empirical evidence to date has demonstrated associations between nutrition and cognitive impairments in older adults specifically with the relation between glucose hypo-metabolism and neurodegeneration. Therefore, providing an alternative source of neuronal fuel could reduce neurodegeneration and consequently, dementia in older adults and adults with Mild Cognitive Impairment (MCI). Previous studies have used Medium Chain Triglycerides (MCTs) and ketogenic diets as a source of ketone bodies to improve cognitive functions in older adults with MCI or Alzheimer's disease. However, the current study relies on the consumption of the whole food component (coconut oil) that is rich in medium chain fatty acids, to induce ketosis.

Methods and analysis: The Medical Research Council's complex intervention framework was used to design a feasibility study following a randomized controlled study design. Thirty-one individuals (mean age 74 ± 5.6, 14 men and 17 women were randomised to receive either 30 ml/day of coconut *(n 18)* or sunflower oil *(n 13)* for 6 months. Recruitment, retention, adherence, fidelity was investigated. Quantitative data consisted of anthropometric, dietary, quality of life, cognitive and blood ketone measures at baseline, three and 6 months. Qualitative data was collected through open ended questionnaires and semi- structured interviews.

Results: Ninety-one percent of participants completed the study (n=28/31). Twenty-three participants (82%) adhered to consuming both oils for 3 months and 20 participants for 6 months (71%). At 3 months, 13 of the15 (87%) participants adhered to coconut oil and 11 of the15 (73%) participants for 6 months. Recruitment of MCI patients was challenging due to limitations in diagnosis, thus more older adults *(n 26)* than MCI patients *(n 5)* were recruited for the study. During the interviews at 6 months, participants reported no issues with the

study processes and procedures. The participants also reported that they were able to incorporate the oil into their diet. Cohen d analysis on cognitive measures demonstrated a small effect size in the direction of benefit in cognitive measures in the coconut oil group. No change was detected in blood ketone measure, quality of life and dietary measures.

Conclusion: Recruitment, retention, indicative results, and participant acceptability data suggest that the intervention is feasible for older-adults and adults with MCI. The findings support the development of a future fully powered Randomised Controlled Trial (RCT) to measure long term effects. The data will inform the design of a RCT that will be adequately powered to assess the effectiveness of the intervention on cognitive measures and quality of life. The findings from a future study, using this food-based intervention have potential to improve cognition and quality of life in older adults and adults with MCI, and in so doing reduce the risk of dementia.

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List of abbreviations:

AD: Alzheimer's disease

Apo E4: Apolipoprotein Ɛ4

CHO: Carbohydrate

CMRg: cerebral glucose metabolic rate

CO: Coconut Oil

Covid-19: Coronavirus

DASH: dietary approaches to stop hypertension

DK: Dietary Ketogenesis

KD: ketogenic diet

LCFA: Long Chain Fatty Acids

m-ACE: mini Addenbrookes Cognitive Examination

MCFA: Medium Chain Fatty Acids

MCI: Mild Cognitive Impairment

MCT: Medium Chain triglycerides

MD: Mediterranean diet

MIND: Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay

MMSE: Mini Mental State Examination

MRC: Medical Research Council

OA: Older Adults

QOL: Quality of Life

RCT: Randomised Controlled Trial

SO: Sunflower Oil

β-OHB: Beta-hydroxy butyrate

Acronym:

DICe: Dietary Intervention on Cognitions

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A doctoral thesis is often described as a solitary endeavour; however, the long list that follows definitely proves the opposite.

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Author’s Declaration I hereby declare that the work presented in this thesis has not been and will not be submitted in whole or in part to another University for the award of any other degree.

Signature: 

Chapter 1: Introduction

1.1. Chapter Overview

This introductory chapter sets the foundations for the study. It describes the aim of the study and explains the rationale for this intervention. It further outlines the author's research journey and how the author's background has influenced the research process and their experience of the study.

1.2. Context of the research

Increase in lifespan and percentage of ageing population is a worldwide success story and health conundrum (Callahan et al., 2014). Specifically, with an ageing population, frailty and dementia have become public health problems (Beard et al., 2016, Dent et al., 2017). Thereby they reflect the associated complexity of the ageing process underpinned by often unclear pathophysiological processes (Lim et al., 2018, Sampson, 2012). Thus, establishing the importance of focusing on the improvement of health and wellbeing will improve quality of life in later years.

The Word Health Organisation (WHO) defines dementia as "a syndrome in which there is deterioration in cognitive function beyond what might be expected from the usual consequences of biological ageing" (WHO, 2017). Dementia results from a variety of conditions that affect the brain (WHO, 2017). Alzheimer's disease (AD) is the most common form of dementia and contributes to 60-70% of cases; other common forms of dementia include: vascular dementia, dementia with Lewy bodies and other types of dementia (WHO, 2017). Dementia is currently a global public health issue; as a new diagnosis is made every 3 seconds (Alzheimer's Disease International, 2015). The 2014 report, "The trajectory of dementia in the UK–making a difference," estimated that a two or five year delay in the onset of dementia would reduce the number of people with the disease in the UK by 19% and 33% respectively, by 2050 (Lewis et al., 2014). It is estimated that about one third of cases of Alzheimer's disease worldwide are attributable to modifiable risk factors, many of

which are nutrition and lifestyle dependent (depression, mid-life obesity, mid-life hypertension, and type 2 diabetes) (Jennings et al., 2020). Therefore, behaviour or interventions which delays progression of age-related neuropathology could help to reduce the individual risk and population burden of the disease.

With no effective treatments for dementia, research has addressed the efficacy of multi-dimensional interventions against dementia, mostly based on lifestyle modifications, to reduce the progression of the disease (Canevelli et al., 2016). Lifestyle interventions could slow or reverse cognitive decline and frailty in older adults thus, improving their overall quality of life and cognitive performance (Canevelli et al., 2016, Buchman and Bennett, 2013). A growing body of evidence has focused on the association between dietary habits and cognitive performance (Canevelli et al., 2016). The positive influence of the adoption of specific diet and nutrition-related habits on the cognitive trajectory throughout the life span has been increasingly investigated (Canevelli et al., 2016). Studies have investigated the relation between whole diets (Mediterranean diet, Dietary Approaches to stop Hypertension (DASH) diet, ketogenic diet) and dementia risk reduction (B. Allès 2012, Tang et al., 2015, Solfrizzi et al., 2011). The most common advice for prevention of AD is the consumption of the DASH and Mediterranean-DASH intervention for neurodegenerative delay (MIND) diets (Morris et al., 2015d, Morris et al., 2015b). These diets are recommended because of the relationship between high blood circulating cholesterol concentrations and increased risk of AD (Reed et al., 2014, Notkola et al., 1998). However, only recently there has been an increased interest in dementia prevention through ketosis and manipulation of metabolic substrates.

Thus, the aim of this study is to evaluate the feasibility of a dietary intervention to overcome age-related neuropathy and improve cognitive functions and quality of life on older adults and adults with MCI. The results of this study will help inform the design of a future randomised controlled trial (RCT) that could provide a food based, cost effective, simple intervention that could reduce cognitive decline and delay dementia in the older population.

1.3. Thesis outline

The following outline describes the layout of the chapters included in the thesis as it reports on the different stages of development of the intervention before evaluating its feasibility:

Chapter 2 provides an in-depth literature review that focused on explains the effect of age-related cerebral glucose hypometabolism on cognitive decline. Based on this mechanism, it elaborates on the evidence available that demonstrates the potential role of dietary ketosis and coconut oil in overcoming this phenomenon and reducing age related cognitive decline.

Chapter 3 reports the methodology and theoretical underpinnings of the study, specifically explaining the philosophical approach utilised in the development and evaluation of the dietary intervention. The Medical Research Council (MRC) complex interventions framework was used in the development of the intervention (Skivington et al., 2018). A mixed method pragmatic approach was used for data collection to facilitate the process evaluation of the intervention.

Chapter 4 expands on the study design and its development based on the Medical Research Council complex interventions framework. The chapter provides a detailed protocol design of the different stages of the intervention and the study process and procedures. It also provides a detailed explanation of the different aspects of the intervention.

Chapter 5 summarises the findings from the quantitative and qualitative results of the study. The first section provided the results of the quantitative measures of the study in response to study objectives (1,2 and 3) (refer to chapter 2, section 2.6). The data provides information regarding the feasibility of the intervention and the outcome measures. While section 2 (Chapter 5) provides the results of the qualitative data, that focused on the study participants experience in response to objective 4 (refer to chapter 2, section 2.6) to facilitate the process evaluation of the intervention.

Chapter 6 brings together the discussion of the key research findings, strengths, limitations, and recommendations for future research. It focuses on the outcomes of the study and reports on the process evaluation of the intervention based on the MRC complex interventions framework (Craig et al., 2008).

Chapter 7 is the final chapter, which presents a summary of the thesis while reporting on contributions of the study to the scientific community. It also suggests recommendations for future research in the area.

1.4. Author's Research Journey

As a Public Health Nutritionist, my interest has always been in dietary intervention programs that aim at improving the health of the population. I am a firm believer of Albert Einstein's saying: "The doctor of the future will heal the world with food not medicine". During my training as a nutritionist, I volunteered and worked in multiple sectors and always enjoyed working with a multitude of different people in the community and always enjoyed viewing the real-life impact of the work done. On a personal level, I have seen the effect of Alzheimer's disease on people. Especially, how it affects not only the person with the diagnosis but the family and also every single person around them. I lost my dear grandmother to dementia after years of helplessly watching her struggle. It was heart breaking to lose her slowly with every single day, to suddenly feel like talking to a stranger in the shape of a loved one. With dementia you lose the person while the body still remains, reminding you of all you have lost and still have to lose. The sense of helplessness and hopelessness that accompanies a dementia diagnosis is overwhelming.

I was therefore very excited when the opportunity to explore a food based dietary intervention that could potentially impact age related cognitive decline and AD came up as part of the full-time PhD studentship. This was an opportunity to combine my interest in dementia research to make a positive difference, or at least to give a sense of hope to people. Thus, providing me an avenue to delve into dementia research, and to potentially make an impact on the field (no matter how minimal) provided me with inspiration and motivation throughout this project.

From the beginning, I was aware of my lack of cognitive neuroscience knowledge and experience. At the time I believed this lack of knowledge was a weakness. However, throughout the duration of this research, I have found that this lack of prior knowledge was actually an advantage. As despite making the process of learning about cognitive measures and brain functions more difficult, it pushed me to immerse myself in the literature to

develop the skills needed to design and implement this study. It also has allowed me to approach the topic from a more feasibility and compassionate rather than a clinical perspective.

This project has helped me grow as a researcher, nutritionist and most importantly a human being. When reaching out to potential participants, I never expected how welcoming they were and how widely they opened their homes, hearts, and lives for me. I think one of the things that could have potentially impacted the adherence and retention rates of the study was the relationship that I managed to develop with the study participants. Between our study sessions, phone calls and emails we built a relationship based on trust and respect that I will forever cherish. During Covid-19 lockdown in 2020 I was worried about losing contact with the participants who had already started the study; however, they were very collaborative and went out of their way to ensure their continuation in the study. They even sent me emails to check up on me as they knew I was an international student living alone in the UK and far away from family. One of them even tried learning Arabic to be able to say welcome me into his house using my own language. This humane aspect of research is what kept me motivated and inspired throughout the project; especially with the multiple changes and delays that Covid-19 caused.

By the end of my research journey, I gained more skills than I expected and left learning a lot more than I could have ever imagined. The positive feedback from the study participants, their motivation and willingness to take part in similar future research was the best outcome of this study. I have found out that the field of dementia research is very rewarding and inspiring, despite the sadness that surrounds dementia itself.

Chapter 2: Literature Review

2.1. Introduction

This chapter provides an introduction to the relation between diet and dementia, presenting an overview of available literature. The chapter then examines what is known about glucose hypometabolism and the effect of dietary ketosis on cognition in older adults. The chapter concludes by outlining the rationale for the study.

2.2. Diet & Dementia

There is growing research about the pathophysiological mechanisms underlying cognitive impairment and the role that diet might have on modulating brain function (Bandayrel et al., 2011, B. Allès 2012, Francis and Stevenson, 2018, Jennings et al., 2020, McGrattan et al., 2019) . Evidence suggests the potential role of dietary interventions in protection against age related cognitive decline (Vauzour et al., 2017, McGrattan et al., 2019, Scarmeas et al., 2018) . The mechanisms underlying these relationships remain unclear, but it is suggested that anti-inflammatory and anti-oxidative mechanisms have neuroprotective effects (Heneka et al., 2015, Lee et al., 2010, McGrattan et al., 2019, Chakrabarti et al., 2011).

Thus, there has been an increased interest in examining the role of the Mediterranean diet (MD) and dietary approaches to stop hypertension (DASH) dietary patterns for dementia prevention due to their anti-inflammatory effects (Casas et al., 2016, Tangney et al., 2014, Coelho-Júnior et al., 2021). The Mediterranean dietary pattern focuses on a high intake of fruits, vegetables, legumes and cereals; moderate consumption of oily fish and dairy; and low consumption of meat, sugar and saturated fat (Scarmeas et al., 2006). Olive oil is the main source of dietary fat in this diet pattern and wine is consumed in moderation with meals (Scarmeas et al., 2006).

Anti-inflammatory dietary patterns such as the Mediterranean diet (MD) and dietary approaches to stop hypertension (DASH) may play a neuroprotective role and aid in prevention of AD (Siervo et al., 2021, McGrattan et al., 2019) . Dietary components consumed within these diets due to consumption of food rich in anti-oxidants, polyphenols

and omega-3 fatty acids have anti-inflammatory neuroprotective properties (Siervo et al., 2021). Based on epidemiological studies, adherence to Mediterranean diet is inversely correlated with insulin resistance (Mattei et al., 2017), inflammation that causes oxidative stress (Arpon et al., 2016, Richard et al., 2014) and AD risk (Gu et al., 2010, Scarmeas et al., 2006). The Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND diet) was identified by researchers at Rush University through epidemiological data (Jack Jr et al., 2013). The MIND diet is a combination of the Mediterranean diet and the Dietary Approaches to Stop Hypertension diet (DASH diet) (Morris et al., 2015c).The study demonstrated that AD risk is diminished depending on the MIND diet adherence score (Jack Jr et al., 2013). The MIND diet breaks down 15 food components into "brain health food groups" and "unhealthy food groups" (Table 2.1).

Table 2.1 MIND Diet Food components.

Brain Healthy Food Groups	Unhealthy Food Groups
Green leafy vegetables	Red meats
Other vegetables	Butter and stick margarine
Nuts	Cheese
Berries	Pastries and sweets
Beans	Fried food
Whole grains	
Fish	
Poultry	
Olive oil	

The Mediterranean and DASH diets demonstrate promising association with cognitive impairments and dementia risk reduction. A meta-analysis of 9 prospective cohort studies (34,168 participants) concluded that higher adherence to a MedDiet is associated with a 17% risk reduction of MCI development and 40% of AD (Wu and Sun, 2017). However, inconsistencies exist between and within the studies (Olsson et al., 2015, Samieri et al., 2013, Andreu-Reinón et al., 2021) thus, the evidence remains inconclusive as a pooled analysis showed no association between Mediterranean diet adherence, MCI and dementia **(**Coelho-Júnior et al., 2021**).** These studies highlight the role of diet in dementia risk reduction; however, recent research has focused on the metabolic aspects of dementia and the potential role of diet in alleviating these metabolic disruptions (Taylor, 2018, Cunnane et al., 2020). Other than anti-inflammatory and anti-oxidative pathways there has been a great interest in metabolic targeting dietary interventions in the prevention and treatment of AD (Swerdlow, 2012).

2.3. Alzheimer's as a metabolic disease:

As previously mentioned, AD is the most common type of Dementia, making up around 60-70% of cases, and this number increases with older adults. Thus, the focus on cognitive healthy ageing focuses on AD aetiology and prevention (Sánchez-Izquierdo and Fernández-Ballesteros, 2021). The aetiology for AD remains unclear and not well understood (Burns, 2009). Scientists suggest that multiple factors increase risk and contribute to the development of the disease (Taylor, 2018). The most common theory of AD development focuses on the abnormal Aβ accumulation in the brain, which ultimately leads to AD (Swerdlow et al., 2010). However, research has demonstrated that people can have normal cognition despite the presence of Aβ plaques, thus, the plaques alone do not cause AD and can't be used as biomarkers for severity of the disease (Swerdlow and Newell, 2012). In recent years, there has been more research on the role of mitochondrial dysfunction on AD pathogenesis (Swerdlow et al., 2010, Swerdlow et al., 2014, Swerdlow and Khan, 2004). As evidence demonstrates significant metabolic disruptions at the early stages of AD, potentially during the pre-symptomatic phase(Kennedy et al., 1995, Small et al., 2000). Brain functions require a significant supply of energy, in the form of glucose (Frackowiak et al.,

1981, Ishii et al., 2009, Del Sole et al., 2008). However, people with AD exhibit a decrease in brain glucose metabolism and utilisation (Frackowiak et al., 1981, Ishii et al., 2009, Del Sole et al., 2008).

Studies using cytoplasmic hybrid techniques support the relation between mitochondrial dysfunction and AD (Wilkins et al., 2014, Swerdlow et al., 2017). Cytoplasmic hybrid cells are produced by the fusion of enucleated cells containing mitochondrial DNA (mtDNA) with nucleated cells repleted of mtDNA, then mtDNAs migrate to the nucleated cell, replicate an establish aerobic metabolism (Wilkins et al., 2014). Cytoplasmic hybrid cells containing mtDNA of platelets form AD patients compared to health age-matched controls demonstrated a significant decrease in aerobic metabolism in AD cells (Sheehan et al., 1997, Silva et al., 2012, Silva et al., 2013). This suggests that mitochondria and mtDNA play a role in bioenergetic deficiency observed in AD patients.

However, it remains unclear whether this metabolic impairment is a cause or effect of AD (Silva et al., 2013, Swerdlow, 2012). Nevertheless, there is great interest in metabolic targeting interventions in the prevention and treatment of AD (Swerdlow, 2012). The Manipulation of energetic substrates and metabolism through diet may be a potentially effective preventive approach to AD (Swerdlow, 2011).

2.3.1. Brain Energy Metabolism

Despite making up only 2% of total body weight, the brain requires 20% or more of total body energy (Holliday, 1971, Sokoloff, 1999). Glucose serves as a main source of energy to the brain (Sokoloff, 1999). GLUT 1, the non-insulin dependent glucose transporter aids in the transportation of glucose across the endothelium of the blood brain barrier (Magistretti and Pellerin, 1996, Magistretti and Pellerin, 1999). Glucose then enters the neurons via GLUT 3 or astrocytes via GLUT 1. Brain energy metabolism is based on neuronal energy metabolism , although some neuronal metabolism relies on astrocytes for substrate production (Magistretti and Pellerin, 1996, Magistretti and Pellerin, 1999).

2.3.2. Cerebral Glucose Hypometabolism

There is a link between AD and impairment in cerebral glucose metabolism (Swerdlow, 2012). A reduction in the cerebral metabolic rate of glucose occurs long before onset of clinical signs of cognitive impairment or neuronal loss (Craft et al., 2000, Cunnane et al., 2011, Croteau et al., 2017, Lange et al., 2017). Positron emission tomography (PET), using fluorodeoxyglucose (FDG) as a marker provides insight into cerebral glucose metabolic rate (CMRg) as it allows the measurement of glucose uptake by the brain tissues (Phelps et al., 1979). The CMRg of the normal brain is approximately 100-120 g/day (Owen et al., 1967). However, when compared to age matched older adults with normal cognition, mild AD patients have a 20-25% reduction in brain CMRg with some regional reductions as high as 33% (Nugent, 2014, Castellano et al., 2015). The cause of glucose hypo-metabolism remains unclear, but it has been attributed to defects in brain glucose transport, disruption in glycolysis, impairment in insulin functions or mitochondrial impairment (Hertz et al., 2015, Hoyer, 1992) and suggested to affect the AD pathology.

Glucose uptake in the brain is primarily mediated by non-insulin dependent transporters (GLUT 1 and GLUT 3), expression of both transporters is decreased in AD (Simpson et al., 1994). However, insulin dependent receptors and GLUT 4 are expressed in neurons in the hippocampus which is an integral region for memory and learning in mammals (Grillo et al., 2009). In rats, GLUT 4 translocation in the hippocampus was induced by an increase in glucose mediated increases in plasma-insulin levels (McEwen and Reagan, 2004). This indicates the important role that insulin plays in hippocampal brain glucose metabolism (McEwen and Reagan, 2004, Piroli et al., 2007). Thus, regional and systematic reduction in insulin sensitivity could influence hippocampal glucose metabolism (Calvo-Ochoa and Arias, 2015).

Mitochondrial impairment is thought to be one of the leading causes for AD development (Cunnane et al., 2020). The mitochondrion is the primary contributor of neuronal Adenosine tri-phosphate (ATP)(David et al., 2005). The brains of individuals with AD exhibit downregulation in expression of mitochondrial enzymes crucial for energy production (Sims et al., 1987, Manczak et al., 2004). However, the cause of mitochondrial defects in AD remains unclear.

Apo-Lipoprotein E (Apo E) is a polymorphic protein with three common alleles, APO epsilon 2, APO epsilon 3, and APO epsilon 4 (Mahley et al., 2006). Carriers of the APO E4 gene have alterations in brain energy metabolism (Perkins et al., 2016) as they demonstrate reductions in measures of glucose metabolism and mitochondrial functions in comparison to non-carriers of APO E4 (Perkins et al., 2016). Apo E4 has been recognized as a risk factor for sporadic and late-onset familial Alzheimer disease (AD) (Mahley et al., 2006). *APOE4* homozygotes have up to 15 times increased risk of AD while *APOE4* heterozygotes have up to 4 times the risk for AD in comparison to risk neutral *APOE3* homozygotes (Perkins et al., 2016).

Cerebral glucose hypo-metabolism could lead to chronic brain energy deprivation which causes a deterioration in neuronal functions leading to a reduction in synaptic functionality and further decline in glucose metabolism (Cunnane et al., 2011). Thus, this creates a vicious cycle of neuronal damage leading to the exacerbation of cognitive impairment (Cunnane et al., 2011).

2.4. Dietary ketosis and Cognition

2.4.1. Cerebral Ketone metabolism

Cerebral glucose hypo-metabolism could potentially be a key factor that contributes or progresses cognitive decline in older adults (Cunnane et al., 2011). Thus, improving energy uptake by the brain by using ketones could help reduce the progression of cognitive impairment. Research has shown that bypassing systematic glucose metabolism in the brain by inducing ketosis can increase ketone availability for neurons (Cunnane et al., 2011) thus providing an alternative energy source.

Ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone) are water-soluble molecules produced from fatty acids by the liver when blood glucose levels are low (Gershuni et al., 2018).They are the by-products of the breakdown of fatty acids in the body (Pan et al., 2000). ß-OHB and acetoacetate are two forms of ketone bodies that are utilized by the brain as a back-up source of energy when glucose supply is insufficient (Sokoloff, 1999). Ketone bodies can support basal neuronal energy needs and around half of the neurons activity dependent oxidative needs (Lange et al., 2017). Serum levels of ketone

bodies are increased either by: 1) an increase in mobilization of endogenous fatty acids due to prolonged fasting (Pan et al., 2000), 2) ketogenic diet (KD) (Freeman and Kossoff, 2010, Kossoff and Hartman, 2012), and intake of ketogenic agents, such as medium-chain triglycerides (MCT) or ketone esters (Henderson, 2008, Henderson et al., 2009).

Ketosis refers to the production of ketone bodies for use as an alternative energy source when blood glucose level is low (Williams and Turos, 2021). Ketosis is the result of increased mobilization of fatty acids due to a decrease in glucose availability (Pan et al., 2000) in cases of prolonged fasting or ketogenic diet consumption. However, dietary ketosis using ketogenic agents have different mechanisms. MCT intake can induce ketosis, as MCTs are rapidly absorbed by enterocyte into the portal vein gaining direct access to the liver, which is different than absorption of short and long chain fatty acids which enter the lymphatic system first (Ciavardelli et al., 2016, Stanfield, 2012). Ketone esters are bound ketone bodies that are hydrolysed and absorbed intact which results in an elevation of serum ketone levels. Ketogenic agents increase serum ketone levels until the ketone bodies are metabolised in the body (Henderson, 2008). It is estimated that the liver can synthesize 185g of ketone bodies per day (McPherson and McEneny, 2012). Mitochondria in the liver converts acetyl-CoA from beta-oxidized fatty acids into ketone bodies: acetoacetate, Beta-hydroxyl butyrate (ß-OHB) and acetone (Stanfield, 2012).

Glucose supplies about 95% of the brain's energy needs, however, it utilises ketones instead in case of an increase in plasma ketone concentration (Croteau et al., 2017, Cunnane et al., 2011). The cerebral metabolic rate of ketones (CMRk) which measures brain ketone utilisation is dependent on plasma ketone concentration (Hasselbalch et al., 1996). Studies using positron emission tomography imaging and a ketone tracer (11C-acetoacetate) demonstrated that brain ketone uptake remains normal in ageing, MCI, and AD (Lying-Tunell et al., 1981, Castellano et al., 2015, Vandenberghe et al., 2020).Thus, increasing cerebral ketone uptake to combat the effect of glucose hypo-metabolism on brain functions has become a target for therapeutic interventions in AD (Freemantle et al., 2006, Costantini et al., 2008, B. Allès 2012).This method is often referred to as "brain energy rescue" (Cunnane et al., 2020). Recent clinical studies have shown the association between brain energy

rescue using ketones and improvement in cognitive functions in MCI and AD(Jennings et al., 2020).

i. Dietary Interventions

Only recently have dietary interventions become a subject of interest in dementia and cognition studies due to the increased interest in understanding glucose and ketone metabolism in older adults (Freemantle et al., 2006, Ota et al., 2016). Studies demonstrate that dietary induced ketogenesis (DK) can increase ketone availability to the brain, which has beneficial cognitive effects in individuals with mild to moderate AD and MCI (Reger et al., 2004, Henderson et al., 2009, Krikorian et al., 2012a, Rebello et al., 2015). DKs can be achieved either by low carbohydrate ketogenic diets (with 20-50 grams intake of carbohydrate a day) (Westman et al., 2007) or the supplementation of 20-70 g of MCT/day (especially those containing the eight and ten carbon fatty acids or the usage of ketone esters) (Krikorian et al., 2012a). The effectiveness of ketogenesis in increasing ketone levels can be determined either by measuring beta-hydroxyl butyrate in blood or ketone bodies in urine (Krikorian et al., 2012a). However, little is known about the effectiveness of different kinds of ketogenic interventions on cognitive functions in older adults.

ii. Approach for Literature Review:

A scoping review was conducted to identify the scope of research on the effect of dietary induced ketogenesis and cognitive functions in older adults. The scoping review was selected to provide the relevant empirical background for this study, as the relation between dietary ketosis and cognitive functions is comparatively new to the field and a developing area of research. This methodology supports the inclusion of relevant available literature on the topic irrespective of the quality of the studies. Thereby, it will enable the identification of the gaps in the literature and inform the design of the dietary intervention.

The research questions for the review included:

- What dietary interventions have been conducted to investigate the effect of DK on cognition in older adults?
- What are the gaps in the current literature and possible recommendations for future studies?

2.4.2. Scoping Review Methodology

The current scoping review was guided by the methodological framework developed by Levac et al. (Levac et al., 2010) which is the updated version to the initial scoping review framework that was developed by Arksey and O'Malley (Arksey and O'Malley, 2005). The framework consists of five major steps. 1) Identifying the research question, 2) searching for relevant studies, 3) selecting studies, 4) charting the data, collating, summarising, and 5) reporting the results. This methodology is recommended for areas of research that have yet to be thoroughly reviewed, as it allows the exploration of the existing literature for the identification of research gaps when the research conducted to date in a specific area is diverse (Levac et al., 2010).

Identifying the research question: Inclusion and exclusion criteria

Studies that utilized a dietary intervention of any study design (ketogenic diet or Medium Chain Triglyceride supplementation) to induce ketogenesis in older adults (aged 60 years and above) were included in the review. Age 60 years and above was used to define older adults as it is the standard cut off point used by the UN (United Nations) and WHO (World Health Organization) (United Nations, 1982). Interventional studies, such as randomized control trials (RCTs), case studies, pilot and feasibility studies that documented the effect of ketogenesis on cognitive functions in older adults were included. Studies that were conducted on individuals living with different types of cognitive impairment were included in the review. Studies disseminated in languages other than English were excluded.

I. SEARCHING FOR RELEVANT STUDIES: SEARCH TERMS

A search on the relevant range of material was undertaken to provide an overview of the current and available knowledge to help identify the research questions. The review was carried out by searching the literature using search terms that represented the population, intervention and outcome (Miller and Forrest, 2001). Only peer reviewed interventional studies were included.

Table 2.2. Scoping Review search terms

Population	Older-adults or “Older adults” or Geriatrics or Seniors or Dementia
Intervention	Ketosis or "ketogenic diet" or "ketogenic agents" or "ketone body metabolism" or "ketone synthesis" or ketones or "ketonic acids" or hyperketonaemia or keto* or ketone* or MCT or "medium chain triglycerides”
Outcome	Cognition or Memory or Mnemosyne or "Memory testing" or "cognitive functions" or "cognitive impairment"

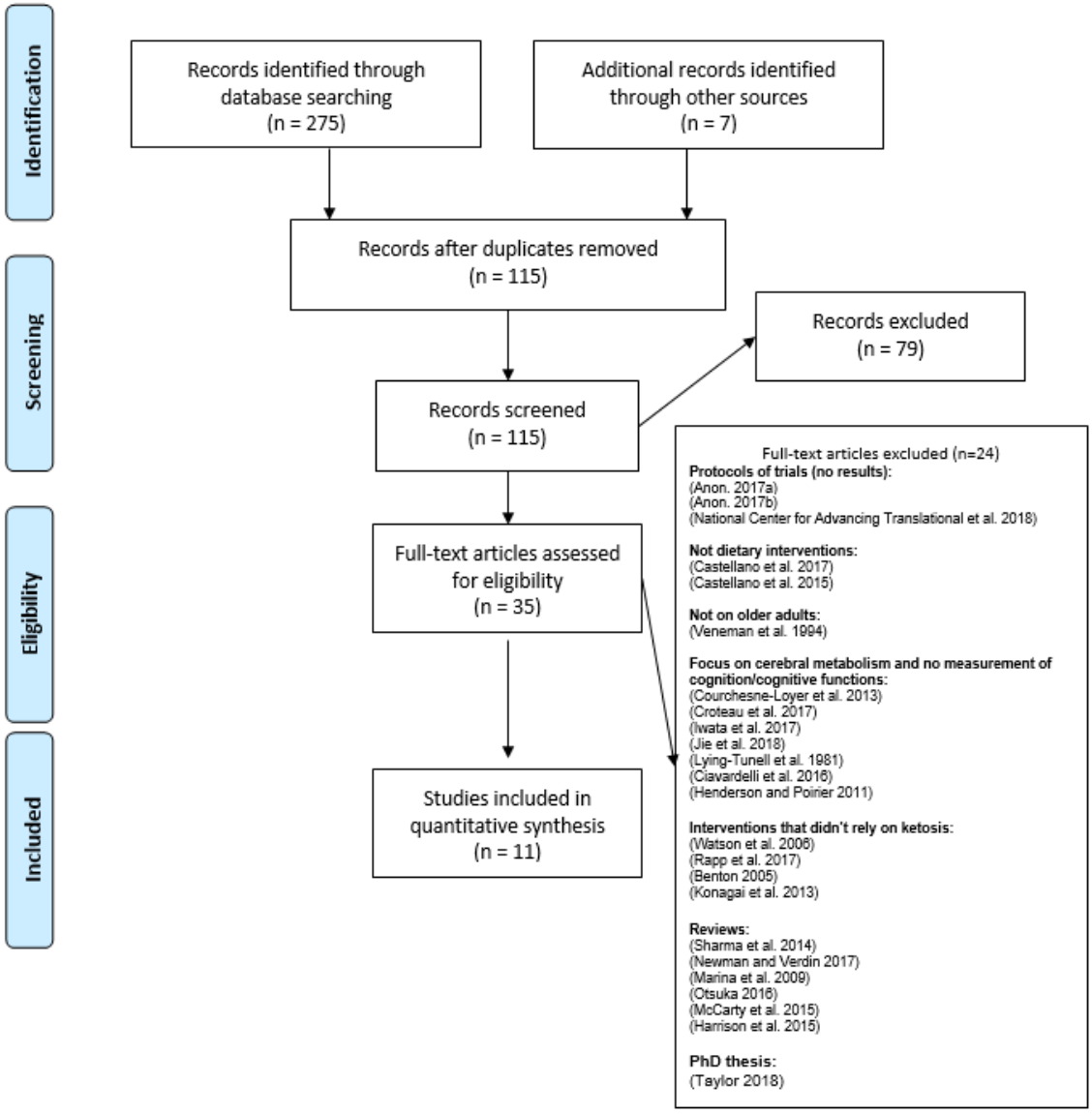
The search terms were adapted for searching each database (updated in August 2021). A search was run through the databases of Medline (1971-2019), PsychInfo (1998-2019), Cochrane (CENTRAL) (2014-2019), PubMed, Scopus (1970-2019), Web of Science, CINAHL (1971-2019), Elsevier (2003-2019). The search included published peer reviewed literature from the date of inception of each database.

II. SELECTING STUDIES

The electronic search strategy was developed based on key terms from other studies and the usage of MESH terms in the afore-mentioned databases. Reference lists of key papers were checked and key word searches in Google Scholar were performed to identify studies. The database search was conducted between July 2018 and March 2019 and updated in August 2021. All studies were then exported into Endnote Bibliographic software for

screening. Duplicates were deleted and abstracts were screened to check for eligibility. The PRISMA-ScR checklist was used in documenting the selection process (Tricco et al., 2018) . The quality of included studies was assessed using Critical Appraisal skills Program-RCT toolkit (CASP-RCT), however, all studies were included irrespective of their quality as scoping reviews focuses on scoping all available literature rather than high quality studies only (Levac et al., 2010).

Figure 2.1. PRISMA-ScR checklist for screened and included studies



From: **Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal. pmed1000097**

III. CHARTING THE DATA

Data from the chosen studies were extracted using a checklist that was adapted from the Cochrane data extraction and assessment form (Higgins JPT, 2019) to insure the standardisation of the process and improve rigour. Data extracted included: type of study, methods, randomization, sample size, location, duration, outcome measures, intervention, administration method, medical condition of target population, age of participants, APO E4 status of participants, exclusion and inclusion criteria, adherence, drop-out rates, and funding sources.

2.4.3. Results

There were 115 studies identified across all databases. Of these, 79 studies were excluded after the initial screening, which included the title and abstract. The remaining 35 studies were fully screened for eligibility and only 14 studies of these met the eligibility criteria for inclusion in the review (refer to table 1). Narrative and descriptive numerical analysis were used to report all the study results. Studies were grouped together according to the type of intervention; MCT supplementation or ketogenic diet.

I. STUDY SETTING

Across the 14 included studies; participants were recruited from different settings; either through databases of universities or community research centres, care homes, hospitals, and memory clinics. Most of the studies were conducted in the United States (*n 9*) (Maynard and Gelblum, 2013, Reger et al., 2004, Krikorian et al., 2012a, Rebello et al., 2015, Henderson, 2008, Newport et al., 2015, Taylor, 2018, Henderson et al., 2020) and Japan (*n 3*) (Ota et al., 2016, Abe et al., 2017, Ohnuma et al., 2016). Nine of the fourteen studies were RCTs (Abe et al., 2017, Reger et al., 2004, Ota et al., 2016, Krikorian et al., 2012a, Rebello et al., 2015, Henderson, 2008), three were controlled pilot studies (Krikorian et al., 2014, Taylor, 2018, Ohnuma et al., 2016) and only two were case studies (Newport et al., 2015, Maynard and Gelblum, 2013) (refer to table 2.3).

Table 2.3: Table Summarising Study Characteristics

Author-Date	Study Design	Intervention	control	Location	Funding
Abe et al. 2017	Randomized controlled parallel group trial	MCT+ L-leucine+ cholecalciferol	Group 2: LCT+ L-leucine+ cholecalciferol Group 3: control- no supplements	Japan	Nisshin Oillio group ltd.
Henderson et al. 2009	Double blind placebo controlled parallel group study	AC-1202	Placebo- similar in taste and appearance to AC-1202	USA	Accera Inc.
Krikorian et al. 2012	RCT	Low CHO diet (5-10%)	High CHO diet (50%)	USA	Veronica Atkins; National Institute of Health
Krikorian et al. 2014	Controlled pilot study	Low CHO diet (5-10%)	High CHO diet (50%)	USA	N/A
Maynard and Gelblum 2013	Case studies	Caprylic triglycerides	N/A	USA	Accera Inc.
Newport et al. 2015	Case study	MCT + Coconut oil	N/A	USA	N/A
Ohnuma et al. 2016	Open label observational study	Axona	N/A	Japan	Nestle
Ota et al. 2016	RCT	Ketogenic meal	Isocaloric meal	Japan	Ryoshoku Food science Institute
Rebello et al. 2015	RCT	MCT	Placebo- canola oil	USA	N/A
Reger et al. 2004	RCT	Neobee	Placebo (LCT)	USA	Accera Inc.
Taylor et al. 2018	Feasibility pilot-controlled study	Very high fat ketogenic diet + MCT	N/A	USA	N/A
Fortier et al.2021	RCT	MCT-ketogenic medium chain triglyceride [kMCT]	high-oleic acid sunflower oil	Canada	Nestle

Phillips et al. 2021	Randomised crossover trial	Ketogenic Diet	Diet with low-fat healthy-eating guidelines	New Zealand	N/A
Henderson 2021	Placebo-Controlled, Parallel-Group, Randomized Clinical Trial	AC-1204	Placebo- similar in taste and appearance to AC-1204	USA	Accera

II. INTERVENTION CHARACTERISTICS

- **Type of dietary intervention**

All the 14 studies were involved interventions with MCT supplementation or low carbohydrate (CHO) diets. Of these, most of the studies used MCT supplementation (*n 10*) (Ohnuma et al., 2016, Maynard and Gelblum, 2013, Reger et al., 2004, Rebello et al., 2015, Ota et al., 2016, Henderson, 2008, Abe et al., 2017, Newport et al., 2015, Henderson et al., 2020, Vandenberghe et al., 2020, Fortier et al., 2021),low CHO ketogenic diet (*n 3*) (Krikorian et al., 2014, Krikorian et al., 2012a, Phillips et al., 2021a) or both MCT and low CHO diet (*n 1*) (Taylor, 2018) to induce ketosis in participants.

The amount of MCT administered ranged between studies from 6 g/day (Abe et al., 2017) to 165 g/day (Newport et al., 2015). It is suggested that dietary ketosis can be achieved by the supplementation of 20-70 g of MCT/day (Krikorian et al., 2012a) to the normal diet. Only one study supplemented participants with less than 20 g/day of MCT (Abe et al., 2017) and participants were provided with 6 g/day MCT along with 1.2 grams of L-Leucine amino acid and 20 micrograms of cholecalciferol. It is unknown if ketosis was achieved in this study as circulating blood ketone concentrations were not tested. L-Leucine amino acids and cholecalciferol were supplemented to increase muscle strength and functions (Abe et al., 2017). L-leucine and cholecalciferol play a role in improving muscle function but had no impact on cognition in this study. Individuals taking the MCT (with L-Leucine and cholecalciferol) supplements showed a 30.6% improvement in MMSE (Mini Mental State Examination) score in comparison to participants supplemented with long chain fatty acids

(with L-Leucine and cholecalciferol) or the control group where no supplementation was provided (Abe et al., 2017).

In another study, a multivitamin (containing Vitamin D, Calcium, and Phosphorus) was provided in addition to very high fat ketogenic diet with MCT supplementation. The multivitamin was provided to prevent micro-nutrient deficiencies due to the strict diet that might lack in some micronutrients (Taylor, 2018). In a case study conducted by Newport et al., (2015) the participants were provided with 165 mls of MCT per day along with 35 ml of Coconut oil (Newport et al., 2015). Coconut oil was supplemented with MCT as it is a rich source of Medium Chain Fatty Acids that could help to induce ketosis (Newport et al., 2015)

- **Administration of the Dietary Intervention:**

i. MCT

The method of administration of MCT differed between studies included in this review. The MCT were supplemented either through mixing powdered MCT sachets with liquid or meal replacement drinks (Henderson et al., 2009, Henderson et al., 2020), ketogenic meal (Meihi817-B 50) made of mixing MCT in hot water (Ota et al., 2016), or mixing MCT with food (Abe et al., 2017) . Table 2.4 outlines the different methods that MCT were used to induce ketosis. In a feasibility study, Ohnuma and colleagues (2016) used "Axona Graduating Dosing Plan" which is a four-step titration method recommended by Acerra Inc. (Ohnuma et al., 2016). For this method initial supplementation of Axona was 10 g for 2 days. The volume of MCT was increased gradually every 2 days to reach 20 g/d, then 30g/d and finally 40 g/day remaining at this intake for 3 months (Ohnuma et al., 2016). This approach aimed to limit gastrointestinal symptoms associated with MCTs such as nausea, abdominal pain, and flatulence in participants with mild to moderate Sporadic AD (Ohnuma et al., 2016). The participants in the study reported a reduced the number of adverse events compared to a previous study using Axona as a source of MCT (Henderson et al., 2009) which helped improve their adherence to the intervention (90% had more than 80% compliance to the intervention). However, 2 out of 24 participants (8%) reported flatulence and abdominal pain and dropped out of the study due to their inability to tolerate the MCT (Ohnuma et al., 2016).

Table 2.4: Table Summarising the different methods of MCT Supplementation

Study	Duration	Sample Size	Gender	Mean Age	APO E4 Status	Population	Volume	Method of administration	Ketone level	Adverse Events
Abe et al. 2017	90 Days	38-2dropped out	11 M 27 F	86.6	N/A	Frail Elderly	LD + 6 g/d MCT 6 + 1.2 g L-leucine + 20 µg cholecalciferol	Tube containing cholecalciferol and leucine given before dinner. MCT was mixed with food	N/A	N/A
Henderson et al. 2009	90 days	152-12 dropped out	67 M 85 F	78	72 Apo E4 +ve 80 Apo E4 -ve	Mild to Moderate AD	10 g AC1202 once a day first 7 days; 20 g/day from days 8 to 90	Sachets were mixed with 8 oz. glass of liquid or meal replacement drink	Elevation in B-OHB in APO E4 -ve (p= 0.008)	Adverse events in AC1202, GIT
Maynard and Gelblum 2013	Ranged from 6-48 Months	8	6 M 2 F	84.5	One Apo E4 +ve	Mild to moderate AD	N/A	20 g/day caprylic triglycerides, two cases used 10 g/day	N/A	Mild gastrointestinal upset

Newport et al. 2015	75 days	1	M	63	Apo E4 +ve	Younger Onset Sporadic AD	35 ml coconut oil + 165 ml/d medium chain triglycerides	Oil was distributed into 3 to 4 servings per day	N/A	N/A
Ohnuma et al. 2016	90 Days	24	12 M 10 F	63.9	7 Apo E4 +ve 15 Apo E4 -ve	Sporadic AD	40 g/day Axona powder	Four step dose titration- 10 g/d for 2 days, 30 g/day for 2 days and after that 40 g/day	Ketone bodies: increased three fold from 114.5 ± 105.4 µM to 322.6 ± 240.2 µM during first month then remained constant	Flatulence and abdominal pain
Ota et al. 2016	9.5 days ± 6.9 days between 2 study visits	20- 1 dropped out	6 M 13 F	66.1	N/A	Healthy Elderly- no cognitive impairment	20 g/day MCT	Emulsified in meal	Increased plasma ketone levels ($p<0.001$)	N/A

Rebello et al. 2015	168 Days	4- 2 dropped out	1 M 1 F	68	2 Apo E4 +ve 2 Apo E4 -ve	MCI	56 g/day MCT	MCT oil	B-OHB increased in APO E4-ve in baseline (0.19 µM) and remained constant at week 4 (0.02 µM) and 24 (0.01 µM). Increase in B-OHB in APO E4 +ve during all study visits; from 0.06 µM to 0.39 µM to 0.54 µM)	Reoccurring GIT dysfunction
Reger et al. 2004	2 study visits	20	N/A	74.7	5 Apo E4 +ve 15 Apo E4 -ve	AD and MCI	40 ml/day NeoBee	MCTs were blended with 152 ml heavy whipping cream to create emulsified test sample	significant increase in B-OHB levels (p =0.025) in treatment group	N/A

Taylor et al. 2018	90 Days	15-5 dropped out	7 M 8 F	73.1	N/A	AD or Amnestic MCI	VHF-KD- 70 % fat (10-40% MCT) and multivitamin	Dietary adjustment and vitamin supplementation pills (vitamin D, calcium, phosphorus). MCT oil was mixed with food to supply 10 % of fat in first week then increased slowly to 40 %.	Presence of urine acetoacetate (60.6%) significant increase in B-OHB ($p<0.001$) and returned to normal after washout	No serious adverse events MCT associated diarrhoea (50 %)
Fortier et al. 2021	6 months	83	45 F 38 M	72	19 Apo E4 +ve 64 Apo E4 -ve	MCI and AD	A ketogenic drink containing medium chain triglyceride (ketogenic medium chain triglyceride [kMCT]; 15 g twice/day	125 mL of kMCT drink twice a day with breakfast and supper (total of 250 mL/day) after a gradual titration in the first 2 weeks. The daily dose was titrated from 50 to 125 mL, twice a day,	B-OHB increased significantly in the kMCT group compared to placebo ($P < .0001$)	GI events (75% of participants)

								during the first 2 weeks		
Henderson 2021	26 weeks	413- 81 did not complete study	245 F 168 M	76.7	128 Apo E4 +ve 285 Apo E4 -ve	mild-to-moderate AD	AC-1204 (20 grams of caprylic triglycerides)	graduated dosing plan during the first 2 weeks (beginning with 10 g of IP and increasing by 10 g every fourth day until a final daily dose of 40 g was reached	mean B-OHB levels obtained 1 h post dose in the AC-1204 group for this current study were 0.271 mM at Week 8 (Day 56), 0.272 mM at Week 17 (Day 119), and 0.250 mM at Week 26 (Day 182).	GIT disorders, diarrhoea, nausea, vomiting. 3 severe adverse events: Colitis, diarrhoea, nausea 13 subjects in each treatment group experienced at least one SAE

ii. Ketogenic Diet

There were 4 studies that examined the effect of adjustments to habitual diets using ketogenic diets that are low in carbohydrates to induce ketosis (Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018, Phillips et al., 2021a) (Refer to Table 2.5). All of these studies limited carbohydrate (CHO) intake of participants to no more than 20 grams/day (Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018, Phillips et al., 2021a).

Table 2.5: Table summarising the different ketogenic diets used

Author	Duration	Sample Size	Gender	Mean Age	APO E4 status	Population	Diet	Adherence	Ketone level
Krikorian et al. 2012	6 weeks	23	10 M 13 F	70.1	N/A	MCI	Low CHO diet (5-10%, 20 g/day CHO)	No drop outs	Detection of Acetoacetate (ketone bodies) in urine of low CHO diet group
Krikorian et al. 2014	6 weeks	7 -2 dropped out	2 M 3 F	72	N/A	MCI	Low CHO diet (5-10%, 20 g/day CHO)	2 were withdrawn due to lack of available data (28.5%)	Significant increase in ß-OHB levels (p=0.03)
Taylor et al. 2018	90 Days	15- 5 dropped out	7 M 8 F	73.1	N/A	AD or Amnestic MCI	VHF-KD- 70 % fat (10-40% MCT) and multivitamin	5 dropped out due to caregiver burden (33%)	60-80% consumption of MCT, detection of urine acetoacetate (60.6%), significant increase in serum ß-OHB (p<0.001) that returned to normal after washout
Phillips et al. 2021	12 weeks	26- 1 dropped out	16 M 10 F	69.8	17 Apo E4 +ve	AD	KD- 6 % CHO	81% adherence (21 completed) - 1 drop out due to side effects	12-week mean blood beta-hydroxybutyrate level of 0.95 ± 0.34 mmol/L

Krikorian and colleagues (Krikorian et al., 2012a) restricted CHO intake to 20 g/day but did not alter total energy, fat and protein intake for 6 weeks in older adults with MCI in two of

the studies. Participants were randomized to either a high CHO diet (50% of total energy intake) or the low CHO ketogenic diet (5-10% CHO intake). They received educational and counselling sessions at the baseline visit to help them follow the dietary requirements (Krikorian et al., 2012a) which is similar to the educational sessions provided by Phillips and colleagues (Phillips et al., 2021a). They were also provided with information about the macronutrient content of common foods and sources of fat, CHO, and protein. They had weekly contact with the researchers to ensure protocol compliance and to allow them to ask any questions regarding the diet. Pre and Post intervention dietary intake was measured using food diaries to analyse dietary intake and assess adherence to the diet plan (Krikorian et al., 2012a, Phillips et al., 2021a). Participants were provided with oral and written instructions for food and beverage portion estimation using a portion poster (Nutrition Consulting Enterprises, Framingham, MA, USA) along with instructions for recording quantities of food and beverages consumed (Krikorian et al., 2012a). The results of the dietary assessments showed that all the participants adhered to the diet. However, at the end of the study only one participant out of 12 expressed the willingness to continue the low CHO diet (Krikorian et al., 2012a). Ketone bodies measured in urine increased in participants who followed the low CHO diet (Krikorian et al., 2012a). A follow up study conducted by these researchers followed the same dietary adjustments on 7 participants but in this study blood ketone levels were measured to assess ketosis (Krikorian et al., 2014). Studies have shown that blood and capillary measurement of Beta-hydroxyl butyrate (ß-OHB) are more sensitive than urinary ketone measurements to reflect metabolic status (Turan et al., 2008). Of the seven participants, two were removed from analysis due to the lack of available data to permit robust quantification. Five participants with MCI followed the low CHO diet for six weeks. A significant increase in blood ketone levels was detected in the study ($p=0.03$).

Taylor and colleagues, (2018) used a combination of MCT supplementation and a very high fat (VHF) ketogenic diet to achieve optimum ketosis. In this study participants were also provided with a multivitamin to prevent micronutrient deficiencies (Taylor, 2018). The diet limited CHO intake to 20 g/day (2-10% of total energy intake) and protein to 20% while fat intake made up 70% of daily energy intake to achieve 1:1 ratio of food between fat and non-fat sources. Participants gradually added MCT to the diet through mixing of MCT oil with

food and beverages after attending cooking demonstrations. In the first week, MCT supplied 10% of the total fat intake, which was increased to 40% of energy intake by the end of 3 months duration of the study. The dietary intervention achieved ketosis which was evidenced by the significant increase in plasma ß-OHB ($p<0.001$) in plasma. There was a high dropout rate in the study (*n 5*; 33%) which was attributed to increased carer burden due to the restrictiveness of the diet, especially in individuals with advanced dementia (Taylor, 2018). Overall, the diet was tolerated as evidenced by the three day food records, but adverse events such as diarrhoea due to MCT oil were reported by the study participants (Taylor, 2018).In the study conducted by Philipp and colleagues, participants were provided with a 1 hour diet instruction session during which they were taught how to use blood glucose and ketone monitor (Phillips et al., 2021a). Participants were randomised either to a low CHO diet in which CHO made 6% of energy intake or a low fat health diet. A 10 week washout period was set after 12 weeks, after which participants resumed their diets. Participants were provided with two standardised emails per week and a 10 minute video regarding dietary intake. They were also provided with key fact sheets about both diet plans. Of 26 participants 21 completed the KD and 18 achieved physiological ketosis. Overall the diet was tolerated well and the only reported adverse event was irritability. Furthermore, half of the study participants stated their intention to continue the ketogenic diet post intervention.

- **Outcome measures of cognition and ketogenesis**

An outcome measured in 10 studies was altered ketone concentrations in blood and urine (Henderson and Poirier, 2011, Ohnuma et al., 2016, Ota et al., 2016, Reger et al., 2004, Rebello et al., 2015, Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018, Phillips et al., 2021a, Fortier et al., 2021). Circulating blood ß-OHB concentrations were measured in 9 studies (Henderson and Poirier, 2011, Ohnuma et al., 2016, Ota et al., 2016, Reger et al., 2004, Rebello et al., 2015, Krikorian et al., 2014, Phillips et al., 2021a, Fortier et al., 2021, Henderson et al., 2020) to assess ketone levels. All of the studies that measured blood ketone concentrations demonstrated increased ketones in individuals taking MCT (Henderson and Poirier, 2011, Ohnuma et al., 2016, Ota et al., 2016, Reger et al., 2004,

Rebello et al., 2015, Krikorian et al., 2014, Phillips et al., 2021a, Henderson et al., 2020, Fortier et al., 2021). While one study measured urinary ketones using urine strips (Krikorian et al., 2012a), another study used both blood and urine tests to measure ketone concentrations (Taylor, 2018).

All of the fourteen studies measured the changes in cognitive functions as primary outcomes (refer to table2.6). Of the fourteen studies, seven showed statistically significant improvement in either overall cognitive functions (Reger et al., 2004, Henderson et al., 2009, Abe et al., 2017, Taylor, 2018) or improvement in specific subsets of memory functions (Ota et al., 2016, Krikorian et al., 2014, Krikorian et al., 2012a, Phillips et al., 2021a, Fortier et al., 2021) . Most commonly used test was the Mini Mental State Examination (MMSE) (Henderson, 2008, Rebello et al., 2015) and ADAS-Cog (Maynard and Gelblum, 2013, Abe et al., 2017) or both (Reger et al., 2004, Taylor, 2018, Newport et al., 2015, Ohnuma et al., 2016), both of these are commonly used measure to assess the over-all cognitive functions. Other domain specific cognitive measures were used such as Trail making test, verbal fluency, and verbal paired-associate learning (VPAL) have also been reported (Krikorian et al., 2014, Krikorian et al., 2012a, Reger et al., 2004, Rebello et al., 2015, Ota et al., 2016, Fortier et al., 2021). Most of the studies showed significant improvement in cognitive and memory functions in relation to ketogenesis in comparison to pre-intervention scores and/or the scores of the control group. Some studies reported the improvement in cognitive functions detected through changes in cognitive test results, however, the improvement was not statistically analysed (Maynard and Gelblum, 2013, Newport et al., 2015, Rebello et al., 2015). Individual changes that may not be statistically significant does not provide robust empirical evidence for future RCTs and or causation analysis. Case studies (Maynard and Gelblum, 2013) reported that participants who had mild AD demonstrated improvement in cognitive functions by the end of the intervention after supplementing 30 g/day of Caprylic Triglycerides to their dietary intake. However, some of the findings from this study do not support the generalisation of the results. For example, greater improvement in MMSE scores was detected in patients who were diagnosed with Mild AD prior to the intervention in comparison to their counterparts who had moderate AD. Additionally, 2 participants out of the 8 participants used only 10g/day of

the CT (Maynard and Gelblum, 2013). The duration of the CT intake ranged from 6 months to 4 years (Maynard and Gelblum, 2013).

Table 2.6. Table Summarising the outcome measures and intervention effects in the different studies

Author-Date	Population	Sample Size	Intervention	Cognitive Measures	Ketone level
Abe et al. 2017	Frail elderly	38 2 dropped out (5%)	LD+6g/day MCT+ 1.2 g/day L-leucine +20 micrograms/day cholecalciferol	Significant Improvement in MMSE score, p=0.017	N/A
Henderson et al. 2009	Mild to moderate AD	152 12 dropped out (8%)	20 g/day AC 1202 (MCT)	Significant Improvement in ADAS-Cog score (p=0.0148) after 90 days.	Increase in ß-OHB in APO E4 -ve (p= 0.008)
Krikorian et al. 2012	MCI	23	Low CHO diet (20 g/day)	Significant improvement in V-PAL scores (p=0.01); no effect on Trail Making test.	Detection of Acetoacetate (ketone bodies) in urine of low CHO diet group
Krikorian et al. 2014	MCI	7 2 dropped out (28.5%)	Low CHO diet (5-10 %)	Significant Improvement in Trail making test B scores (p=0.01) Non-significant improvement in List Recall score (p=0.07)	Significant increase in ß-OHB levels (p=0.03)
Maynard and Gelblum 2013	Mild to moderate AD	8	20 g/d CT	Non -significant improvement in MMSE scores (P=0.3735)	A/N

Newport et al. 2015	Younger onset sporadic AD	1	35 ml coconut oil + MCTG–165 ml/day	ADAS-Cog score improved by 6 poimts.	N/A
Ohnuma et al. 2016	Mild to moderate Sporadic AD	24 2 dropped out (8%)	40 g/day Axona powder (MCT)	Non-significant improvement in MMSE and ADAS-Cog scores (P>0.05)	Ketone bodies: increased three fold from 114.5 ± 105.4 µM to 322.6 ± 240.2 µM during first month then remained constant
Ota et al. 2016	No dementia-older adults	20 1 dropped out (5%)	Ketogenic meal (20 g MCT)	Significant improvement in Global score (p=0.017)	Significant increase in plasma ketone levels (p<0.001)
Rebello et al. 2015	MCI	6 2 dropped-out (33%)	MCT (56 g/day)	Improvement in ADAS-Cog	Elevation in ß-OHB in APO E4-ve participants in baseline (0.19 µM) then it remained constant at week 4 (0.02 µM) and week 24 (0.01 µM). Increase in ß-OHB in APO E4 +ve participants during all study visits; from 0.06 µM to 0.39 µM to 0.54 µM)
Reger et al. 2004	AD and MCI	20	Neobee (MCT) 40 ml/day	Significant improvement in ADAS-Cog scores (P=0.04) in APO E4 negative participants.	Significant increase in ß-OHB levels observed 90 mins after treatment (p=0.007). ß-OHB continued to increase between 90 mins and 120 mins in APO E4 +ve but remained constant in APO E4 -ve participants

Taylor et al. 2018	AD	15 5 dropped out (33%)	VHF-KD 70% fat (10-40% MCT) and multivitamin supplementation	Improvement in MMSE score (p=0.05) Statistically significant improvement in ADAS-Cog scores (p=0.001)	Detection of urine acetoacetate (60.6%); significant elevation in serum ß-OHB (p<0.001) that returned to normal after washout
Fortier et al. 2021	MCI and AD	83	A ketogenic drink containing medium chain triglyceride (ketogenic medium chain triglyceride [kMCT]; 15 g twice/day	Free and cued recall (Trial 1; *P* =0 .047), verbal fluency (categories; *P* = 0.024), Boston Naming Test (total correct answers; *P* = 0.033), and the Trail-Making Test (total errors; *P* = 0 .017) improved significantly in the kMCT group compared to placebo.	B-OHB increased significantly in the kMCT group compared to placebo (P < .0001)
Phillips et al. 2021	AD	26- 21 completed	Ketogenic diet (6% CHO)	Improvement in ACE-III (p=0.12), significant improvement in ADCS-ADL (p=0.037) & QOL-AD (p=0.031)	12-week mean blood beta-hydroxybutyrate level of 0.95 ± 0.34 mmol/L
Henderson et al. 2020	AD	412	AC-1204 (20 g caprylic triglyceride)	No significant difference between placebo & intervention group	mean B-OHB levels obtained 1 h post dose in the AC-1204 group for this

				at 26 weeks; ADAS-Cog 11 (p=0.25), ADCS-ADL (p=0.38),	current study were 0.271 mM at Week 8 (Day 56), 0.272 mM at Week 17 (Day 119), and 0.250 mM at Week 26 (Day 182).

- **Quality of Life**

Cognitive interventions can improve the quality of life for people with mild cognitive impairment (Phillips et al., 2021b). A study conducted by Phillips and colleagues in 2021, demonstrated that the dietary intervention using ketogenic diet improved quality of life of participants. As participants who followed the diet showed an improvement in their daily functions as there was clinically meaningful two point improvement in their ADCS-ADL scores (Phillips et al., 2021b). However, in another study conducted by Henderson and colleagues in 2020, no significant change in quality of life of patients with mild to moderate AD was detected (Henderson et al., 2020) with no statistically significant (p=0.38) change in ADCS-ADL scores in participants consuming AC-1204.

Changes in cognitive functions could lead to an improvement or decline in quality of life of older adults (Banerjee et al., 2006, Hurt et al., 2010). Thus, the results from these studies would suggest that it is important to assess quality of life for people with MCI as part of cognitive interventions.

- **APO E4**

Previous studies have shown that APO E4 status affects metabolism in relation to ketone absorption and utilization (Henderson and Poirier, 2011). The relationship between APO E4 and ketosis was demonstrated in the study conducted by Henderson and colleagues (2009) (Henderson et al., 2009) where the APO E4 status of participants had an impact on the ß-OHB concentration in the blood. ß-OHB level increased over 120 minutes after administration of MCT in APO E4 positive individuals but remained stable after 90 minutes of administration in APO E4 negative individuals (Henderson et al., 2009). Individuals who were APO E4 negative demonstrated an increased improvement in their cognitive functions

in comparison to their APO E4 positive counterparts (Reger et al., 2004, Rebello et al., 2015, Maynard and Gelblum, 2013, Henderson et al., 2009, Henderson et al., 2020). On the other hand, in the study conducted by Maynard and Geblum (2013), APO E4 had no effect on study outcomes as the APO E4 positive participants who were supplementing the diet with Caprylic Triglycerides intake showed an improvement in MMSE scores after the intervention (Maynard and Gelblum, 2013). However, APO E4 status of participants was not measured in all of the studies (Ota et al., 2016, Abe et al., 2017). Thus, more studies are needed to understand the effect of APO E4 gene on DK and cognition.

2.4.4. Findings from Scoping Review

The aim of the review was to identify the scope of the current evidence between Dietary Ketogenesis (DK) and cognitive functions in older adults to identify the gaps in the literature in the field. Whilst relatively few studies were identified, there was a positive association between dietary induced ketogenesis and cognitive functions in older adults (Reger et al., 2004, Henderson et al., 2009, Krikorian et al., 2014, Krikorian et al., 2012a, Abe et al., 2017, Ota et al., 2016, Taylor, 2018, Phillips et al., 2021b, Fortier et al., 2021). Studies that were conducted on individuals with no to mild cognitive impairment showed increased improvements in cognition (Reger et al., 2004, Rebello et al., 2015, Maynard and Gelblum, 2013) in comparison to studies conducted on individuals with more advanced cognitive impairments (Ohnuma et al., 2016, Reger et al., 2004, Taylor, 2018, Maynard and Gelblum, 2013). Suggesting that interventions are likely to be more effective in earlier stages of dementia (MCI or mild AD) in comparison to interventions in later stages of the disease. One of the reasons for this observation could be attributed to the ability of participants to adhere to the intervention or to other factors that remain unclear such as extent of neuronal damage.

The efficacy of DK on cognition was investigated by measuring changes in cognitive functions. MMSE and ADAS-Cog were the most commonly used outcome measures in the studies (Reger et al., 2004, Taylor, 2018, Newport et al., 2015, Ohnuma et al., 2016, Henderson, 2008, Rebello et al., 2015, Maynard and Gelblum, 2013, Abe et al., 2017). These tests measure the overall cognitive functions (Folstein et al., 1975, Rosen et al., 1984) of

individuals and might not reflect mild changes that might occur in different areas of memory (e.g. executive memory, orientation which might improve Quality of Life) and inadvertently improve the life of the persons living with dementia . The effect of the intervention on subsets of cognitive functions was further confirmed by studies that demonstrated an improvement in long-term or executive memory despite the lack of change in overall cognitive results tested by MMSE or ADAS-Cog (Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018, Fortier et al., 2021). Suggesting that often the changes may not be reflected or captured through overall cognitive measurements.

Examination of the 14 studies demonstrated that the benefits of DK on cognitive functions of older adults remains unclear. Statistically significant improvement in overall cognitive functions (MMSE and ADAS-Cog) was demonstrated in four studies (Reger et al., 2004, Henderson, 2008, Abe et al., 2017, Taylor, 2018) while five other studies showed improvement in subsets of cognitive functions specifically in executive functions and verbal memory (Ota et al., 2016, Krikorian et al., 2014, Krikorian et al., 2012a, Fortier et al., 2021, Phillips et al., 2021b). Whilst the studies showed a significant correlation between ketogenic diet and cognitive functions, the small sample size and the high dropout rate limit the generalisability of the results. Moreover, the inconsistencies within and between studies in terms of study designs, types of interventions, and outcome measures might limit the application of such interventions in a clinical setting.

I. LIMITATIONS

In general, the studies identified provide evidence that suggest an association between DK and cognitive functions in older adults. However, confidence in these findings is limited due to several issues.

a) Generalizability and credibility

Most of the studies were pilot studies, which explains their short duration and small sample size. Seven studies did not report planned sample size or power calculations (Rebello et al., 2015, Ota et al., 2016, Krikorian et al., 2014, Abe et al., 2017, Ohnuma et al., 2016, Reger et al., 2004, Taylor, 2018) and three studies did not report funding sources (Taylor, 2018, Rebello et al., 2015, Newport et al., 2015). Seven studies were funded by industry (Ohnuma

et al., 2016, Maynard and Gelblum, 2013, Reger et al., 2004, Henderson, 2008, Abe et al., 2017, Henderson et al., 2020, Fortier et al., 2021) which could impact the credibility of the results due to the conflict of interest (Nestle, 2016). Furthermore, the combination of healthy older adults with cognitive impairment patients (MCI, AD), makes it difficult to evaluate the effect of the intervention in specific stages of life/dementia.

b) Inconsistencies between studies

A major limitation of these studies was the lack of consistency and replicability between studies. Interventions using MCT were dominant in the studies (*n 10*) (Henderson et al., 2009, Reger et al., 2004, Maynard and Gelblum, 2013, Newport et al., 2015, Ohnuma et al., 2016, Ota et al., 2016, Abe et al., 2017, Fortier et al., 2021, Henderson et al., 2020) . There was a lack in consistency in interventions as the method of administration, volume and duration of the intervention differed between studies that used MCT supplementation to induce ketosis. Furthermore, the outcome measures differed between studies. The most common cognitive measures used were the ADAS-Cog (Rebello et al., 2015, Henderson et al., 2009), MMSE (Maynard and Gelblum, 2013, Abe et al., 2017) or both (Reger et al., 2004, Taylor, 2018, Newport et al., 2015, Ohnuma et al., 2016). However, some studies used domain specific cognitive measures such as Trail Making and VPAL (Krikorian et al., 2012a, Taylor, 2018, Fortier et al., 2021). This variability often affects the understanding of changes one may note across studies. The method for measuring ketones in the body also varied between studies as some studies measured blood ß-OHB concentrations (Ohnuma et al., 2016, Reger et al., 2004, Rebello et al., 2015, Ota et al., 2016, Krikorian et al., 2014, Taylor, 2018, Henderson, 2008, Fortier et al., 2021, Henderson et al., 2020, Phillips et al., 2021b) while others measured urinary ketones (Taylor, 2018, Krikorian et al., 2012a). A study comparing measures of ketones in urine and blood has demonstrated that blood and capillary measurement of ß-OHB are more sensitive than urinary ketone measurements in reflecting the patient's metabolic status (Turan et al., 2008). The duration of the dietary intervention in studies ranged from 3 weeks to 6 months. There were also differences in the way in which MCT were administered with MCT provided intravenously, added to food in the form of powder or oil, or mixed with drinks. The amount of MCT differed between studies, ranging from 6 g/day to 150 g/day with different kinds of MCT used (AC-1202, Caprylic Triglycerides).

There were also differences in the range (6 to 152 participants) of people recruited within studies as the participants often had different levels of cognitive impairment. Some studies included people with MCI and AD (Taylor, 2018, Reger et al., 2004), frail elderly (Ota et al., 2016, Abe et al., 2017, Fortier et al., 2021) , only individuals with MCI (Reger et al., 2004, Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018, Rebello et al., 2015) or AD (Taylor, 2018, Newport et al., 2015, Ohnuma et al., 2016, Maynard and Gelblum, 2013, Reger et al., 2004, Henderson, 2008, Henderson et al., 2020, Phillips et al., 2021b), other kinds of cognitive impairment such as sporadic AD (Ohnuma et al., 2016, Newport et al., 2015); which could have an impact the outcome of the intervention as neuronal damage differs between the groups. It is likely that the dietary interventions may affect people differently depending on the level cognitive impairment or dementia. Thus, more studies with larger sample sizes are needed to investigate this effect among people with different levels of cognitive impairment.

II. FACTORS AFFECTING FEASIBILITY

a) Adherence

Most of the studies associated the high drop-out rates to the inability of participants to adhere to the intervention either due to the restrictiveness of the ketogenic diet (Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018) or the gastro-intestinal side effects of MCT intake such as diarrhoea and bloating (Henderson et al., 2009, Maynard and Gelblum, 2013, Ohnuma et al., 2016, Rebello et al., 2015, Henderson et al., 2020). The application of a four-day titration method to supplement the body with MCT showed a reduction in the gastro-intestinal implications that usually accompany MCT consumption in comparison to a previous study that applied a two day titration method (Henderson et al., 2009, Henderson et al., 2020). Thus, in future studies this approach using a four-day titration of MCT could help to reduce dropout rates by reducing risks of MCT associated adverse events.

Dietary modifications using reduced dietary CHO have been studied to achieve ketosis. However, the high drop-out rate revealed the impracticality of utilizing a highly restrictive diet on individuals with advanced cognitive impairments (Taylor, 2018). The high dropout rate could be related to the sugary cravings of some individuals with Alzheimer's disease, which has been established in previous studies (Schiffman, 1997, Ikeda et al., 2002, Kai et

al., 2015). Furthermore, the long-term application of this diet in relation to its restrictiveness could be a burden on participants and their caregivers.

- Psychological Barriers to adherence:

Lifestyles are patterns of behaviours developed since early years and shaped by cultural and social background (Lam and Cheng, 2013). Especially for older adults a lot of behaviours stem for habits followed since early age and into all life stages. Thus, any change in behaviour or lifestyle will require a change in habitual routines which is not easily accomplished especially for older adults with cognitive impairment (Lam and Cheng, 2013).

When it comes to adherence to behavioural change interventions, the mental and cognitive state of older adults might act as a barrier to adherence. Research has shown that people with cognitive impairment respond to lifestyle interventions (Lam et al., 2012). However, their motivation for participation and adherence might be impacted by mood disturbances such as depression and apathy (Lam and Cheng, 2013). Another potential barrier to adherence is the ability of older adults to adapt to a new behaviour and make it a habit (Lam and Cheng, 2013). Adequate understanding of the intervention and benefits plays a role in improving commitment for change and adherence for longer (Lam and Cheng, 2013). However, sometimes knowledge is not enough to translate into behaviour or to change well imbedded ideals based on culture, up bringing, and social background. Education might increase awareness to change habits but might not necessarily translate into behavioural change (Cheng et al., 2011).

There are likely individual differences in how older persons perceive barriers to dietary changes and how they develop strategies to address the barriers. An analysis by McLaughlin and colleagues concluded that the most common barriers are personal preference, lack of knowledge, inconvenience (McLaughlin et al., 2015). Social determinants, such as family and social support, have also been recognised as a powerful influence in food choices and eating patterns (Vanzella et al., 2021). Family support was identified as both a barrier and a facilitator to adherence of dietary recommendations (Cardol et al., 2022).

Traditionally, health promotion activities excluded older people as they were seen as unable or unwilling to change their behaviour's and lifestyle (Anderson et al., 2000) . However, life style modification intervention studies for chronic diseases suggest that peer support, self-

efficacy, willingness to adhere, health status, independence and mental conditions are facilitators to adherence in older adults (Jackson et al., 2009, Leijon et al., 2011) .

An understanding of psychosocial factors that impact engagement in healthy lifestyle behaviour's is essential for the development of effective lifestyle interventions (Cardol et al., 2022). Thus, the degree of targeted behaviour change, feasibility and acceptability issues, and required lifestyle changes are important determinants of adherence to consider.

b) Risks

Ketogenic diets in older adults could play a role in exacerbating other diseases such as cardiovascular or renal diseases due to the substitution of carbohydrates with fat or protein (Krikorian et al., 2012a). High fat intake has been associated with cardiovascular diseases due to an increase in blood cholesterol and triglycerides levels (Ascherio, 2002). While a high protein diet could exacerbate kidney disease and increase risk of proteinuria, diuresis and nephrolithiasis (Friedman, 2004). Furthermore, evidence demonstrates a relationship between high blood cholesterol concentrations and increased dementia risk (Dufouil et al., 2014, Iwagami et al., 2021, Peters et al., 2020). Thus, a high fat low CHO ketogenic diet might lead to an increase in blood cholesterol level and consequently increase dementia risk in older adults.

Krikorian and colleagues(2012) had some concerns regarding the reduced dietary fibre intake of participants associated with the low CHO diet and its impact on their gastro-intestinal functions especially constipation, which is a common issue with older adults (Krikorian et al., 2012a). Furthermore, Phillips and colleagues reported weight loss among participants following the KD (Phillips et al., 2021a), this poses a risk as older adults and dementia patients are at a high risk of malnutrition (Borda et al., 2021, XIAO et al., 2021) Gastro-intestinal side effects of consumption of MCT such as nausea, bloating, diarrhoea, and abdominal pain were reported in the studies (Henderson et al., 2009, Maynard and Gelblum, 2013, Ohnuma et al., 2016, Rebello et al., 2015). The side effects of MCT consumption on the gastro-intestinal tract are well known from previous studies (Jeukendrup and Aldred, 2004, Marten et al., 2006). Thus, the long-term consumption of

MCT or ketogenic diet might pose a risk on the health and physical well-being of older adults. This was also demonstrated in a review conducted by Lilamand and colleagues (2020) (Lilamand et al., 2020), which discussed the effect of KD on dementia risk.

Summary:

Inducing dietary ketosis can play a role in reducing age related cognitive impairment and development of Alzheimer's Disease (Chatterjee 2020). However, to improve quality of the interventions and provide data on effectiveness it is essential to improve adherence to the DK interventions and overcome the high drop-out rates reported in most studies. The reasoning for high drop-out rates appeared to be attributed to the restrictiveness of the ketogenic diet (Krikorian et al., 2014, Krikorian et al., 2012a, Taylor, 2018) or the gastro-intestinal side effects of MCT intake such as diarrhoea and bloating (Henderson et al., 2009, Maynard and Gelblum, 2013, Ohnuma et al., 2016, Rebello et al., 2015). Thus, utilising food-based approaches using foods that could induce ketosis could potentially aid in reducing these barriers and overcoming issues with drop-out rates (Chatterjee et al., 2020, Fernando et al., 2015). As food based interventions have a higher positive nutrition-related outcomes in community-dwelling older adults than other interventions (Bandayrel et al., 2011). Food based approaches require long-term commitments, but are more likely to be sustainable for longer (Demment et al., 2003, Smitasiri et al., 2007) as they overcome some of the barriers that medical or clinical dietary interventions have (Bandayrel et al., 2011, Demment et al., 2003). Therefore, the next section provides an introduction to using coconut oil which offers an opportunity to provide a food-based approach to induce DK.

2.5. Coconut Oil:

This section provides a description of the composition of coconut oil, which could be used to induce DK. Coconut oil (CO) is a dietary source that is rich in ketone body precursors (Chatterjee et al 2020). CO is derived from the coconut fruit has a unique fatty acid composition, as it is rich source of Medium Chain fatty acids (MCFA) (Fernando et al., 2015).

2.5.1. Coconut oil extraction and uses:

Coconut oil (CO) is extracted from coconuts (*Cocos nucifera L*.) and is traditionally used as cooking oil in multiple areas across the world especially in Malaysia, India, Sri Lanka and Philippines (Krishna et al., 2010). CO production methods vary between countries, it can extracted hot or cold (Krishna et al., 2010). Virgin coconut Oil (VCO) is extracted by collection oil from coconut milk at high temperatures (≤60−80 °C) (Krishna et al., 2010). This method is considered superior to extraction method of refined, bleached and deodorised (RBD) coconut oil (Nevin and Rajamohan, 2004) as it maintains a higher phenolic content in the oil (Dayrit et al., 2011). However, fatty acids composition is the same between VCO and RBD oil (Dayrit et al., 2011, Marina et al., 2009).

2.5.2. Fatty Acid Composition of Coconut oil:

Coconut oil is principally composed of SFA (about 92%), with 62–70% being MCFA (Dayrit, 2015, Chatterjee et al., 2020) making coconut oil unique among dietary fats. The fatty acid content in CO makes it unique, as most animal and vegetable oils are made of primarily LCFAs (≥C14) (Orsavova et al., 2015, Clark et al., 2014) .

Table 2.3. Fatty acid content in Coconut Oil (Chatterjee et al., 2020)

Fatty Acid	Percentage of total FA content (%)	MCFA/LCFA
Caprylic acid; C8	4.6-10.0	MCFA
Capric acid, C10	5.0-8.0	MCFA
Lauric acid; C12	45.1-53.2	MCFA
Myristic acid, C14	16.8-21.0	LCFA
Palmitic acid C16	7.5-10.2	LCFA
Stearic acid C18	2.0-4.0	LCFA

Abbreviations: MCFA: Medium Chain Fatty Acids, LCFA: Long Chain Fatty Acids

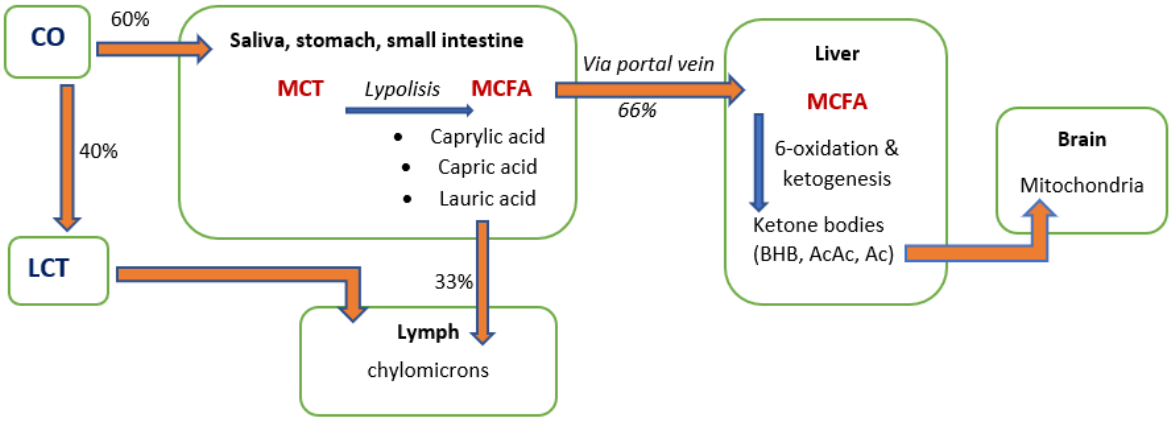
Due to its high saturated fat content, CO has been previously associated with an increased risk of cardiovascular diseases (CVD) and dyslipidaemia (Barnard et al., 2014, Morris and Tangney, 2014). However, recent research demonstrated that long chain fatty acids (LCFAs) in saturated fats are mostly responsible for the increased risk of diseases (Khaw et al.,2018,

Zhuang et al.,2019). As MCFAs that make up the majority of the saturated fat content of coconut oil (C8 (caprylic acid), C10 (capric acid) and C12 (lauric acid) do not affect blood lipid levels (Marten et al., 2006, Fernando et al., 2015, Assunção et al., 2009). Unlike long-chain fatty acids, MCFAs are absorbed differently in the body due to their shorter carbon chain lengths (Huang et al., 2021). Around two thirds of MCFAs are absorbed via the portal vein where they travel in the form of free fatty acids in complex with plasma albumin (Acquistapace et al., 2019) while only one third is incorporated into chylomicrons (Bragdon and Karmen, 1960). Thus, most of MCFAs resist binding to fatty acid binding proteins which reduces their contribution to arterial fat deposits (Fernando et al., 2015). This reduces their impact on the cardiovascular system (Marten et al., 2006, Fernando et al., 2015).

MCFA also differ from LCFA in the way it crosses mitochondrial membrane (Williamson et al., 1968). As MCFAs enter the mitochondria via passive diffusion while LCFA relies on carnitine assistance to cross the mitochondrial membrane (Groot et al., 1976, Williamson et al., 1968, Jezek et al., 1996, Scholte and Groot, 1975). It has been previously argued that lauric acid (C12), which is the makes up the majority of MCFAs in CO does not carry MCFA properties (Dayrit, 2015). However, the absorption, digestion and metabolism of lauric acid is more similar to capric acid (C10) which is another MCFA than other LCFAs such as palmitic acid (C16) (Dayrit, 2015).

MCFAs are directly absorbed into hepatocytes in the liver, where they undergo β-oxidation, lipogenesis and ketone body production (Schönfeld and Wojtczak, 2016). They are metabolised to produce acetoacetic acid (AcAc), acetone (Ac) and 3-β-hydroxybutyrate (βHB) (Fernando et al., 2015). The liver is unable to convert the majority of ketone bodies to Ac-CoA for energy production via Krebs cycle due to the limited amount of β-ketoacyl-CoA transferase. Thus, ketone bodies are transported from the liver to other organs such as heart, brain, and muscles (Schönfeld and Wojtczak, 2016).

Figure 2.2 demonstrating coconut oil MCFA digestion, metabolism and transportation to the brain and other organs.



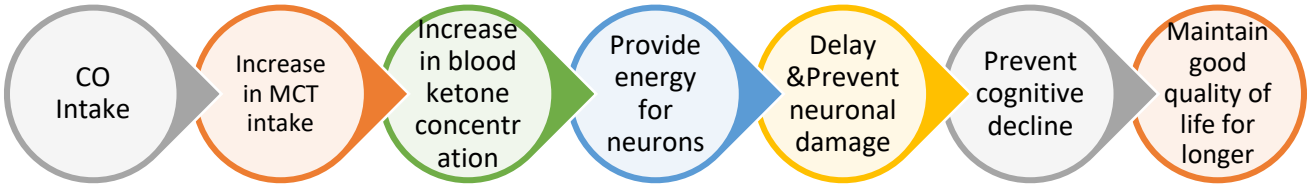
Abbreviations: CO, coconut oil; LCT, long chain triglycerides; MCT, medium chain triglycerides; MCFA, medium chain fatty acids; BHB, beta-hydroxybutyrate; AcAc, acetoacetate; Ac, acetone.

2.5.3. Potential neuroprotective effect of CO:

Increased ketone levels, obtained through a balanced healthy diet containing ketone precursors such as CO and MCT, may provide an alternative energy source in the disrupted glucose metabolism that features in AD and other neurodegenerative diseases (Augustin et al., 2018{Ota, 2016 #310, De la Rubia Ortí et al., 2017, Benlloch et al., 2019, Włodarek, 2019)}. A study was conducted to analyse the effect of coconut oil on cognitive functions of older adults with Alzheimer's disease (De la Rubia Ortí et al., 2017). 22 control group; 22 intervention group. 80% of them were females. Results showed an improvement in the patients overall cognitive performance based on the results from MMSE. However, in the overall population, there was a 39% improvement in cognitive functions; where there was 65% improvement in orientation, 50% in calculation and concentration, 14% in fixation, 25% in memory, 30% in language construction. These results demonstrate that coconut oil could support improvements in cognitive functions in older adults. However, the study had a few limitations including the fact that 80% of the participants were females and all of them had severe Alzheimer's disease and were living in residential care. Moreover, geriatric depression and other mental conditions that could affect the results of the trial were not

taken into consideration; and the medication taken by the participants could be responsible for the improvement in cognitive functions (De la Rubia Ortí et al., 2017).

Figure 2.3. Demonstrating the potential effect of coconut oil on cognitive functions and Quality of Life



2.6. Summary

The literature review provided an overview of the 11 interventions that evaluated the effect of DK on memory in older adults. The review concluded that DK led to an improvement in cognitive functions, but evidence remains inconclusive due to methodological limitations. One of the main limitations of the majority (n= 7/11) of the studies conducted on DK and cognition was retention and adherence rates. Participants drop-out rates were high, and adherence was low; either due to side effects of the intervention (Gastrointestinal issues with MCT supplementation) or restrictiveness of the dietary intervention (ketogenic diet). The results would suggest there is a need for research on the feasibility of using such interventions in older adults to overcome the barriers to adherence and high drop-rates observed. The present research was developed to evaluate the feasibility and efficacy of the intervention to aid in informing the design of a future trial that will evaluate the effectiveness of the intervention.

2.6.1. Aims & Objectives

The aim of the present study was to investigate the feasibility, pilot the design and delivery of an RCT to assess the effect of a dietary intervention using CO on improving cognition and quality of life in adults with MCI. If the study is feasible, the findings will inform the design of a larger RCT to test the effectiveness of a dietary intervention using coconut oil intake on memory and quality of life in older adults.

Primary Objectives:

1. To estimate adherence rate of participants to dietary oil intake.
2. To test the procedures of the intervention (delivery of the intervention, recording and monitoring of adverse events, estimate recruitment and retention rates, and refine the selection of outcome measures in preparation for an RCT that would test the effectiveness of the intervention).
3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future RCT.
4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.
5. To determine the acceptability of randomisation and of the intervention in participants and obtain feedback about the study procedure from study participants.

Secondary Objectives:

1. To provide preliminary estimates of the clinical effect of dietary coconut oil on cognitive functions in adults with MCI
   Outcome measures to be considered:
   a. Difference in the cognitive executive measures in participants taking coconut oil.
   b. Differences in overall cognitive measures in participants
   c. Differences in verbal memory measures in participants.

2. To provide preliminary estimates of the potential effect of dietary coconut oil on quality of life in participants.

3. To assess the dietary energy and macronutrient (carbohydrate, fat, and protein) intake of participants.

The next chapter will outline the methodological considerations and explore the philosophical underpinnings of the current study.

Chapter 3: Methodology

This chapter outlines the methodological and theoretical background of the current study. The chapter explains the Medical Research Council (MRC) complex interventions framework used to design and model the dietary intervention to assess its feasibility (Skivington et al., 2018, Craig et al., 2008). It also explores the research philosophy and methodological underpinnings of the study while explaining the rationale for using a pragmatic mixed method approach to facilitate the process evaluation of the intervention. The research methods will be covered separately in Chapter 4.

3.2. Study Design

This study was designed using the Medical Research Council (MRC) complex intervention framework (Craig et al., 2008) to evaluate the feasibility of a dietary intervention using coconut oil in older adults and those with Mild Cognitive Impairment. It was designed as a feasibility study to better understand the efficacy of the intervention and the experiences of the study participants to inform future research.

The current study, which is the dietary intervention on cognition (DICe) is a complex intervention as it looks into changing the dietary behaviour of study participants to improve their cognition and quality of life. In healthcare settings, complex interventions which are defined as interventions with “several interacting components” (Craig et al., 2008, Campbell et al., 2000) are commonly used to influence behaviour change (Craig et al., 2008, Campbell et al., 2007, Moore et al., 2015). The Medical Research Council (MRC) provides a guidance for designing and evaluating complex interventions to improve health (Craig et al., 2008, Campbell et al., 2007, Campbell et al., 2000). The guidance aims to help researchers choose appropriate methods for evaluating the impact of complex interventions (Craig et al., 2008, Campbell et al., 2007, Moore et al., 2015). Best practice requires complex interventions to be developed systematically starting with identifying the key uncertainties in the design (Craig et al., 2008, Campbell et al., 2007, Molina-Azorin et al.,2017, Hallberg and Richards, 2015). The main elements of the development-evaluation-implementation process of

complex interventions are developing an intervention; piloting and feasibility; evaluating the intervention; implementation and reporting at each stage (Craig et al., 2008). This guidance was used to design the DICe study to ensure that the most appropriate research method was applied. This process begins by identifying the relevant, existing evidence base, ideally through carrying out a literature review to identify research gaps and develop the intervention (Craig et al., 2008).

3.2.1. Rationale

A scoping review was conducted to explore the different interventions that evaluated the effect of DK on cognition in older adults (for more details see Chapter 2). The review concluded that methodological limitations and uncertainties (large range in sample size, intervention methods and outcome measures; high drop-out rates) it was not possible to draw strong conclusions about the efficacy of these interventions. In the presence of uncertainties with the design of a complex intervention, feasibility and piloting methods are utilised (Craig et al., 2008) to inform the design of future interventions (Campbell et al., 2007). The merits of both pilot and feasibility studies were considered. Pilot trials use the same design and method as the subsequent larger main trial (Arain et al., 2010, Lancaster et al., 2004). Whilst feasibility studies are designed to build the foundation for the planned intervention study (Tickle-Degnen, 2013) and answer the question "Can this study be done?" (Orsmond et al., 2015). Feasibility studies inform the design of the main trial; they also helps determine any uncertainties in the study design thus reducing methodological design flaws and research waste (Blatch-Jones et al., 2018, Orsmond et al., 2015). Therefore, playing an important role in optimising complex public health intervention by evaluating the study design prior to assessing the effectiveness of an intervention (Blatch-Jones et al., 2018). Hence, a feasibility approach was the most suitable for this study because it allowed the exploration of the identified uncertainties in the study design.

3.2.2. Feasibility Studies:

Feasibility studies play an important role in the development of an intervention as they can inform sample size calculations, test study design, data collection methods, outcome

measures, recruitment procedures and the practicality and acceptability of the intervention (Blatch-Jones et al., 2018, Lancaster et al., 2004). Guidance published by Moore et al. (2015) highlighted that despite Randomised Controlled trials being the "gold standard" of research, they do not provide enough information about the delivery of an intervention by a service provider and its outcomes (Moore et al.,2015). A process evaluation on feasibility and the delivery of an intervention prior to an RCT is essential to help stakeholders understand the implementation of interventions and are vital in building an evidence base to inform the design of the intervention (Moore et al.,2015). It is important to incorporate considerations about implementation early on in the development and evaluation phase of a complex intervention (Craig et al., 2008, Campbell et al., 2007). Implementation is a highly active process which uses strategies to integrate evidence-based health interventions into practice (Moore et al.,2015, Hallberg and Richards, 2015). Given that multiple trials struggle with recruitment adherence and retention of participants, this information on implementation is key, especially when the study aims to understand the role of food consumption on a regular basis (Bower et al., 2014, Raftery et al., 2015). Therefore, the current study aimed at evaluating the feasibility of the intervention to investigate the gaps identified in the literature (adherence, outcome measures, retention) and its applicability to inform the design of a more robust clinical study in the future.

3.2. Research Philosophy

Randomised Clinical Trials (RCT) are considered to be the most robust study design to investigate the effectiveness of health treatments (Stolberg et al., 2004). There are two main types of RCTs: "explanatory" or "pragmatic" based on their aims (Wasan, 2014, Bench et al., 2013). Pragmatic RCTs aim to answer the question "Does this intervention work under usual conditions?" while explanatory trials evaluate the effectiveness of an intervention by answering the question "Does this work in ideal conditions?" (Wasan, 2014, Thorpe et al., 2009). On one hand the explanatory RCT tests the efficacy of an intervention based on a strict inclusion criteria which increases internal validity while reducing its external validity and generalizability (Loudon et al., 2015, Bench et al., 2013). While pragmatic RCTs are primarily designed to test the effectiveness of an intervention and whether an intervention works in normal conditions (Treweek and Zwarenstein, 2009, Thorpe et al., 2009). The aim of a trial and the research question determines whether the study is more pragmatic or

explanatory (Thorpe et al., 2009, Loudon et al., 2015). The pragmatic-explanatory continuum indicator summary (PRECIS) tool was developed by Thorpe and colleagues to help trialists design their study (Thorpe et al., 2009, Loudon et al., 2015). PRECIS recognises that the aim of the trial determines the design decisions made across the 10 study design domains. The PRECIS tool was used to guide decisions made for the study (see table 3.1) (Thorpe et al., 2009).

The design of the current study incorporated both pragmatic and explanatory components However, the design leans more towards the pragmatic end of the continuum as the study focused on feasibility of the dietary intervention not effectiveness. A limited number of clinical trials are purely pragmatic or explanatory (Loudon et al., 2015), as both components reinforce each other in a clinical environment (Wasan, 2014). A balance between pragmatic and explanatory qualities is found when both components mutually strengthen and complement each other to create a robust framework for a trial design (Loudon et al., 2015, Treweek and Zwarenstein, 2009, Wasan, 2014). Some literature demonstrates the importance of information provided by pragmatic trials on care in the real world (Loudon et al., 2015, Kent and Kitsios, 2009, Tunis et al., 2003). As explanatory trials that focus on efficacy of an intervention in ideal situations cannot be generalized to the wider community and be used in routine care (Loudon et al., 2015, Thorpe et al., 2009, Kent and Kitsios, 2009, Tunis et al., 2003). While a pragmatic approach is inclusive to all patients with a specific condition and could be more generalizable in the wider community (Kent and Kitsios, 2009, Tunis et al., 2003, Treweek and Zwarenstein, 2009). It is essential that the limitations of both pragmatic and explanatory trials are assessed critically before generalizing information to the care process (Loudon et al., 2015, Kent and Kitsios, 2009, Treweek and Zwarenstein, 2009). This study design therefore utilised the pragmatic approach.

Table 3.1: Design Components in DICe study based on PRECIS tool.

Pragmatic components	Explanatory Components
Participants: Broad Inclusion criteria, multiple sources for recruitment	Comparison Intervention: Placebo group using sunflower oil
Intervention Flexibility: no specific directions on oil consumption	Follow up intensity: Participants were contracted monthly for follow up to increase adherence and monitoring
Primary trial outcome: Primary outcome is on practicality not effectiveness	Participant compliance: Measured and used for data analysis
Analysis of primary outcome: no restriction in analysis based on non-adherence	

3.3 Methodological Underpinnings

The pragmatic approach was used in the present study for the development and evaluation of the dietary intervention. This was because pragmatic RCTs are designed to evaluate the efficacy and effectiveness of an intervention in which it will be provided (Thorpe et al., 2009). The pragmatic theoretical perspective is not committed to one philosophical approach which provided a broad framework to work from (Creswell, 2003, Bowling, 2014). Theoretical perspectives consist of assumptions or different ways of looking at the world that provides a framework for interpreting research observations (Bowling, 2014). Based on the MRC guidance for complex interventions, both quantitative and qualitative approaches are needed to properly conduct feasibility studies (Craig et al., 2008, Moore et al., 2015). The two different approaches are derived from different philosophical understandings and were used in the development of the current study.

3.3.1. Process Evaluation

Complex intervention research goes beyond asking whether an intervention works in the sense of achieving its intended outcomes (Skivington et al., 2018). It provides attention to the conditions needed to realise an intervention's mechanisms of change and the resources required to support the intervention's reach and implementation in the real world (Skivington et al., 2021). Feasibility studies look at shifting the focus from the effectiveness to whether and how the intervention will be acceptable, implementable, cost effective, scalable and transferable across contexts (Skivington et al., 2021). A feasibility study is designed to assess predefined progression criteria that relate to the evaluation design (i.e. reducing uncertainty around recruitment, data collection, retention, outcomes, and analysis) or the intervention itself (i.e. optimal content and delivery, acceptability, adherence, likelihood of cost effectiveness, or capacity of providers to deliver the intervention) (Craig et al., 2011, Skivington et al., 2021).

Process evaluation is a crucial part of developing and piloting a complex intervention (Moore et al., 2015), as it can help determine why an intervention fails unexpectedly or has unanticipated consequences, or why it works and how it can be optimised (Bonell et al., 2012). Assessing the feasibility of an intervention falls within the process evaluation of an intervention, as it helps improve the understanding of the impact and implementation of an intervention to inform the design of a future study (Moore et al., 2015). Multiple methods can be used to conduct a process evaluation of an intervention, but it is recommended to use an integration of qualitative and quantitative research methods (Griffiths and Norman, 2012), especially, as this allows one to capture subjective experiences that may not necessarily be reflected when using a pure quantitative research approach.

3.3.2. Philosophical Approach

Qualitative approaches are reliant on constructivist or interpretivist philosophical perspectives. Their aim is to understand how people describe their lives in an ordinary setting (Creswell, 2003, Teddlie and Tashakkori, 2006). Whilst quantitative approaches are underpinned by positivist claims for developing knowledge (i.e. Cause effect relations or

testing theories) (Creswell, 2003). The pragmatic perspective is not reliant on one system of philosophy but draws liberally from both qualitative and quantitative assumptions (O'Cathain et al., 2007, Creswell, 2009). This is referred to as mixed methods approach (Creswell, 2009) as it enables both methods to complement each other to obtain a deeper understanding of the data (Farquhar et al., 2011, O'Cathain et al., 2007, Tashakkori et al., 1998, Teddlie and Tashakkori, 2006). Mixed-methods approach uses quantitative and qualitative data collection methods (Teddlie and Tashakkori, 2006) with each type of data collection allowing for the exploration of different aspects of a phenomena (Creswell, 2009), which can allow for a greater variety of divergent views (Farquhar et al., 2011, O'Cathain et al., 2007, Tashakkori et al., 1998, Teddlie and Tashakkori, 2006).

Complex interventions using mixed methods are recommended in public health interventions (O'Cathain et al., 2007) to combine evidence from different sources that may not share the same weaknesses especially during a pilot/feasibility stage of an intervention development(Craig et al., 2008, Moore et al., 2015). A mixed method approach is helpful when looking for practical implications as it can help to enhance the interpretation of the results (O'Cathain et al., 2007, Molina-Azorin et al., 2017) and allow the process evaluation of the intervention (Molina-Azorin et al., 2017). At policy level, there has been an increased emphasis on understanding patient experiences with health services and interventions (Moore et al., 2015, Farquhar et al. 2011). Thus, it is important to incorporate patient views on the development of a health interventions would help shape and improve the service provided (Farquhar et al., 2011, O'Cathain et al., 2007). The DICe study incorporated qualitative methods through interviews to gain feedback from study participants aimed to enhance and inform the design of a future trial.

Quantitative data can be used to evaluate the effect of an intervention while qualitative data provides insights into the subjective experiences of participants to the intervention (Moore et al., 2015, (Moore et al., 2015, O'Cathain et al., 2007, Farquhar et al., 2011). Quantitative data alone may answer the research question on adherence but does not explore the underlying reasons for adherence/or not to the intervention. Thus, there is a need for a deeper understanding of the individual's motivations and experiences that might influence their adherence. Qualitative data can be used to generate hypothesis on acceptability of an intervention and of possible outcome measures (Farquhar et al., 2011).

Therefore, various qualitative research methodology including semi-structured interviews, focus groups and open-ended questions were used to explore compliance of the participants in the DICe feasibility study. An inductive approach was used to understand the reasons behind the adherence/or not to the dietary intervention. Qualitative measures allowed the researcher to assess the practicality of the intervention and ability of participants to adhere to it (Farquhar et al., 2011). While also supporting the participants to provide alternative methods that could be used to increase the adherence to the intervention.

The MRC complex interventions framework recommends integrating quantitative and qualitative data for the process evaluation of an intervention (Moore et al., 2015). As the quantitative data allows the testing of the pre-hypothesized causal pathways of the intervention (Griffiths and Norman, 2012); it explores the feasibility of the study design, adherence to the intervention and its impact on cognitive, ketone, anthropometric and dietary. While the flexibility of qualitative data allows a further exploration of the study processes and participants perceptions on the implementation of the intervention (Atkins et al., 2015). Qualitative data allows the exploration of participants responses on their experience which is too complex to be captured quantitatively, this aids in the generation of a theory regarding how the intervention can be implemented (Atkins et al., 2015). Thus, the current study a mixed method approach (i.e., utilising both quantitative and qualitative research methods) to evaluate the impact of the intervention and aid the process of evaluation.

3.3.3. Logic Model

In process evaluations, the logic models represent the underlying theory of interventions in simple, diagrammatical form (Baxter et al., 2014). A logic model includes details regarding who the intervention is targeted for and the content of the intervention which can be documented using the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) (Refer to Appendix 14). While also documenting the target population, the intervention outcomes, and mechanisms of change and impact (Baxter et al., 2014). A logic model was not used during the development phase of the DICe

intervention; however, the results of the feasibility study will be used to inform the model for a future RCT. Since, the logic model allows for considerations of how the intervention would achieve expected outcomes (Moore et al. 2015).

Guidance for using the logic model suggests the need for a theoretical framework as the basis for an intervention (Baxter et al., 2014, Howlett et al., 2019). It is recommended to incorporate behaviour change models as theoretical frameworks for complex interventions (Howlett et al., 2019).

As the current study is a feasibility study, the findings from the qualitative data focusing on the participants rationale for involvement and experience during the study will help determine the best behaviour change model that could be used to elicit behaviour change.

3.4. Summary:

This chapter has outlined the methodological approach and theoretical underpinnings of the current study. The MRC complex interventions framework recommends evaluating the feasibility of an intervention whilst integrating quantitative and qualitative data to facilitate process evaluation of an intervention (Moore et al., 2015). The quantitative data allows the testing of the pre-hypothesized causal pathways of the intervention (Griffiths and Norman, 2012); it explores the feasibility of the study design, adherence to the intervention and its impact on cognitive, ketone, anthropometric and dietary. The flexibility of qualitative data allows a further exploration of the study processes and participants perceptions on the implementation of the intervention (Atkins et al., 2015). Thus, the current study utilised both quantitative and qualitative research methods to evaluate the impact of the intervention to inform the process evaluation. In the next chapter, the specific study processes and procedures including data collection, analysis and monitoring methods will be discussed.

Chapter 4: Methods

This chapter focuses on the development of the intervention informed by the evidence base (refer to Chapter 2) and testing the feasibility of the intervention based on the MRC framework (refer to chapter 3). The dietary intervention was designed to test the feasibility and acceptability of procedures for recruitment, allocation, retention, adherence to inform the viability of conducting a full-scale evaluation of effectiveness of this specific dietary intervention (Moore et al., 2015). It presents the data collection methods used to answer the research questions to achieve the study aims and objectives. It also provides details on the study processes and procedures including sampling methods, recruitment, data collection methods and analysis used in the study.

4.1. Study Design

A randomized controlled pilot study using coconut oil versus sunflower oil (see Figure 1 below) was undertaken. The study followed a parallel pilot trial design in which participants were randomized to either receive 30 ml/day coconut (intervention group) or sunflower oil (control group) over a 6-months period. The oil administered replaced the cooking/vegetable oil usually used by the participants. This prevents performance bias resulting from different experience between groups and the preferred outcomes of the potential participants. The randomized controlled component allows the evaluation of the study procedures, design, and outcome measures in preparation for a full scale RCT in the future.

This feasibility study was in line with the guidance proposed by Eldridge et al. 2016 and reported using the Standard Protocol Items: CONSORT extension for randomised pilot and feasibility trials (Eldridge et al., 2016). The trial was registered on clinical trials.gov; **NCT: 1718/IRASREZ/1.**

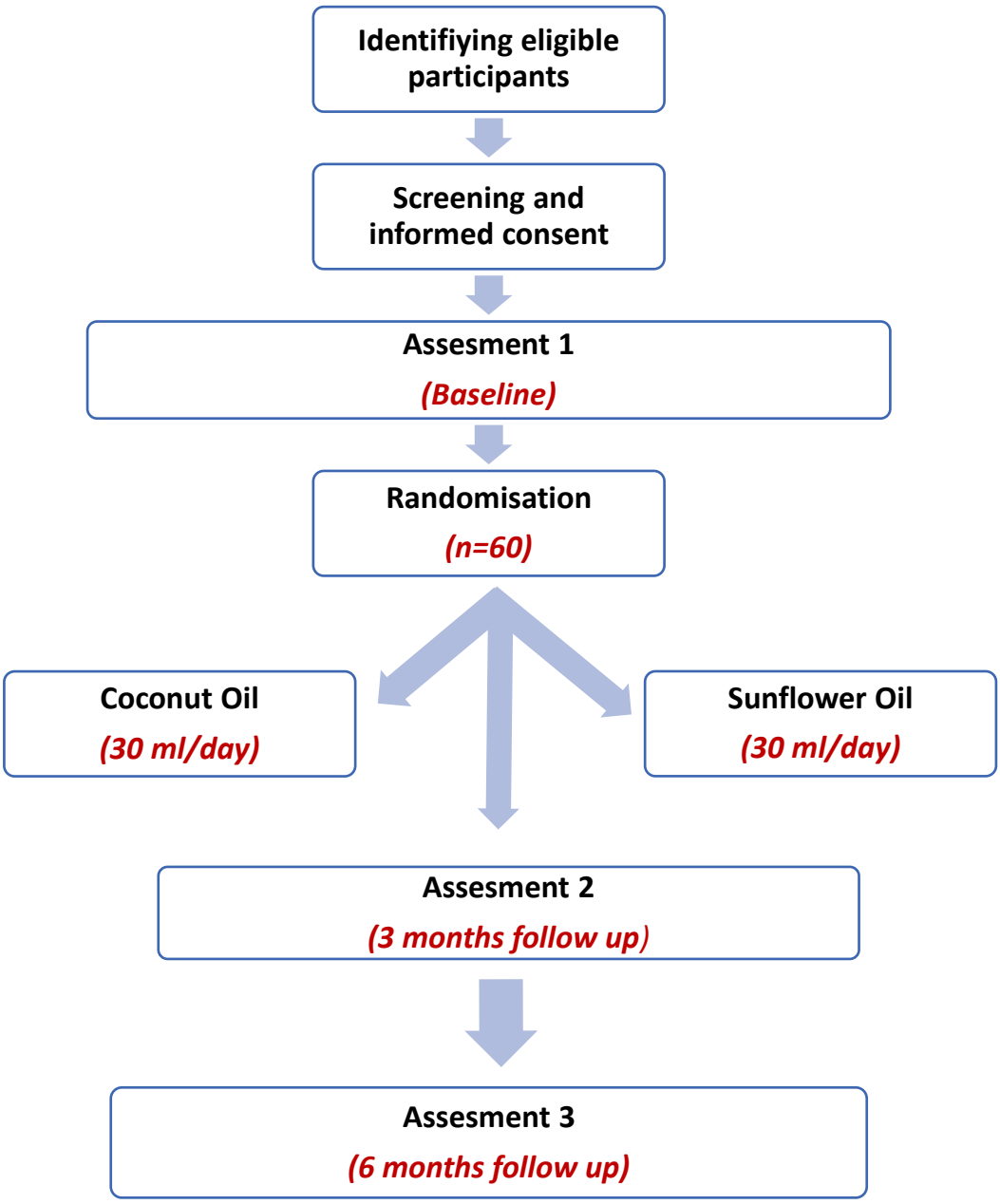


Figure 4.1: Dietary Intervention on Cognition (DICe) study flowchart

4.1.1. Intervention Design

The protocol of this study can be found in appendix 1. Written informed consent to take part in the study and conduct genetic screening was obtained from all participants before testing (consent form in appendix 4). Participants either came to Bournemouth University or met the researcher at an agreed upon location for their initial visit (V0). During that visit the researcher answered any questions that the participant had, explained the study design,

and asked participants to read the participants information sheets (refer to appendix 3) before signing the consent form (refer to appendix 4). After that, participants had three study visits (V1, V2, V3) which were conducted at a time and place according to the participant's preference to ensure that they were comfortable (keeping in line with the COVID-19 regulations and University policies). Any queries that participants may have had were discussed during these visits.

During the first visit (V1) baseline measures were collected and participants were provided with their allocated oil. The second visit took place after three months (V2) and a follow up visit 6 months after baseline (V3). During the second visit, participants were asked to complete the adherence questionnaire (refer to appendix 6). Blood ketone concentration, body weight and height of the participant were measured. During the third visit (V3) the researcher repeated all the measures used in the first visit. Participants were contacted monthly by phone during the intervention to check their adherence level. Details of the calls and phone logs were documented.

After the 6 months intervention, participants were asked to either take part in a one on one in depth semi-structured interview or focus group to provide their feedback on the intervention. If the participant chose the interview, they were conducted at the end of the third visit. All of the study participants opted for the one on one in depth interview option.

1. **Intervention Group:**

Coconut Oil Group:

Participants in the intervention group- Coconut Oil group received 3x 1 Litres jar of "Lucy Bee" raw coconut oil (Lucy Bee, UK) that was provided to them at the end of the first and second visits. They were also provided with a leaflet of suggestions on methods to incorporate the oil in their diet and different recipes (appendix 13). Recipes were provided to participants to help them utilize the oil more (Appendix 12) and facilitate the usage of the oil especially at the beginning of the intervention.

Dietary Ketosis:

Dietary ketosis can be achieved by the supplementation of 20-70 g of MCT/day (Krikorian et al., 2012b) as coconut oil is made of around 63% MCFA then 30 ml of oil a day provides

around 21g/day MCFA. Coconut oil intake of 30 ml/day is consistent with the UK Government dietary guidelines for saturated fat intake which is 29 g/day for males and 23 g/day for females (PHE, 2016). According to the National Diet and Nutrition Survey (NDNS), men aged 19-64 years old consume around 1974 kcal/day while those aged 65 and above consume an average of 1940 kcal/day (PHE, 2018). Women aged 19-64 years old consume an average of 1575 kcal/day which is higher than average energy intake of females aged 65 and above which is 1486 kcal/day (PHE, 2018). Thus, 30 ml of coconut oil will provide 270 kcal which would contribute 13.6-14% of total fat intake in men (aged 19-64, 65 and above respectively) and 17-18% in women (aged 19-64, 65 and above respectively). According to the NDNS, fat intake in men contributes 32.6-33.7% to their total energy intake (aged 19-64, aged 65 and above respectively). While that of their female counterparts makes up 33.7-33.8 % of their total energy intake (PHE, 2018). Thus, a 30 ml consumption of oil remains within the recommended levels of daily dietary fat intake of the target population.

2. **Control Group:**

Participants in the control group received 3 Litres of "K.T.C" sunflower oil (K.T.C., UK) during the first and second visits. They also received leaflets (appendix 12) and recipes to allow them to incorporate the oil into their diet (appendix 13). Among vegetable oils, sunflower oil is among the few that are low in omega 3 fatty acids (0.2%) that have been linked to improved cognitive functions of adults (Chiu et al., 2008). Moreover , sunflower oil is low in saturated fats (10.1 %) that have been attributed to dyslipidaemia and cardiovascular diseases (Vartiainen et al., 2009).

4.2. Patient and Public Involvement

Public and Patient Involvement (PPI), Engagement and Participation research encompasses working with patients/service in the development of research (Ocloo and Fulop, 2012, Kearney et al., 2017). PPI is essential in the development phase of interventions as it allows the involvement of the public in the decision making process(Kearney et al., 2017).The study design was discussed with people in the target population during a "memory roadshow event" held by DHUFT. During the event the researcher presented the study flowchart to OA and adults with dementia who provided their opinion on the design and concept of the

intervention. Based on the discussions with people with dementia and older adults some of the study documents were amended to clarify the different stages of the intervention. Pictures and more detailed data were added to the flowchart to make it easier to understand and to support participants with staying up to date with the different study procedure. Furthermore, the consulted participants recommended providing some recipes using CO and methods to use it while cooking. That is because they anticipated it would be difficult to use the oil as most of them had never cooked with CO before. Informed by feedback, the participant information sheet was simplified along with the study flowchart that was provided as a separate A5 document to allow participants to post it on their fridge as a reminder. Recipes and leaflets for different methods of oil usage were also developed and tested. The acceptability of the flavour of the oil in CO recipes was evaluated in people from different age groups at a Bournemouth University public engagement event. People who consumed the food thought it was acceptable and that the CO did not impact the flavour of the food.

4.3. Sample Size:

As this is a feasibility study and due to the lack of clinical/statistical references for the cognitive measures used, and their significant effect in relation to ketosis (minimal clinically important difference), it was not possible to conduct a formal sample size calculation. One of the objectives of this study is to provide data for the sample size calculation for a future full-scale trial. A Confidence Interval approach was used to estimate sample size required to establish feasibility (Thabane et al., 2010).

Thus, the sample size calculation for the current feasibility study is based on estimations of adherence, recruitment, and retention rates; along with estimation between subject variability (SD) and within-subject correlation, which are required to estimate the sample size for the future full-scale RCT. A total of 60 participants, with 30 participants in each group will allow the estimation of:

- An adherence rate in each group circa 80% with a 95% confidence interval +/- 14%.
- A recruitment rate circa 50% with a 95% confidence interval +/-9%.

- A retention rate circa 80% with 95% confidence interval +/-10%.
- A between subject standard deviation for a standardised outcome variable (i.e., SD=1) at baseline with 95% confidence interval of (0.85, 1.22).
- A moderate correlation of 0.5 between pre- and post-values would give a 95% CI of (0.38, 0.76), assuming 48 participants with both sets of data.

4.3.1 Participants

The study aimed at recruiting sixty adults with a confirmed Mild Cognitive Impairment (MCI) diagnosis (see eligibility criteria) in Dorset, UK.

i. Eligibility Criteria:

Table 4.1. Table summarising DICe intervention inclusion/exclusion criteria of MCI patients.

Inclusion	Exclusion
MCI Diagnosis	Type I or type II diabetes diagnosis
Above 18 years old	History of hypercholesterolemia
	Alzheimer's disease diagnosis
	Neurological disorders (other diagnosed disorders in addition to MCI)
	Unable to communicate in English
	Major physical disabilities (blind, deaf) or unable to use their dominant hand

However, after 3 months of active recruitment (October 2019 to January 2020), only 3 participants were recruited within 3 months demonstrating the difficulty of recruiting adults with a confirmed diagnosis of MCI (Refer to chapter 5, 5.1.2. Recruitment:). As it appeared unlikely to recruit required numbers of participants that met the inclusion criteria originally set out within the required timeframe, the inclusion criteria were amended to include older

adults (OA) over the age of 65, irrespective of their cognitive status after discussion with the supervisory team and review of available literature.

Table 4.2. Table summarising DICe intervention inclusion/exclusion criteria of older adults

Inclusion	Exclusion
Above 65 years old	Type I or type II diabetes diagnosis
	History of hypercholesterolemia
	Alzheimer's disease diagnosis
	Neurological disorders (other diagnosed disorders in addition to MCI)
	Unable to communicate in English
	Major physical disabilities (blind, deaf) or unable to use their dominant hand

a. Rationale for Inclusion/Exclusion Criteria:

Individuals with a diagnosis of Type I or Type II Diabetes were excluded from the study due to the risk of diabetic ketoacidosis that could result from an increase in blood ketone concentration. Uncontrolled diabetes could play a role in the development of pathological ketosis (Kanikarla-Marie and Jain, 2016) as there is an increase in concentration of ketones produced by people with diabetes. This is associated with reduced insulin levels, increased counterregulatory hormones (glucagon) levels, along with impaired ketone clearance (Kanikarla-Marie and Jain, 2016).

As coconut oil is rich source of saturated fatty acids (Marina et al., 2009) which are associated with dyslipidaemia and cardiovascular diseases (CVD) (Katan et al., 1994, Barnard et al., 2014). Individuals with a history of hypercholesterolemia were excluded from the study to reduce CVD risk.

Individuals with neurological disorders such as Parkinson's disease, Alzheimer's Disease, Lewy body dementia were excluded due to the potential effect of the aforementioned disorders on cognitive functions and the results of cognitive measures used to assess the impact of the intervention on cognition.

Due to time and financial restraints, the cognitive measures used could not be adapted to another language or conducted on individuals with major physical disabilities (deaf, blind, mute). The tests require writing; reading and communicating in English language; thus, individuals who were not able to perform such tasks were excluded.

4.4. Screening and Recruitment

A range of approaches were used to identify and recruit participants. Participants were recruited from the local community through public engagement activities, newspaper advertisements (New Milton newspaper, Bournemouth Echo, Dementia friendly magazine), social media (Twitter, Facebook, ADRC newsletter) and posters across Dorset (bus stops, Restaurants, coffee shops, libraries), word of mouth and Join Dementia Research.

Adults who had MCI diagnosis and have previously given consent to be contacted to participate in research within Dorset Healthcare NHS University Foundation Trust (DHUFT) database were contacted. People with MCI were also identified and contacted by nurses within memory assessment clinics within DHUFT. Furthermore, flyers for the study were posted in memory assessment clinics across Dorset. Community organisations that run group meetings or events for older people (memory cafes, memory walks) were contacted by email or phone and were provided with study posters.

Join Dementia Research is an NIHR supported platform that was created to help link researchers with participants interested in dementia research. The study was publicized on the platform for both groups (MCI and older adults), participants were sent an invitation email to inform them about the study and that they matched the inclusion criteria. Recruitment was conducted across Dorset (UK) from October 2019 to October 2020.

The study researcher telephoned those who expressed interest in taking part in the research, describe the study in more detail, answer questions and went through the remaining screening criteria (see section ‘Exclusion criteria’) over the telephone. After that, interested individuals who meet the criteria were sent an email containing the Participant Information Sheet, Study flowchart, and Participant agreement form. A meeting was scheduled with the researcher to answer any questions and receive written informed

consent before commencement of the study. Those not eligible were informed over the telephone.

Participants were given the choice to decide regarding the meeting location to ensure that they were comfortable. Study procedures were either conducted in participant's houses or at Bournemouth University Campus.

Meetings with potential participants were set up to screen for eligibility and familiarise participants with all study procedures by verbal explanation with the aid of participant information sheet (Appendix 3), DICe Study flowchart (appendix 2) and APO E4 factsheet (appendix 15). Health history questionnaires were used to screen for the exclusion criteria; diabetes, high cholesterol, Alzheimer's disease, other neurological disorders (Parkinson's disease, Traumatic brain injury) or other major physical impairments (deaf, blind, unable to use dominant hand).

4.5. Informed consent process

Informed written consent was taken by the study researcher who is Good Clinical Practice (GCP) accredited in a location chosen by the participant (their homes or Bournemouth University Campus). Participants were asked to provide informed written consent (appendix 4) before proceeding with any study procedures.

4.6. Randomisation

Randomized control trials depend on the act of random allocation of participants to either the control or intervention group which ensures that on average both groups share similar characteristics (Stolberg et al., 2004). Thus, differences observed between outcome measures at the end of the study could be attributed to the intervention rather than characteristics of participants (Viera and Bangdiwala, 2007).

To ensure good allocation concealment, random allocation was email based and administered by the study statistician. Randomisation was carried out on a 1:1 basis and utilised a computer-based random sequence generator (sealed envelope). Variable-sized blocks (2,4 and 6) were used to ensure approximately equal numbers in the two trial arms. No stratification was used for randomization.

The researcher of the study knew the allocated group of each participant to ensure that the correct oil (coconut or sunflower) was delivered to them. Participants also were not blind to the intervention due to the easily recognizable differences (Flavour, smell, consistency) between both oils. However, participants were not informed that the study focuses on Coconut Oil but instead were told that the study was looking into the feasibility of an intervention using vegetable oils and their effect on cognition. This was done to ensure adherence to the research group (CO or SO) and reduce placebo effect which would affect the study results.

4.7. Outcome Measures

As this is feasibility work, a broad range of outcomes were included. Outcomes were assessed at baseline and at 3 and 6 months. Anthropometric measures were assessed by the study researcher either in participant's homes or Bournemouth University (BU) campus. Cognitive measures were assessed at the same time and location with breaks in between; to reduce fatigue. Self-reported questionnaires (presented in a large font) were completed by participants. Food diaries were completed by participants in their homes for 4 days at their own pace and the posted or emailed to the study researcher. The following section will address the different study procedure and outcome measures while explaining how each assessment was conducted.

1. Genetic screening:

Apo-lipo protein E4 genetic screening was conducted during the first visit. A buccal sample was collected from participants using a buccal swab; the sample was sent to the laboratory at St. Thomas' Hospital to test for the APO E4 genotype. Previous studies demonstrated the

effect of APO E4 status on metabolism in relation to ketone absorption and utilization (Henderson and Poirier, 2011). This association is also reflected by the effect of dietary induced ketogenesis on cognitive functions in older adults as individuals who were APO E4 negative demonstrated an increased improvement in their cognitive functions in comparison to their APO E4 positive counterparts (Reger et al., 2004, Rebello et al., 2015, Maynard and Gelblum, 2013, Henderson et al., 2009). Thus, APO E4 genotype screening was utilized to further understand the effect of APO E4 status on dietary ketosis and cognition. Results of the genetic test were available 2 weeks after collection of the sample; the sample was destroyed by the lab after analysis. In case the participants opted into knowing the result of the test; the researcher sent a report of the test result to their GP and informed participants to arrange a visit with their GP to get the results. In case they opted out; they were not contacted regarding the test after the sample was collected and were not informed of the results.

2. Demographic/descriptor variables

Age, sex, education, employment, marital status, household composition, medication, comorbidities, and physical activity were collected through a questionnaire (refer to appendix 7). The questionnaire provided data on the participants medical history (Illness, medications used), physical activity, level of education, relationship status and living conditions. These factors could affect the study outcome measures as they affect, dietary intake, physical and mental wellbeing, and cognitive functions.

3. Adherence

Measuring adherence is quite challenging (Mihalko et al., 2004, Martin et al., 2000). Monitoring the amount of oil used by participants using open ended questionnaires and the results of Beta hydroxyl butyrate tests (Newman and Verdin, 2017) was used to investigate the adherence of participants to the oil intake.

Beta hydroxyl butyrate levels were assessed using Abbott freestyle Optimum Neo (Abbott, US) which is a blood ketone meter at baseline, and after 3 and 6 months of the initiation of the intervention, to measure plasma ketone bodies concentrations. The amount of oil used was checked after 3 and 6 months, and at random times during the intervention through phone calls. Logs and records of the phone calls were saved on a password protected computer.

4. **Blood Ketone**:

Capillary blood ketone level of participants was assessed by measuring Beta hydroxyl butyrate (β-OHB) levels using Abbott Freestyle Optium Neo meter. This measure acts a biomarker to assess the impact of ingestion of coconut oil on blood ketone levels. The meter readings were obtained using an electrochemical blood ketone sensor in which a 5-ml capillary blood sample was applied to an electrochemical strip inserted into the sensor and the β-OHB concentration was displayed in mmol/l after 30 seconds. B-OHB levels were measured during each visit as they were used as biomarkers of adherence to coconut oil intake (Gilbert et al., 2000). B-OHB is used to monitor dietary ketosis and in some ketogenic diet intervention studies, B-OHB level is used for validation of their adherence to the diet (Norgren et al. 2019). The β-OHB range of DK has been suggested to be 0.5–3.0 mmol/L and sometimes slightly higher but with a threshold of 6–7 mmol/L in human studies (Norgren et al. 2019). Capillary B-OHB test measures was chosen due to it being less invasive than venous measures as finger prick testing is less invasive and risky than venous blood collection.

5. Dietary Intake

Four-day food diary records (refer to appendix 7) were used to explore the dietary energy and macronutrient intake of participants at baseline and after 6 months. Participants were asked to report their food intake for four consecutive days (3 weekdays and one day of the weekend) at baseline and post intervention to document all the food, drinks, and dietary supplements they consumed. Participants were provided with a physical and e-copy of the

food diary and had the choice to fill it in and send it via post or email. Data from the food diaries was analysed using Nutritics software (UK) (Nutritics, 2019) to extract macro and micro nutrient intake of participants.

6. Anthropometric measures

- Height was measured to the nearest 0.1 cm using the Leicester Portable stadiometer (UK) on which participants stood barefoot with heels together and arms by their sides and looking ahead.
- Body weight was recorded using the SECA Class III (SECA, UK) digital weighing scale.
- Body Mass Index was calculated using both weight and height measures using the formula: BMI= weight (kg)/ Height $(m)^2$

7. Cognitive Measures

Different scales and/or tests were used to assess the specific cognitive measures to ensure that the relevant functions were covered to support feasibility.

a) **Over-all cognition:**

ACE III and mini Addenbrookes Cognitive Examination (m-ACE) (Hsieh et al., 2015) was used to assess over-all cognition of participants. While Addenbrooke's Cognitive Examination -III is the full scale with a total score or 100; the m-ACE is a shorter version of the same.

The ACE-III is a brief cognitive test that assesses five cognitive domains, namely attention/orientation, memory, verbal fluency, language, and visuospatial abilities (Mioshi, Dawson, Mitchell, Arnold, and Hodges, 2006). The total score of ACE-III is 100 while that of m-ACE is out of 30; higher score indicates better cognitive functioning. This test is often used as a screening tool (to ensure participants do not have cognitive impairment), used commonly in clinical practice and also used as a general measure of cognition for the study participants. Both ACE-III and m-ACE have three parallel versions, which allows for repeat testing and is therefore better than the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). ACE-III was initially used to assess overall cognition in only

one participant (JD3) as she was the first participant of the study, but due to the time taken to complete ACE -III, this was replaced by the m-ACE and the shorter version of m-ACE was used for all the other participants. This decision was taken in consultation with the research team, specifically, to reduce the overall assessment time which was already quite long (2 hours), especially in older adults long testing periods can often leave the participant feeling agitated and stressed. M-ACE version A was used for the baseline data and version C was used after 6 months to reduce practice effect.

b) **Executive functions:**

Trail Making (Dean C Delis, 2001) **:** The Delis Kaplan Executive Function System (D-KEFS) consists of various executive tests and Trail Making is one of them which has 4 conditions including a visual cancelation task and three connect-the-circle tasks. It is a commonly used measure of processing speed and executive functioning (Jurick et al., 2022). The Trail Making Test (TMT) is one of the most widely used instruments in neuropsychological assessment as an indicator of speed of cognitive processing and executive functioning (SÁNchez-Cubillo et al., 2009). Condition 4: Number Letter Switching, which is a measure of inhibition and switching and also measures the executive function of being able to switch between 2 conditions (number and letter) was used as an executive measure. This task also reflects the flexibility associated with switching on a visual-motor sequencing task. The other two conditions (2 and 3) provide a norm for the letter and number switching independently. These measures, help understand whether a deficient score on the switching condition is related to a deficit in one aspect of executive function impairment in one or more underlying component skills. The time taken and the accuracy is a key measure for these tests.

While completing the trail making if the participant made four errors on the task was discontinued. For each condition, the task was discontinued after a specific time limit. If the participant had begun drawing a connection (Condition 2-4) at the end of the time, he or she were allowed to complete that response before being told to stop, and that response was scored as completed within the time limit.

Condition 2: Number Sequencing: In the Number Sequencing Response Booklet the researcher asked the participant to connect the numbers (while ignoring the letters) in chronological order starting at one and finishing at number 16. They were asked to connect the numbers as quickly possible. The task was timed by the researcher and any errors were noted.

Condition 3: Letter Sequencing: In this task participants were asked to connect the letters sequentially starting at A and completing the task when they reached the end (Letter P). Again, the instruction was for them to complete the task as quickly. The task was timed by the researcher and any errors were noted down.

Condition 4: Number-Letter Switching: In this condition, participants were asked to switch between the numbers and letters while connecting then. For example, they would start at number 1 and switch to A, then continue to 2 and then the letter B and so on. They were again asked to connect these numbers and letters as quickly as possible, with the time and any error noted by the researcher.

c) Verbal Memory

Verbal Fluency**:** is another subtest from the Delis Kaplan Executive Function System (D-KEFS). Participants are given a letter at a time, and they are expected to give as many words as they can beginning with that letter (in a minute). The letters FAS and BHR will be used at baseline and 6 months respectively to reduce practice effect (Wechsler, 2010). Word fluency is often a sensitive indicator of executive function and reduced performance on this is often used clinically to measure executive functions, especially linked to brain dysfunction (Miceli et al., 1981). Research suggests that patients with frontal lesions have reduced letter and category fluency (e.g., Baldo and Shimamura, 1998). This test is also sensitive to hemispheric lesions, for example patients with left frontal lesions produce fewer FAS words than patients with right frontal lesions (Benton, 1968). Similarly, patient with left dorsolateral and superior medial frontal lesions switched categories less frequently but produce normal cluster size (Troyer, Moscovitch, Winocur, et al., 1998a). A higher score of FAS and BHR in 180 seconds indicates better verbal fluency.

Category Fluency: another subtest from the Delis Kaplan Executive Function System (D-KEFS) battery. Studies have reported a greater deficit in category fluency in MCI patients when compared to normal ageing and AD (Brandt and Manning, 2009). Participants were asked to come up with as many words as they can from a particular category (e.g., animals or items of clothing). Animals' category was used at baseline and Items of clothing was used after 6 months to reduce practice effect. A higher category score in 60 seconds indicates a better fluency (Wechsler, 2010).

Word List*:* Wechsler Memory Scale- Third Edition (WMS-III) (Wechsler, 2010).Studies suggest that word-list memory measures are useful in identifying cognitive difficulty in pre symptomatic AD prior to any changes in neuropsychological total scores. (Thomas et al., 2018). A list of 12 words is read out to the participants and they are asked to provide as many words as they can remember. This list of words is repeated 4 times to allow participants to learn the words. The results of each trial were recorded. After that another list B (interference) of 12 other words is read out and participants are asked to provide the words before being asked to provide the words of the first list to assess short duration recall. After 25 minutes, participants were once again be asked to provide the list of words to assess delayed recall and complete a recognition task. Results from both recall trials were recorded based on number of correct words provided. A higher score indicates better memory and recall abilities.

Digit Symbol: subset from Wechsler Adult Intelligence Scale - Fourth UK Edition (WAIS-IV UK) (Wechsler, 2010) and is widely used for assessing speed and attention in MCI patients (Nordlund et al., 2005). It was used to assess the processing speed of participants. Participants were provided with a sheet of number and symbols and will be asked to fill in the symbol for the designated number. They were given 120 seconds to complete as much of the numbers as possible and the results were recorded. A higher score indicates better processing speed.

Digit Span (forward and backward): subset from Wechsler Adult Intelligence Scale - Fourth UK Edition (WAIS-IV UK) (Wechsler, 2010) and widely used for assessing working memory in

MCI and AD patients. Studies demonstrated a decrease in digit span score in MCI patients when compared to AD patients (Kessels et al., 2011, Kurt et al., 2011) The test consists of two subtests, digits-forward (DF) and digits-backward (DB). Both subtests rely on short term retention abilities and auditory attention (Howieson and Lezak, 1995). DF primarily measures attention, while DB measures working memory, as it requires data manipulation and mental tracking (Kurt et al., 2011, Johnstone et al., 1995, Howieson and Lezak, 1995). It was used to assess working memory of participants. For the Digit Span Forward, a sequence of digits was read, and participants were asked to repeat the digits in the same sequence. For the Digit Span Backward, the researcher read a sequence of digits and asked the participants to repeat the same digits but in reverse order. Sequences start with 2 digits and continue to increase in length (maximum of 9) were administered in both conditions. A higher score indicates better working memory.

d) Visual spatial abilities

Supermarket Task (Tu et al., 2015). This is a tablet-based test that was conducted on an iPad and was used in patients with MCI and dementia in the past (Tu S, Wong S, Hodges JR, Irish M, Piglet O, Hornberger M (2015). It is a novel tool that was used to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia.

8. Quality of life

The Alzheimer's diseases cooperative scale- Mild Cognitive Impairment- Activities of Daily Living (ADCS-MCI-ADL) (Galasko et al., 1997), is a questionnaire comprising 24 questions, Participants were asked to reflect on the last 4 weeks and answer questions regarding their daily activities. Answers to the different questions totals a score of 53, with a higher score indicating greater self-perceived independence and better quality of life.

9. Process measures

a) Questionnaires

An open-ended adherence questionnaire was used at the three months follow up to assess adherence of participants to the intervention and the reasoning behind adherence/non-adherence (refer to appendix 6). It also provided insights on any barriers to oil intake. The main question was whether the participant was adhering to the oil intake and whether they faced any barriers to adherence.

b) Interviews:

Semi structured interviews with open ended questions were conducted at the end of the study to provide feedback on the participants' experience in the study (process, protocol, randomisation, outcome measures and adherence). The interviews were conducted either face-to-face in person or virtually via video conferencing to collect in depth information from participants.

The aim was to understand participants' experience of implementing the dietary change by allowing them to 'tell their story'—what they did and how—as well as identifying barriers and enablers to the adherence and maintenance of the intervention. Furthermore, it allowed participants to provide any feedback regarding cognitive changes that might have impacted their well-being without having an impact on a measurable skill. The interviews were also used to allow the participants to express and reflect on their experience with the intervention and to provide recommendations for a future study. This data helped identify any problems with the feasibility of the intervention which helped inform the design of a future trial. The interview topic guide was developed based on the study outcomes, aims and objectives. Data collected from the interviews would inform the process evaluation of the intervention.

4.8. Data Analysis

4.8.1. Quantitative Analysis

Statistical analysis:

Comparisons between groups were made using a repeated-measures ANOVA, with Bonferroni corrections to compare the pre- and post- intervention results (i.e., cognitive

measures, quality of life, dietary intake). Within group results were examined using paired t-tests. Data was reported as mean, standard deviation (SD) and percentage change. The threshold for statistical significance was determined a priori as $P \leq 0.05$.

Descriptive statistics were utilized to quantify and characterize feasibility of the intervention. Continuous variables were described using their means and standard deviations (SD). Paired t-tests were used to analyse differences in cognitive functions prior to and post the dietary intervention. Statistical tests were two-tailed, and significance was set at $p < 0.05$. Repeated measures ANOVA was performed to analyse differences in cognitive functions at baseline and after 6 months intervention. Statistical analysis was performed using SPSS. The current study is a feasibility study and hence the participants are a very small sample size. The cognitive measures were part of this feasibility rather than aimed to measure cognitive differences.

Six separate repeated measure multivariate ANOVA were undertaken for each of the cognitive measures i.e., memory, trail making, Digit Span (Backward and Forward), category and semantic fluency, Digit coding, overall cognition (M-ACE, QOL) where the repeated measure dependent variable with time (pre-and-post), and independent variable was the two-oil group (i.e., coconut or sunflower oil) the relevant cognitive measures. Post-hoc t-tests were then completed if there was a main effect or interaction in the ANOVA.

A set of additional analysis was conducted to compare some categories between the trial arms. These categories include:

- Dietary Carbohydrate Intake:
    - low (less than 5-10% of total energy intake)
    - normal (40-50% of total energy intake)
    - high (more than 50% of total energy intake)

Total carbohydrate intake of participants could influence the production of ketones in the body. As an increased carbohydrate intake (>50% of total energy intake) raises blood glucose concentrations and consequently reduces ketosis in the body (Westman et al., 2003).

4.8.2. Qualitative Analysis

Data produced from the open-ended questionnaires, interviews were recorded , transcribed and thematically analysed using N-Vivo version 12 software (Nvivo, 2020). Audio-recording were transcribed by researcher. Analysis followed the principals of thematic analysis by Braun & Clarke (Braun and Clarke, 2006). To start the thematic analysis the researcher familiarized themselves with the data. Going through the six phases of thematic analysis, the data was reduced from the audio-recordings of the discussion to a framework of themes and sub-themes. A member of the supervisory team coded 10% of the interviews before a discussion ensued between supervisory team and researcher on the development of theme (Flick, 2004). The triangulation of data using this method improves rigour of the data as it reduces personal impact on code and theme development (Flick, 2004, Thurmond, 2001). Themes developed form the data will help inform the design of a future trial.

4.9. Participant withdrawal from the study

If a participant decided to withdraw from the study, they informed the researcher. If the participant was willing to provide a reason, the study researcher found out why they wished to withdraw from the study. The participant was asked if they were willing to give permission to retain data collected before withdrawal for use at final analysis, or whether the data should be destroyed.

4.10. Ethics

The study was reviewed and received a favourable opinion by the National Health Service (NHS) Harrow Research Ethics Committee (240254). With Bournemouth University acting as the study sponsor. The study was performed subject to Research Ethics Committee (REC) & Health Research Authority (HRA) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval. This study was be conducted in accordance with the Research Governance Framework for Health and Social

Care and GCP. The older adults' arm of the study was reviewed and received ethical approval by Bournemouth University Research Ethics Panel (Ethics ID 29406).

4.11. Adverse Events

All Adverse events (AE) possibly related to the DICe intervention were closely monitored, documented, and reported. Participants were asked to report all adverse events related to consumption of oil to the study researcher. Adverse events were reported on a case report form and reported to the chief investigator (CI) who was the first supervisor. The CI assessed any AE to establish if it should be classified as a Serious Adverse Event (SAE) according to the National Research Ethics Service definition. If the AE was not defined as 'serious', it was recorded in the study site file, and the participant was followed up by the research team. The study team communicated with the participant's General Practitioner (GP) to decide on whether to withdraw the participant from the study. In case of a pattern of events, decision was made within the research team to stop the intervention.

4.12. Project Management and Safety Monitoring

The study researcher managed the day-to-day management and coordination of the study and reached out to other members of the research team when needed. The CI was responsible for the overall management of the project. The research team had regular meetings to discuss study progress.

A full risk assessment was undertaken using BU's online Risk Assessment Tool, ensuring that risk is minimised against physical, mental, emotional, and social harm to the participants, and that the researcher is likewise protected. The researcher had an emergency first aid training and followed the lone worker policy (Appendix 8) set by Bournemouth University when collecting data off-campus.

i. Monitoring and Auditing

The research study was monitored by Governance staff from BU to ensure that it was being conducted in accordance with the protocol, the UK Policy and Framework for Health and Social Care Research and GCP guidelines. All trial related documents were made available on request for monitoring and audit by the Research Ethics Committee and BU.

ii. Compliance

The CI ensured that the study was conducted in compliance with the principles of the Declaration of Helsinki (1996) and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and Trust policies and any subsequent amendments.

Steps were taken in order to minimise the risk of protocol deviations and non-compliance, accidental protocol deviations can happen at any time, but if they did occur, they were documented and reported to the Chief Investigator and sponsor immediately.

iii. Data protection and data storage

All data collected during the study was kept strictly confidential and in accordance with General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018. Questionnaires were allocated a participant ID; they did not contain any identifying details. Access to data was controlled by the CI and was restricted to members of the research team and complied with research governance policies and procedures. Personal contact details were stored separately from the de-identified study information on secure password-protected computers. Study documents (paper and electronic) will be retained in a secure location after the trial has finished. All source documents will be retained for a period of 5 years following the end of the study.

iv. Dissemination

As sponsor for the study, Bournemouth University is the main data controller, and as such owns the data arising from the study. On completion of the study, the data was analysed, and a final study report written. The results will be made available on clinicaltrials.gov (NCT:

1718/IRASREZ/1) and likewise results from the study will be disseminated in national and/or international conferences. Papers based on the results of the study will be published in high quality peer reviewed journals. Reports of the study results will also be sent to study participants.

4.13. Covid-19 Impact

The Covid-19 pandemic has had a significant negative impact on the study delivery and meeting required timelines. On March 20, 2020, the United Kingdom government imposed nationwide lock down to reduce the infection rates of the virus. During that time, 18 study participants were taking the oil. The researcher-maintained contact with all the participants through phone calls and emails to check on adherence and their well-being; phone calls and emails were documented. However, due to lockdown measures the researcher was unable to meet the participants in person for the 3 months visit and it was conducted virtually either via Zoom or phone. The researcher asked the participants the questions to the adherence questionnaire and recorded the answers. A question was added regarding their physical activity and dietary changes due to the impact of lockdown. Furthermore, the researcher could not collect anthropometric data in-person, so participants were asked to self-report their weight in kilograms using personal weighing scale. This poses a limitation to the results due to the variance of scales used and the inability to validate the weight reported. Height was not measured, and participants did not report their height at 3 months. However, this is unlikely to affect the results as little, if any change would be expected over three months (Fernihough and McGovern, 2015). Blood ketone concentrations were also not evaluated at three months due to national lockdown measures. Oil was disinfected and delivered to participants doorsteps to enable them to adhere to the intervention. Participants were also asked to provide photographic images of any leftover oil using smartphones, to help in monitoring adherence.

Some 6 months visits were also conducted during lockdown, in these individual cases the testing session was adapted to be conducted virtually via Zoom. Different study procedures were implemented to adapt to conducting the cognitive assessments virtually. Participants were provided with physical copies of the Trail Making tests (conditions 2,3 and 4) and digit

symbol test. The cognitive measures along with the food diaries were posted to study participants. All other measures were conducted virtually during a two-hour Zoom meeting. Participants were asked not to open the envelope with the measures until asked to by the researcher during the virtual session. During the session, the researcher conducted all cognitive assessments per protocol and asked participants to complete the physical measures while timing them. After finishing the measures, participants were asked to take pictures of them and send them to the researcher via email to record. Participants were asked to report their weight however blood ketone measures were not tested. Semi-structured interviews were conducted via zoom and recorded at the end of the session.

After the easing of lockdown measures on the 4th of July 2020, the researcher resumed in-person research activities but took extra precautions while meeting participants. However, with participant consent, study visits were conducted in out-door areas (gardens) while both the researcher and participant wore a mask, maintained 1 metre distance and all equipment was properly disinfected before and after each session. Participants were asked to conduct the blood ketone tests on themselves under the supervision and guidance of the researcher. Body weight and height were measured as per protocol. All other outcome measures were assessed as per protocol. However, sessions were conducted virtually in case the participant was shielding.

Due to the high risk of Covid contamination with saliva samples, all samples were destroyed by the lab at St. Thomas Hospital at the beginning of the pandemic. Thus, Apo E4 was only assessed in 3 study participants. Upon completion of the risk assessment, it was decided that it was too risky to try collecting buccal samples, so APO E4 screening was not conducted in most study participants (25/28). Thus, the Covid-19 pandemic and associated lockdown impacted the delivery and evaluation of the study. Measures were taken to continue the study with the minimal disruptions and without increasing participant burden. Adaptations to study procedures were discussed with the supervisory team and communicated to the sponsor and NHS trust.

Chapter 5: Results

This chapter presents the quantitative and qualitative findings from this pilot RCT feasibility study. The findings are presented in three parts that relate to the study objectives.

In the first part, quantitative data presented focusses on objectives 1 and 2 of the study which relate to assessing adherence, recruitment, and retention rates and study procedures.

Objectives 1 and 2:

1. To test the procedures of the intervention (estimate recruitment and retention rates, recording and monitoring of adverse events, study procedures, to refine the selection of outcome measures in preparation for an RCT that would test the effectiveness of the intervention).
2. To assess adherence rate of participants to consuming dietary vegetable oils (coconut and sunflower oils)

In the second part, results from the cognitive, dietary, and anthropometric (i.e., body weight and height) outcome measures are presented to address study objectives 3 and 4.

3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future RCT.
4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.

   The outcome measures included cognitive measures, blood ketone concentration measure, dietary intake, and nutrition- related outcome measures (anthropometric measures).

The third part presents qualitative data from interviews and open-ended questionnaires about the acceptability of the intervention and randomisation process. It also presents feedback from participants regarding their experiences (acceptance of study design, barriers & difficulties encountered, satisfaction levels) of their involvement in the study.

5. To determine the acceptability of randomisation and the intervention from participants and obtain feedback about the study procedure.

After presenting the results, an overall summary is provided at the end of the chapter.

PART 1

5.1. Study Procedures

The first objective of the study was to test the study procedures by estimating recruitment and retention rates to refine the selection of outcome measures for a future RCT. The procedures included screening and recruitment, retention, and adherence rates.

5.1.1. Screening process

The screening process was carried out by screening the eligibility criteria of potential participants against a checklist based on the inclusion/exclusion criteria (Refer to chapter 4, section 4.2.1. for further details on the inclusion/exclusion criteria of the study). For participants recruited through the DHUFT database and JDR platform, screening was conducted directly from potential participant records. For participants recruited through the ADRC, posters and the local community; screening was conducted via phone by asking the participants a series of screening questions to determine eligibility before setting up a meeting.

The screening process met the needs of the study by reducing the participant burden and time if they were not eligible to take part in the study from the beginning. It also supported the research process to ensure that meetings were scheduled only with participants who met the study criteria.

5.1.2. Recruitment:

The study had two recruitment phases. The first phase was delivered between October 2019 to January 2020 to recruit potential participants with a confirmed diagnosis of Mild

Cognitive Impairment (MCI). The second phase recruited older adults without a confirmed MCI diagnosis between January 2020 to October 2020.

During the first phase of recruitment (between October 2019 to January 2020) a recruitment target of 60 participants with a confirmed diagnosis of MCI was set (based on study inclusion criteria – see section 4.2.1). A number of approaches were utilised for the identification of potential participants and recruitment. First, these included advertisements of the study published in local newspapers and a local magazine to reach people with dementia and carers across Dorset. However, no participants were recruited to the study using these strategies as only one participant responded but did not meet the eligibility criteria. The researcher then approached the National Institute for Health Research (NIHR) Join Dementia Research (JDR) platform and registered the study in December 2020. From screening the register of 26 potential participants with MCI, 13 people met the eligibility criteria and were contacted either by phone or email. Of the 13 people screened, only 2 people consented and enrolled into the study while the others did not reply to phone calls and emails. Another approach explored was to work with Dorset Healthcare NHS University Foundation Trust (DHUFT) memory assessment clinics and liaising with the memory assessment nurses to access their database of potential participants with MCI. The database consisted of all people who consented to be contacted for research (160 people in total). Of the 160 people on the database, 8 people met the eligibility criteria and were contacted by a member of staff from the Research and Development Department at DHUFT. If potential participants were interested in the study and consented to contact by the researcher, the researcher contacted them by phone or email to set up a meeting. Of the 8 eligible participants, 4 consented and enrolled in the study. To summarise, taken together using these approaches were able to identify 34 potential participants diagnosed with MCI, of which 13 participants did not meet the inclusion criteria. Of the 22 participants who met the inclusion criteria, only 6 (27.2 %) consented and were enrolled in the study.

Given the low number of people with a confirmed diagnosis of MCI recruited over 3 months to reach the target number of participants for the study, a different strategy for recruitment was introduced. Further to discussion with the supervisory team, the inclusion criteria was adapted to target older adults without a confirmed diagnosis of MCI but likely to have some memory loss as part of normal ageing (Richardson et al. 2019). As the aim of the study was

to evaluate the feasibility of the intervention, the inclusion of older adults (OA) without a diagnosis of MCI would allow the evaluation of feasibility, meeting the study aim and objectives.

This change in strategy for recruitment necessitated a change in the study inclusion criteria. The adapted inclusion criteria were as follows:

- Adults with a confirmed diagnosis of MCI within the last year
- Older adults (over the age of 65) with no diagnosis of MCI

Recruitment of older adults followed a similar approach to recruitment and screening of adults with a diagnosis of MCI. However, different strategies were used for recruitment including placing study flyers in local libraries, bus stops, and coffee shops and 11 potential participants contacted the researcher expressing interest in the study. Furthermore, older adults were recruited from Join Dementia Research (JDR) and 65 potential participants were identified from the database, meeting inclusion criteria. Also, potential participants were invited to take part from the participant pool at Bournemouth University's Ageing and Dementia Research Centre (ADRC). A flyer outlining the study was sent to all participants in the monthly ADRC newsletter and 15 potential participants expressed interest. To summarise, a total of 91 participants (older adults) were screened for eligibility and 80 were contacted by the study researcher either via phone or email. Of these ,28 (35%) older adults with no formal diagnosis of MCI were enrolled into the study.

Title 4.1: Table summarizing number of participants screened, contacted, and recruited in the DICe study per group.

	MCI			Older Adults		
	screened	Eligible/ Contacted	Recruited	Screened	Eligible/ Contacted	Recruited
JDR	26	13	2	65	58	15
DHUFT	160	8	3	N/A	N/A	N/A
ADRC	N/A	N/A	N/A	15	13	9
Local Community	1	0	0	11	9	4

Of the 101 potential participants who were contacted, 15 refused to take part in the study reporting their unwillingness to commit to take the oil for 6 months. One of the potential participants refused to take part due to fear of the finger prick testing and three people reported having caring duties with limited time to commit to the study procedure. The rest of the people contacted did not reply or provide a reason for not taking part in the study. Once recruited, participants provided informed consent and then completed the study measures at 1, 3- and 6-months study visits.

Due to the small sample size and the feasibility aspect of the study, participants from both groups of older adults and adults with a diagnosis of MCI were grouped together prior to randomisation. To summarise, a total of 278 participants were screened (people with a confirmed MCI diagnosis, n= 187; older adults without a confirmed MCI diagnosis, n= 91) were screened for the study. Of these, 34 participants (21.8%) who met the inclusion criteria were enrolled in the study over a 24-month period (October 2018-October 2020), see Table 4.2 for demographic details.

Table 4.2: Demographic details of all the participants enrolled in the DICe study

Age (years)	Mean: 74 ± 5.6 Range 66-87
Gender Men Women	 14 Men (41%) 20 Women (59%)
Participant Group	6 people with a confirmed MCI diagnosis (15%) 28 Older Adults without a confirmed MCI diagnosis (85%)
Living situation	11 living alone (32%) 23 living with partner/family (68%)
Education Level	6 GCSE (18%) 13 A-levels (38%) 21 higher Education/Diploma (61%)
Health condition	1 Anxiety (3 %) 2 Hyperthyroidism (5%) 1 Arthritis (3%) 3 Hypertension (8%)

i. Impact of Covid-19:

In the second phase of the study, recruitment of older adults (with no confirmed MCI diagnosis) started in January 2020. However, due to the restrictions imposed by the Covid-19 pandemic from March 2020 to July 2020, there were delays in recruitment, initiation of the intervention and loss of contact with some study participants. Finally, the third phase of recruitment started in July 2020 to October 2020 after which time recruitment was stopped due to the time constraints of the PhD.

5.1.3. Retention

Participants from both Mild Cognitive Impairment (MCI) and Older Adults (OA) groups were combined together due to the small sample size. The process for recruitment, randomisation, follow up assessments and analysis are presented in the consort diagram (Figure 1).

There were 34 participants enrolled in the study and randomized to either Coconut oil (CO) or Sunflower oil (SO) group. Of these, 28 participants (82.4%) completed the study; 15 in the CO group (53.6%) and 13 (46.4%) in the SO group.

There were 3 participants lost to follow-up (2 in CO group, 1 in SO group) and 3 participants who withdrew from the study. For the 3 participants who were lost to follow-up due to Covid-19 pandemic as they were shielding, the researcher contacted these participants up to a maximum of 5 times via email and two times per week via phone leaving a voice message over a 5-week period. The reasons for not responding are unknown.

Therefore, 31 participants were included in the overall calculations of retention and adherence.

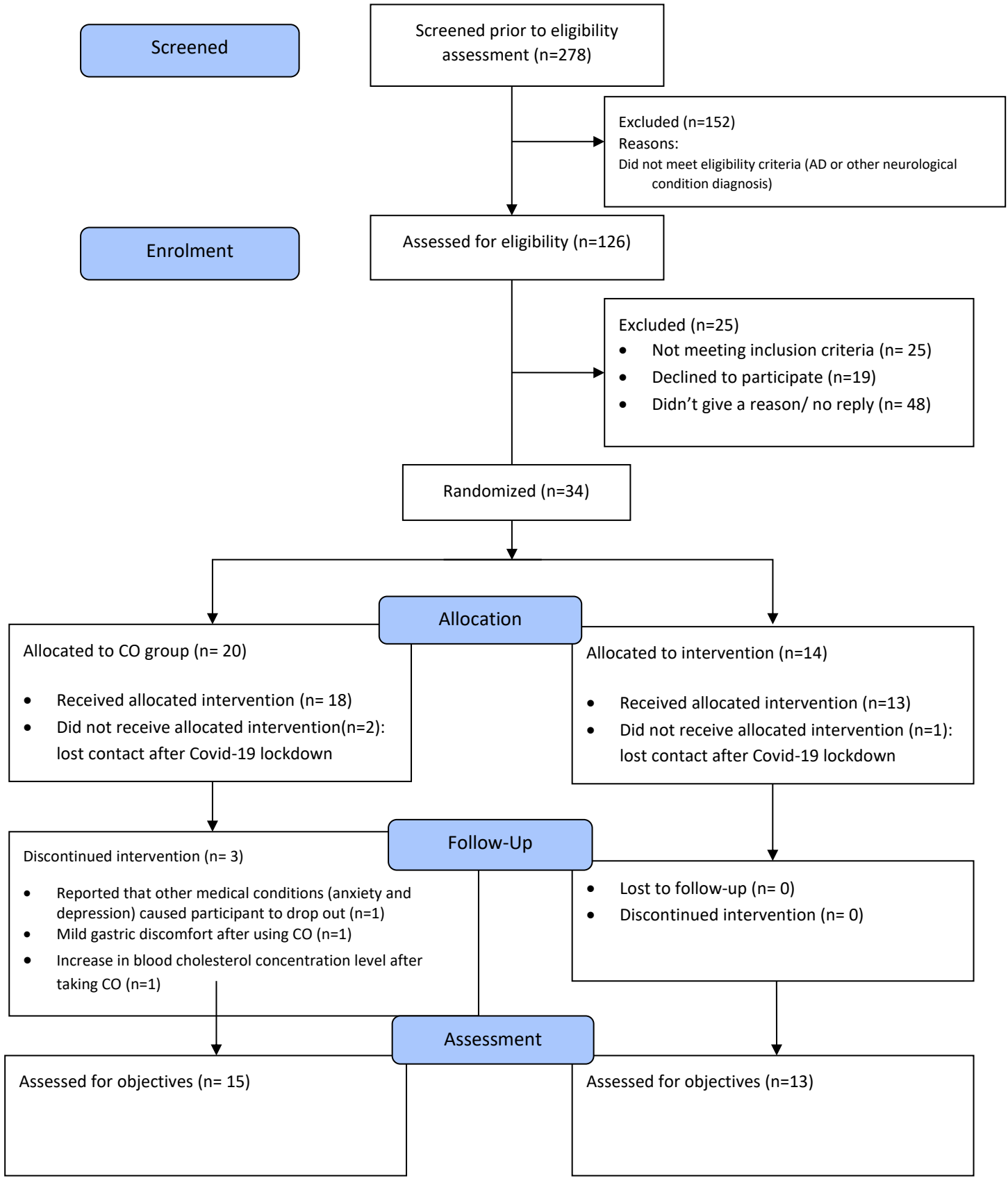
The withdrawal rate from the study was low (8.8%, 3/31). Of this group of 31 participants, 3 withdrew from the CO group and did not successfully take the CO within the first 3 months after providing baseline data. One of the participants had a diagnosis of MCI and the other 2 participants were older adults without a confirmed MCI diagnosis. The researcher emailed the 3 participants who withdrew from the study, asking for their reason for withdrawing. The participants provided the following reasons:

- One participant reported that participation in the study caused an added burden on them especially that they struggled with mental health problems (anxiety and depression).
- One participant reported mild gastric discomfort after taking the CO.
- One participant reported an increase in blood cholesterol level 3 months after taking the CO by reporting blood test results.

None of the participants recruited to the SO group withdrew from the study.

In total, 28 participants completed the study of 31 people recruited and completed the study (retention rate: 91%).

Figure 5.1: Consort Diagram representing DICe Study participants (MCI and OA's) flowchart



The table below, represents the demographic characteristics of the 28 participants who completed the study.

Table 5.3: Characteristics of all the participants who completed the study for each intervention group

	Coconut Oil (n=15)	Sunflower oil (n=13)
Age (years) mean ± SD Range	 72.3 ± 4.6 66.0-83.0	75.3 ± 6.1 67.0-87.0
Gender (n) Men Women	 9 6	 4 9

5.1.4. Adverse Events

No serious adverse events were reported in the study. However, one participant reported an adverse event of gastrointestinal (GI) upset associated with the consumption of coconut oil. As a consequence, the participant withdrew from the study. Minor GI problems were also reported by two other participants. However, they reported managing the side effects by consuming the 30 ml coconut oil in smaller amounts throughout the day (twice to three times per day, 10-15 ml each time) instead of consuming all the coconut oil at one mealtime.

Furthermore, another participant in the CO group reported concerns following an increase in circulating blood cholesterol concentration to 6 mmol/L after 3 months (above normal concentrations of 5 mmol/L). This led to their withdrawal from the study because of their concern taking CO and its effect on raising blood cholesterol concentration (Chinwong et al., 2017). However, this participant reported to the researcher a further increase in their blood cholesterol concentration 3 months after withdrawing from the study. Thus, it is unclear if the increase in blood cholesterol concentration reported during the study was attributed to taking the CO.

5.1.5. Data Collection Procedures

In this section the procedures for data collection from the cognitive, dietary, and anthropometric measures are presented at baseline and at 3 months and 6 months follow-up. Table 5.3 provides a monthly overview for the number of participants assessed and when the measurements were conducted. Data was collected between October 2019 and April 2021.

Table 5.4: Table summarising monthly Patterns for DICe study procedures

Dates	Baseline Assessment	3 months follow up	6 months follow up
October 2019	2		
January 2020	5	1	
February 2020	8		
March 2020	8		
April 2020		4	1
May 2020		3	
June 2020		11	
July 2020			2
August 2020	3		6
September 2020	7		8
October 2020	1		1
November 2020		3	
December 2020		6	
January 2021		1	
February 2021			
March 2021			5
April 2021			5
total	34	29	28

Baseline visits were conducted either in a quiet room on the Bournemouth University campus or at the participant's home depending on their preference. Each visit lasted for up

to 2 hours including a rest break. At the baseline visit, all participants completed the body weight, height, and blood ketone (beta-Hydroxyl Butyrate) concentration measures (see chapter 4, section 4.6). All participants completed the cognitive measures, quality of life questionnaire, and health history questionnaire (refer to appendix 5) and 4-day food diary (refer to appendix 7). They were then provided with their allocated oil along with a leaflet explaining how to incorporate the oil into their diet (refer to appendix 12) and some recipes using 30 ml of their allocated oil (refer to appendix 13).

Table 5.5 presents the demographic details of the participants in both groups at baseline. Both the mean and age range of participants were similar in both intervention groups. Of the 18 participants in the CO group, 50% (n=19) were women, but of the 13 participants in SO group there were less men (n=4) than the CO group but the same number or women (n=9).

Table 5.5. Demographic characteristics of participants randomised allocation to intervention group at baseline

	Coconut Oil (CO) (n=18)	Sunflower oil (SO) (n=13)
Age (years) Mean ± SD Range	 72.4 ± 4.8 66.0-83.0	 75.4± 6.2 67.0-87.0
Gender	9 Men 9 Women	4 Men 9 Women

The three months and 6 months follow up visits were booked within 10 days of the original baseline assessment data if possible. During some visits there were technical issues with the supermarket task which is one of the cognitive measures that was used (an application used to test visuospatial memory). The application did not load, or it abruptly closed during testing, thus some data was missing.

Covid-19 Impact on data collection:

Due to the Covid-19 pandemic and associated lockdown, 26 of the 3 months and 15 of the 6 months follow up study visits were done virtually using Zoom. Where the three months

follow up sessions were conducted virtually (n=26), participants were asked to complete the open-ended questionnaire and send it to the study researcher (refer to appendix 6). A phone call was arranged with the participant, and they were asked to report their weight and provide pictures of any left-over oils.

Where the 6 months follow up session was conducted virtually, participants were sent copies of the Trial Making tests (conditions 2,3 & 4), the Digit Coding test and the 4-day food diary form. A Zoom meeting was arranged with the participant and the cognitive measures were conducted with the interview at the end of the session. Participants were asked to report their weight on the day of the virtual meeting.

At both 3 and months, it was not possible to measure blood ketone concentration and the data is missing.

Table of Measures completed:

Table 5.6. Table summarizing the frequency & condition of completion of study measures at baseline, 3 months, and 6 months in both CO & SO groups.

		Coconut Oil			Sunflower oil		
		Baseline	3 months	6 months	Baseline	3 months	6 months
Weight (kg)	Measured by Researcher	n=15	n=1	n=6	n=13	n=1	n=7
	Self-Reported	n=0	n=14	n=9	n=0	n=12	n=6
Blood Ketone (mmol/L)		n=15	n=1	n=6	n=13	n=1	n=7
Height (cm)		n=15	n=1	n=6	n=13	n=1	n=7
Cognitive measures	Face to Face	n=15	N/A	n=6	n=13	N/A	n=7
	Virtually	n=0		n=9	n=0		n=6

All 28 study participants completed the study measures either virtually or in-person depending on their preference and Covid-19 measures that were in place at the time of data collection.

5.1.6. Adherence

The second objective of the study was to assess the adherence rate of participants to consuming all of the 30 mls/day of the CO and SO for each intervention group. Adherence rates were assessed using an open-ended questionnaire (refer to appendix 6) administered by email at 3 months and semi-structured interviews at 6 months (refer to appendix 9). Based on the participant's responses to questions on adherence and oil intake for both CO and SO oils, the majority 23 (82%) of 28 participants adhered to consuming 30 mls of oil each day by 3 months and 20 (71%) of 28 participants adhered for the 6 months.

At 3 months, in the CO group, the majority (n=13) of the 15 (87%) participants adhered to the CO. By 6 months, there were less participants (n=11) of the 15 (73%) who reported adherence to the CO. While at 3 months for the SO group only 10 of the13 (77%) participants adhered to SO and 9 of the 13 (69%) participants adhered by 6 months.

Table 5.7: Table summarising adherence rates for consumption of 30 mls/day of CO & SO in study participants at 3 & 6 months

	CO (n=15)		SO (n=13)		Total	
	3 months	6 Months	3 Months	6 Months	3 Months	6 Months
Adherence to 30 ml oil intake/day	87% (n=13/15)	73% (n=11/15)	77% (n=10/13)	69% (n=9/13)	81% (n=23/31)	70% (n=20/31)

There were no statistically significant differences in adherence between the intervention groups at both 3 and 6 months (p=0.07).

The open-ended questionnaires and semi-structured interviews were used to assess adherence to consuming both CO and SO and to understand the reasons for adherence or non-adherence.

One of the participants reported the need to remember using the oil and to establish this as part of their daily routine.

"In the beginning just sort of remembering to do it. I think it does take a few weeks to get into the habit of taking it every day but apart from that it was fine" GB13, CO

With regard to the amount consumed and routine, another participant reported using more than 30 mls of the oil sometimes while another used exactly 30 mls every day except during holidays.

"I would say probably at least 30. Sometimes maybe a bit more, I suppose, sometimes a bit less and I use it for cooking." Ms19, SO

"Every day, well apart from a week when we were on holiday but that was before lockdown. I would think around 2-3 tablespoons a day." RP18, CO

However, 4 participants reported using around 1 tablespoon (15 mls) of oil per day as they struggled with taking the 30 mls/day. While 2 participants, reported using 30 mls/day over 3-4 days a week.

"If we're talking an average; out of seven days, four days I used it and three I didn't as an average. When I was full on it was seven days a week…. to take the 30 mls was a struggle each day." JI4, CO

"I would think much less. I'd be lucky if I used two tablespoons per day 30 or 40% of the time." TB20, SO

PART 2

In the second part, results from the cognitive, dietary, and anthropometric (body weight and height) outcome measures are presented.

5.2. Quantitative results

This part of the chapter presents the results from the cognitive, dietary, and anthropometric outcome measures at baseline, 3 months and 6 months and relates to objective 2.

It was intended that the cognitive, dietary, and anthropometric outcome measures would enable estimation of standard deviations and effect size to inform sample size calculations for an adequately powered future RCT.

5.2.1. Cognitive Measures:

Multiple cognitive measures (see chapter 4, section 4.6. for details) were collected from study participants in order to evaluate the feasibility and acceptability of using these measures. In this study the cognitive measures were included as part of the feasibility, and the aim was not to evaluate the change in these cognitive measures post intervention in the two groups (i.e., coconut oil and sunflower oil).

All of the participants (n = 28) completed the neuropsychological assessments, see section 5.1.5) under the supervision of Dr Shanti Shanker (CPsyc). There was no significant difference in ages across the coconut oil ($Mean_{CO}$ = 72.3, *SD* = 4.8) and the sunflower oil group $Mean_{SO}$ = 75.4 *SD* = 6.1).

The study used specific cognitive assessments instead of an overall single measure, as often seen in dietary studies. These were: i) Overall cognition (M-ACE, Hsieh et al., 2015), ii) Memory (WAIS - IV), iii) Executive functions & attention (trail making (DKEFS), category and semantic fluency (DKEFS), and Backward and forward digit span (WAIS -IV)) iv) processing speed (Digit Coding, WAIS – IV).

1. Overall Cognition(M-ACE)

A mixed method ANOVA with two within subject factors, i.e., time (2 levels) and over all cognition scores (6 levels, i.e., attention, memory, fluency, clock drawing, recall and total score) and one between subject factor of oil group (2 levels coconut and sunflower oil) was completed. Mauchly's Test of Sphericity was violated (p = .001) and therefore, a Greenhouse-Geisser corrected values was reported.

There was a main effect of time on M-ACE scores (F (2.22, 57.73) = 3626.81, p=.001) between groups but there was no difference within the groups. However, the attention scores in session 1 (pre-intervention) in coconut oil group (M_{CO} = 3.7, SD= 0.5) were significantly lower (t (14) = -2.25, p = .041) compared to the sunflower oil (M_{so}= 4, SD=0).

2. *Memory*

A mixed method ANOVA with two within subject factors, i.e., time (2 levels) and memory score (5 levels, i.e., first trial, total recall, short delay, delayed recall, and recognition) and one between subject factor of oil group (2 levels coconut and sunflower oil) was completed. Mauchly's Test of Sphericity was violated (P= .001) and therefore, a Greenhouse-Geisser corrected values was reported.

There was a main effect of time on memory (F (1.59, 41.45) = 642.41, p = .001*) and Time (F (1,26) =7.776, p=0.01) in the coconut oil group. The performance on session 1 (pre-intervention) was lower (M = 4.9; SD = 2.6) than session 2 (6 months post, M = 5.9; SD = 2.9) for scores on the delayed recall (t (14) = -2.36, p = .034), however this was not significant based on Bonferroni correction (p = .01).

3. *Executive Functions & Attention*

A. TRAIL MAKING:

A mixed method ANOVA with two within subject factors, i.e., time (2 levels) and trail making performance (2 levels, i.e., total semantic fluency, total category fluency) and one between subject factor of oil group (2 levels coconut and sunflower oil) was completed. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, P= .001, and therefore, a Greenhouse-Geisser corrected values was reported.

There was a main effect of Trail Making performance F (1.15, 29.79) = 113.67, p = .015 with time in both groups. The two-way interaction between time and oil group F (1,26) = 5.56, p= .026 and three-way interaction between trail making performance, time, and oil group F (1.25, 32.49) = 5.95, P= .005 were statistically significant. There were no statistically significant differences within the groups. However, the performance for trail making (condition 4, where participants switched between letter and number) was significantly slower (t (19.2) = 2.248, P= .037) in the coconut oil group (M_{Co} = 110.1, SD= 45.60) compared to sunflower oil group (M_{SO} = 81.1, SD= 18.9).

B. FLUENCY

A mixed method ANOVA with two within subject factors, i.e., time (2 levels) and fluency scores (2 levels, i.e., total semantic fluency, total category fluency) and one between subject factor of oil group (2 levels coconut and sunflower oil) was completed. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, P=.001, and therefore, a Greenhouse-Geisser corrected values was reported.

There was a main effect of fluency score F (1, 26) = 176.63, p= .001 with time in both groups. There were no statistically significant differences within the groups. However, performance on semantic fluency (BHR) scores post intervention (session 2) were significantly lower (t (26) = - 2.09, p= .047) in coconut oil (M_{CO}=38, SD= 10.6) than sunflower oil group (M_{SO}= 45.5, SD= 7.9).

C. DIGIT SPAN:

A mixed method ANOVA with two within subject factors, i.e., time (2 levels) and digit span scores (2 levels, i.e., digit span forwards, digit span backwards) and one between subject factor of oil group (2 levels coconut and sunflower oil) was completed. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, P=.001, and therefore, Greenhouse-Geisser corrected values was reported.

There was main effect of Digit span score F (1, 26) = 19.86, p= .001 with time in both groups. However, there was no significant difference within groups nor across s1 and s2 between sunflower and coconut oil.

4. Processing Speed:

A. DIGIT CODING:

There was no statistically significant effect or interaction on digit coding scores over time within and between both oil groups.

Table 5.8 Summary of ANOVA and paired sample T-test results of Cognitive Measures pre and post intervention in CO & SO groups

Cognitive measures	ANOVA Results	t-test	comments
m-ACE	Main Effect: F (2.22, 57.73) = 3626.81, p=.001	Total m-ACE: P (CO)= 1.00 P (SO) = .44	There were no significant differences within groups pre and post intervention.
Memory	Main effect of memory: F (1.59, 41.45) = 642.41, p = .001 Main effect of Time: F (1,26) =7.776, p=0.01	Trial 1 Recall: P (CO)= .28 P (SO)= .10 Total Recall: P (CO)= .10 P (SO)= .16 Short-delay Recall: P (CO)= .15 P (SO)= .66 Delayed Recall: P (CO) = .03 P (SO)= .38 Recognition: P (CO)= .07 P (SO)= .15	No significant differences within groups pre and post intervention based on Bonferroni corrections (p=.01)
Trail Making	Main effect of Trail Making performance F (1.15, 29.79) = 113.67, p = .015 Two-way interaction between time and oil	Condition 2: P (CO)= .16 P (SO)= .25 Condition 3: P (CO)= .29 P (SO)= .41 Condition 4:	No significant differences within the groups pre and post intervention.

	group F (1,26) = 5.56, p= .026 Three-way interaction between trail making performance, time, and oil group F (1.25, 32.49) = 5.95, P= .005	P (CO)= .10 P (SO)= .07	
Fluency	Main effect of fluency score F (1, 26) = 176.63, p= .001	Sematic fluency: P (CO)= .053 P(SO)= .39 Category Fluency: P (CO)= .06 P(SO)= .61	No significant differences within the groups pre and post intervention.
Digit Span	Main effect of Digit span score F (1, 26) = 19.86, p= .001	P (CO)= .70 P (SO)= .20	No significant difference within the groups pre and post intervention.
Digit Coding	No effect or interaction on scores overtime	P (CO)= .73 P (SO)= .09	No significant difference within the groups pre and post intervention.

5.2.2 Quality of Life

The mean ADCS-MCI-ADL measure was 50/53 at baseline and after 6 months in CO, while it decreased from 52/53 at baseline to 51.5/53 after 6 months in the SO group. This indicates that participants in both groups have high self-perceived independence and good quality of life.

There was no statistically significant interaction or effect on ADCS-MCI-ADL scores over time within and between both oil groups ($p > 0.05$).

5.1.4. Blood ketone concentration

It was intended to measure blood ketone (beta-hydroxyl butyrate) concentrations at baseline and at 3 months and 6 months (refer to chapter 4, section 4.6). Blood ketone measures were used as a biomarker to assess the effect of coconut oil on blood ketone concentrations and to monitor DK.

As previously explained in section 5.1.5, some of the 3 and 6 months follow up study visits were conducted virtually using zoom or phone calls. Thus, it was not possible to conduct the blood ketone tests on some participants as intended due to Covid-19 restrictions (see section 5.1.5). There were 2 of 28 (7%) measures collected at 3 months and 13 of 28 (46%) at 6 months. Thus, 26 samples were missing at 3 months and 15 at 6 months.

Two tailed paired sample t-test demonstrated no statistically significant differences in blood beta-Hydroxyl Butyrate concentrations between baseline and at the 6 months end point, ($p>0.05$) in both groups. The data showed no significant difference between blood ketone concentration pre and post intervention in the coconut oil group as the mean level increased from 0.170.17 ± 0.31 mmol/L at baseline to 0.25 ± 0.27 mmol/L after 6 months. However, blood ketone level post intervention (at 6 months) was collected from only 6 participants out of 15 who were in the coconut oil group.

Table 5.9: Summary of results of Blood Beta-Hydroxyl Butyrate concentrations at baseline, and 6 months in CO & SO groups

	Coconut Oil (n= 15)		Sunflower Oil (n= 13)	
	Baseline Mean ± SD (n=15)	6 months Mean ± SD (n=6)	Baseline Mean± SD (n=13)	6 months Mean ± SD (n=7)
Blood beta-Hydroxyl Butyrate concentration (mmol/L)	0.17 ± 0.31	0.25 ± 0.27	0.13 ± 0.12	0.11 ± 0.06

5.2. Anthropometric Measures (body weight and height)

Measures of body weight and height were collected from participants at baseline, three months and at 6 months (refer to chapter 4, section 4.6. for more details). Due to covid-19 restrictions (see chapter 5, section 5.1.2.), at three months 26 participants, 14 (93%) in CO group and 12 (92%) in SO group were asked to weigh themselves at home using their own scales if available and report their weight. However, at 6 months there were 11 of 15 (73%) in CO and 11 of 13 (84%) in SO group who were asked to weigh themselves. The researcher was able to measure body weight in 4 of 15 participants (26%) from CO group and 2 of 13 participants (15%) from SO group at 6 months.

The table below summarises the measured and self-reported body weight and BMI of the participants at baseline, 3 months, and 6 months. At baseline, the mean (± SD) body weight of participants in the CO group was 77.2 ± 6.8 kg which was not statistically significantly different from that of participants in the SO group (66.8 ± 8.4 kg, p>0.05). After 6 months, no changes in mean body weight from baseline was observed in both CO (76.9 ± 6.7 kg, P>0.74) and SO groups (66.5 ± 8.3 kg P>0.59). At baseline, the mean BMI was 25.8 ± 2.0 and 24.6±4.4 for the CO and SO group respectively. All of the participants had a BMI within the normal range for BMI (18 – 24.99 kg/$m^{2)}$ (Weir and Jan, 2019). Compared with baseline, BMI remained unchanged for both CO (25.7 ± 1.7; p>0.80) and SO (24.5 ± 4.3; p>0.67) groups after 6 months.

Two tailed paired sample t-tests demonstrated no statistically significant changes in body weight (kg) and BMI (kg/m^2) between baseline and the 6 months end point, p>0.05.

Table 5.10 Summary of anthropometric measures at baseline and 6 months in CO & SO groups

	Coconut Oil		Sunflower oil	
	Baseline Mean (N=15)	6 months Mean (N=12)	Baseline Mean (N=13)	6 months Mean (N=10)
Body weight (kg)	77.2 ± 6.8	76.9 ± 6.7	66.9 ± 8.4	66.5 ± 8.3
BMI (kg/m^2)	25.8 ± 2.0	25.7 ± 1.7	24.6 ± 4.4	24.5 ± 4.3

5.3. Dietary Intake:

The dietary energy and macronutrient (CHO, fat, and protein) intake of older adults was assessed using 4-day food diaries at baseline and 6 months (refer to chapter 4, section 4.6 for further details).

In the first part of this section dietary intake at baseline from all the participants (n=31) is presented and compared with the average national intake for older adults (age 65 and above) based on the results of the National Diet and Nutrition Survey 2019 (NDNS, 2019). Then dietary intake at baseline and after 6 months from each of the intervention group is presented to further understand the effect of the dietary intervention on the participant's dietary intake especially regarding CHO and fat intake. The percentage of energy attributable to CHO intake was calculated in both groups as low CHO intake may affect dietary ketosis and ketone metabolism.

5.5.1. Dietary energy and macronutrient (carbohydrate, fat, and protein) intake at baseline

The mean energy intake at baseline was 8043 ± 2724 kJ/day with nearly a 4 -fold difference observed between participants. The mean energy intake was higher than the national daily average intake (NDNS, 2019) 6900 ± 1870 kJ/day.

The mean carbohydrate (CHO) intake at baseline was 184.4 ± 60.4 g/day which is lower than the national average intake based on the NDNS results.

Protein intake in the study participants was greater than the national average intake (67.0 ± 17.6 g/day) based on the NDNS.

Mean fat intake at baseline was 87.6 ± 48.7 g/day which was greater than the national average intake which is 34.4 ±6.5 g/day. Participants dietary fat intake exceeded both dietary reference values (75.3 ± 9.3 g/day) for their age group and average national levels (34.4 ±6.5 g/day) before taking part in the oil-based intervention. After 6 months, a statistically significant reduction in fat intake to 64 ± 21 g/day ($p<0.02$) was observed. Thus,

dietary fat intake decreased to fall within the recommended levels after the 6 months intervention.

Table 5.11. Summary of mean energy and macronutrient (carbohydrate, fat, and protein) intake of participants at baseline (n=28) in comparison to the National Diet and Nutrition Survey (NDNS 2019)

	Mean daily Intake & Range N= 28	NDNS 2020
Energy intake (kJ/day)	8043 ± 2724 5103-18312	6900 ± 1870 3480-10760
Total carbohydrate intake (g/day)	184.4 ± 60.4 44.0-354.0	194.0 ± 56.0 102.0-318.0
Total fat Intake (g/day)	87.6 ± 48.7 48.0-293.0	34.4 ±6.5 22.1-46.3
Protein Intake (g/day)	81.68 ± 36.7 51.0-220.0	67.0 ± 17.6 34.3-105.7

5.5.2 Dietary energy and macronutrient intake for CO and SO groups

Two tailed paired sample T-tests were used to compare dietary energy, carbohydrate, protein, and fat (SFA, PUFA & cholesterol) intake at baseline and at 6 months between the oil intervention groups; $p < 0.05$*.

Table 5.12. Mean Energy, Carbohydrates, Protein and Fat Intake for participants (n=28) at baseline and after 6 months in CO & SO groups

		Coconut Oil (n=15)			Sunflower Oil (n=13)		
		Baseline mean± SD	6 months mean± SD	P-value	Baseline mean± SD	6 months mean± SD	P-value
Energy Intake (kJ/day)	Mean	7565 ± 1927	6058 ± 2057	0.031*	8594 ± 3428	6534 ± 2074	0.109
	Range	5103-12673	1399-9778		5803-18312	1000-9290	
Protein (g/day)	Mean	73.1 ± 23.6	61.3± 11.8	0.095	91.5 ± 46.7	65.1 ± 22.7	0.1
	Range	52.1-96.7	49.5-76.2		54.7-98.2	53.2-79.4	
Total carbohydrate intake (g/day)	Mean	176.8 ± 72.8	158.9 ± 59	0.232	193.2 ± 43.3	164.3± 57.3	0.194
	Range	44.0-354.0	71.0-274.0		128.0-228.0	64.0-221.0	
Total Fat intake (g/day)	Mean	82.0 ± 26.5	61.5 ± 20.3	0.013*	94.0 ± 66.6	66.8± 22.5	0.193
	Range	41.0-121.0	37.0-108.0		45.0-293.0	16.0-100.0	
Saturated Fatty Acids (g/day)	Mean	35.12 ± 17.5	25.07 ± 10.7	0.051	37.21 ± 38.9	22.76 ± 8.89	0.217
	Range	11.4-67.0	13.0-49.0		14.2-161	2.9-35.7	
Poly Unsaturated	Mean	8.44 ± 3.9	7.78 ± 4.02	0.412	10.50 ± 6.9	11.36 ± 4.05	0.707
	Range	2.3-15.6	2.5-17.0		4.0-25.7	5.0-19.0	

Fatty Acids (g/day)							
Cholesterol (g/day)	Mean	165.7 ± 80.3	165.9± 85.9	0.989	268.6 ± 175.8	225.07 ± 122.0	0.360
	Range	88.1-347.0	58.0-359.0		86.0-747.0	77.0-458.0	

The mean energy intake for participants in the CO group was 7565 ± 1927 kJ/d at baseline. After 6 months, there was a statistically significant decrease in energy intake (6058 ± 2057 kJ/d; $p<0.031$). At baseline, the mean energy intake for the SO group was 8595 ± 3428 kJ/d but after 6 months, the mean energy intake was not statistically significantly different from baseline (6535 ± 2075 kJ/d, $p>0.05$).

The mean protein intake for participants in the CO group was 73.1 ± 23.6 g/day at baseline. After 6 months, the decrease in protein intake was not statistically significantly different to baseline (61.2 ± 11.8 g/day; $p>0.05$). At baseline, the mean protein intake for the SO group was 91.5 ± 46.7 g/day but after 6 months, the mean protein intake was not significantly different from baseline (65.1 ± 22.7 g/day, $p>0.05$).

The mean CHO intake for participants in the CO group was 184.4 ± 60.4 g/day at baseline. After 6 months, the decrease in CHO intake was not statistically significantly different to baseline (162 ± 55.7 g/day; $p>0.05$). At baseline, the mean CHO intake for the SO group was 193.2 ± 43.3 g/day but after 6 months, the mean CHO intake was not significantly different from baseline (164.3± 57.3 g/day, $p>0.05$).

The dietary assessment allowed stratification of participants into three groups based on their carbohydrate intake. People consuming a high carbohydrate diet (>50% of daily energy intake), normal carbohydrate diet (10-50% of daily energy intake) and low Carbohydrate diet (5-10% of daily energy intake).

Of the 28 participants, only 1 participant had low CHO intake (9.8% of total energy intake). While the majority of participants (*n* 22) had normal CHO intake (20-49.5%) only 5 participants had high CHO intake (51.5–59.7%).

Due to the small sample size, and the missing ketone data from study participants, it was not possible to statistically evaluate the effect of CHO intake on blood ketone levels in the study participants.

1. Fat Intake:

At baseline, the mean fat intake for participants in CO group was 82 ± 26.5 g/day. There was a statistically significant reduction in mean fat intake after 6 months (61.5 ± 20.3 g/day, $p<0.01$) in the CO group. In the SO group, mean fat intake was 94 ± 66.6 g/day at baseline. However, the reduction in the mean fat intake for the SO group after 6 months was not statistically significant (66.8± 22.5 g/day, $p>0.05$).

At baseline, the mean saturated fat intake of participant in the CO group was 35.12 ± 17.5 g/day. After 6 months, there was no statistically significant reduction in mean saturated fat intake in CO group (25.07 ± 10.7 g/day, $p>0.05$). The mean saturated fat intake in SO group was 37.21 ± 38.9 g/day at baseline. After 6 months, the reduction in mean saturated fat intake was not statistically significant (22.76 ± 8.89 g/day, $p>0.05$).

At baseline, the mean polyunsaturated fatty acids (PUFA) intake of participants in the CO group was 8.44 ± 3.9 g/day. After 6 months, the mean PUFA intake in CO group was not statistically significantly different to baseline (7.78 ± 4.02 g/day, $p>0.05$). The mean PUFA intake in SO group was 10.50 ± 6.9 g/day at baseline. After 6 months, the mean PUFA intake was not statistically significant (11.36 ± 4.05 g/day, $p>0.05$).

At baseline, the mean cholesterol intake of participant in the CO group was 165.7 ± 80.3 g/day. After 6 months, mean cholesterol intake in the CO group remained unchanged (165.90± 85.9 g/day, $p>0.05$). The mean cholesterol intake in SO group was 268.61 ± 175.78 g/day at baseline. After 6 months, the reduction in mean cholesterol intake was not statistically significant (225.07 ± 122.0 g/day, $p>0.05$).

5.4. Sample Size Calculations

In order to meet the third and fourth objective for the study, preliminary estimates of effect sizes were calculated. Standard effect sizes (Cohen's d) were calculated and the effect sizes and description for the size and direction of the effect for the outcome measures are

reported in Table 4.14. Cohen suggests that d = 0.2 is considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. The trends for the estimates of effect size were in the direction of benefit for most of the outcome measures for both CO and So group except for Quality of Life and category fluency measures. However, the trail making condition 4, sematic fluency and digit span measures were not in the direction of benefit in the CO group but in direction of benefit in the SO group. The effect sizes in the direction of benefit were small in all measures.

Table 5.13: Summary of Effect size estimates using Cohen D on outcome measures in CO & SO groups.

Outcome Measure		Group	Cohen's d = (M2 - M1)／SD pooled	Effect Size
Overall Cognition	M-ACE	Coconut Oil	0	No effect
		Sunflower Oil	0.19	Small effect size in direction of benefit
Memory	Initial Recall	Coconut Oil	0.39	Small effect size in direction of benefit.
		Sunflower Oil	0.44	Almost medium effect size in direction of benefit.
	Total Recall	Coconut Oil	0.36	Small effect size in direction of benefit.
		Sunflower Oil	0.39	Small effect size in direction of benefit.
	Short-delay recall	Coconut Oil	0.29	Small effect size in direction of benefit.
		Sunflower Oil	0.12	Small effect size in direction of benefit.
	Delayed Recall	Coconut Oil	0.34	Small effect size in direction of benefit.

		Sunflower Oil	0.2	Small effect size in direction of benefit.
	Recognition	Coconut Oil	0.32	Small effect size in direction of benefit.
		Sunflower Oil	0.36	Small effect size in direction of benefit.
Trail Making	Condition 2	Coconut Oil	0.255	Small effect size in direction of benefit.
		Sunflower Oil	0.28	Small effect size in direction of benefit.
	Condition 3	Coconut Oil	0.28	Small effect size not in direction of benefit.
		Sunflower Oil	0.29	Small effect size in direction of benefit.
	Condition 4	Coconut Oil	0.39	Small effect size not in direction of benefit.
		Sunflower Oil	0.61	Medium effect size in direction of benefit.
Fluency	Sematic fluency	Coconut Oil	0.52	Medium effect size not in direction of benefit.
		Sunflower Oil	0.25	Small effect size in direction of benefit.
	Category Fluency	Coconut Oil	0.67	Medium effect size not in direction of benefit.
		Sunflower Oil	0.19	Small effect size not in direction of benefit.
Digit Span		Coconut Oil	0.07	Small effect size not in direction of benefit.
		Sunflower Oil	0.33	Small effect size in direction of benefit.

Digit Coding	Coconut Oil	0.04	Small effect size in direction of benefit.
	Sunflower Oil	0.30	Small effect size in direction of benefit.
Quality of Life	Coconut Oil	0.14	Small effect size not in direction of benefit.
	Sunflower Oil	0.39	Small effect size not in direction of benefit

Based on the current study sample size, to get the sensitivity, future studies should have an effect size of 0.71 (using G Power). Based on the effect size, G power was used to do correlation t-tests to determine the required sample size for a future trial. A future trial would require a sample size of 16 participants in each group.

Table 5.14: Summary of result of sensitivity analysis using correlation t-tests (Point biserial model)

Input	
tails	**Two**
α err prob	**0.05**
Power (1-β err prob)	**0.95**
Total sample size	**15**
Output	
Noncentrality parameter δ	3.90
Critical t	2.16
Df	**13**
Effect Size (p)	0.71

Table 5.15: Summary of A priori sample size calculation using Correlation t tests (Point biserial model)

Input

tails	**Two**
Effect Size (p)	0.71
α err prob	**0.05**
Power (1-β err prob)	**0.95**
Output	
Noncentrality parameter δ	4.00
Critical t	2.14
Df	**14**
Total Sample Size	16
Actual Power	0.96

Qualitative Data

The third part presents qualitative data from interviews and open-ended questionnaires about the acceptability of the intervention and randomisation process. It also presents feedback from participants regarding their experiences (satisfaction level, barriers, and difficulties) of their involvement in the study.

PART 3

5.5. Qualitative findings and process evaluation:

This section presents the qualitative findings which relates to the fifth objective of the study. Specifically, it includes data from semi-structured interviews conducted with all the participants who completed the study (n=28) at 6 months to explore the acceptability of the intervention and randomisation process. It also presents feedback from participants regarding their experiences of involvement in the study.

The qualitative data presented are based on data collected from 28 interviews conducted at 6 months follow up using the interview guide (see Appendix 9). Interviews were conducted virtually using Zoom instead of face- to- face to conform with Covid-19 restrictions. The mean time taken to conduct these interviews was 12 minutes, ranging from minimum of 7 and maximum of 34 minutes.

The interviews were transcribed verbatim and then coded before any analysis was conducted. The transcripts from the interviews were thematically analysed using an inductive approach based on Braun and Clarke six step thematic analysis process (Braun and Clarke, 2006) using N-Vivo 12 (QSR International Pty Ltd. (2020). To start the thematic analysis the researcher familiarized themselves with the data. Going through the six phases of thematic analysis, the data was reduced from the audio-recordings of the discussion to a framework of themes and sub-themes. A member of the supervisory team coded 10% of the interviews before a discussed ensued between supervisory team and researcher on the development of theme (Flick, 2004).The data from the interviews were coded and then grouped into four major themes: Acceptability of Study Design, Incorporation of oil into diet, limited improvement in health and the positive experiences of participation.

Figure 5.1. Diagram representing the themes collated from the interviews

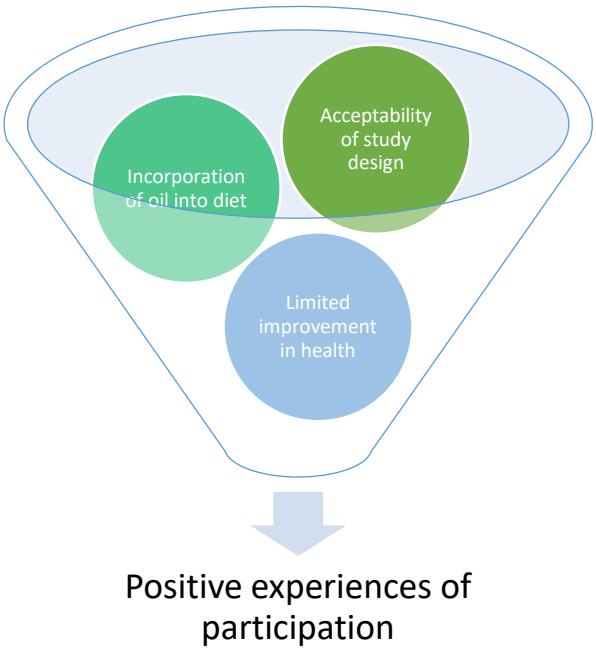


Table 5.14. Summary of themes and subthemes collated from participant interviews

Theme	Subthemes
1.Acceptability of Study Design	• Motivation and high level of engagement • Attitudes to Randomisation • Feelings about study duration • Attitudes to Outcome Measures Used • Views of Genetic Testing
2.Incoporation of oil into diet	• Incorporating oil into normal diet • Issues taking the oil • Amount of oil used • Willingness to continue taking the oil after the study
3. Limited improvement in health	• Effect on Memory and quality of life
4. Positive experiences of participation	• Satisfaction • Supported by contact • Overcoming barriers and challenges

	• Recommendations and factors to consider for a future trial

Theme 1: Acceptability of Study Design

This theme highlights participant's perceptions of the acceptability of the study design and intervention group. It presents the findings about the motivation and engagement of the participants in the study along with their attitudes to randomisation, study duration, outcome measures used along with their views on genetic testing, and over-all satisfaction level.

a) Motivation and high level of engagement

Participants expressed a sense of commitment and interest in the study. During the interviews, participants reported a number of factors that motivated them to participate in the study and commit to it. These included the sense of wanting to help people with dementia, worry about their own cognitive functions and general interest in the study.

'That somebody is doing something about dementia. I am too pleased to be part of any sort of experiment. 'JI4, CO

'And what motivated me to get involved with this research is that dementia as it is they don't give you a lot of hope. It is a lack of hope. There is no magic bullet.

But there's more. There's more to dementia than pills.' MF5, CO

'I found the study interesting and wanted to know more about my own memory as I am getting older.' MD32, CO

There was an altruistic view that by being involved in a study there would be benefits to others in the future, even though the immediate benefit to them may be minimal.

'I just hope the results have a good conclusion and then I would have felt that I helped somehow.' PH12, SO

'I think it is a good thing to volunteer. I had a specific reason to do it as it is dementia, having had that in the family but I think it is good for people to volunteer for things.' LC27, CO

Participants described a sense of accountability and commitment to the study and the research team. Their commitment also included adhering to the oil intake.

'When I started the study, I felt that I couldn't take the 30 ml of oil every day, but I didn't want to disappoint you. I am happy you told me to be more flexible as that allowed me to continue in the study.' DS31, CO

Participants were motivated to take part in the study due to their interest in supporting dementia research.

b) Attitudes to Randomisation:

Participants were asked about their views concerning the study design and the randomisation process to either CO or SO group. They were also asked whether they would have preferred to be in a different group than the one they were allocated to. Most participants (n=26) reported that they accepted and understood the randomisation process. They knew that it was an integral part of the study, and they were aware of it, so they were not disappointed with the findings.

'I didn't have a problem; I wouldn't have volunteered otherwise.' MH7, SO

'I had no feelings about that it was a matter of helping and participating in an experiment and so I basically accepted what was allocated to me.' PP38, CO

Most participants said that they were happy with the group that they ended up in and had no problems with adhering to it.

'Well, I wanted the coconut oil because I really like it. If I got the other oil, I would have used it, but I am glad that I got the CO.' TT10, CO

'I was very glad to have sunflower oil'. MS19, SO

Some participants mentioned that they would have preferred to be in another group but that it did not affect their adherence or willingness to take part in the study.

'I must admit I was hoping to be in the coconut oil group because I have never used it before whereas using sunflower oil as I normally use it didn't seem as if I was doing anything different.' AS2, SO

'It might have been better for the study, because we do cook with sunflower also, then we would have just been doing one thing. But it wasn't a problem for me, but you try something new in the end of the day.' CS17, CO

c) Feelings about study duration:

It was reported that 6 months was an appropriate amount of time to integrate the oil in the diet, as part of mealtimes and to assess any impact of the intervention on cognition. No issues were reported regarding the time frame of the study.

'I've felt that 6 months is a good window of opportunity and if there is anything changing in your body or so then 6 months is good.' MA8, SO

d) Acceptability of data collection process:

The semi-structured interview guide included a couple of questions about data collection methods. The questions focused on relevancy, ease of completion and importance of the measures used.

i) Attitudes to outcome measures used

When asked about the outcome measures of the study, participants only responded about the cognitive measures as a number of different tests had been used. Participants accepted the need for dietary assessment as part of the study and did not comment on the measure used; they mainly focused on cognitive measures in their replies. Participants reported feeling that the measures were easy and relevant as they measured important domains of cognition. However, some of the tests were complicated and hard to complete but the participants found them interesting and tried to ensure that they completed them well.

'They are quite interesting because it is not something I really had to do before and so to test the brain yourself you don't really do it, so it was interesting to have someone do it for me.' PH12, SO

'I have more difficulty with some but that doesn't make them less or more important necessarily.' CS17, CO

Participants described the testing process as straightforward, easy to follow and not too intrusive. They felt capable of tackling the measures and completing them.

'But I am happy with the way it is, I didn't find anything difficult at all, difficult to the point I didn't want to do it. I didn't reach that stage where I didn't want to do it.' PP38, CO

'I felt like I could handle them quite well. I was quite pleased with the results.' DW24, SO

Participants believed that the cognitive measures used were all relevant as they measured different aspects. They enjoyed the different tests which allowed them to identify their own strengths and weaknesses.

'They were interesting and challenging and I think sometimes it makes you feel negative because you can't remember but umm obviously you get to find out this is part of the course to establish what you can remember and what you can't. I think there was a balance there, some were easy, and some were harder and more challenging, but I think there was a good balance.' MH7, SO

'I feel I am less efficient at the visual tests and better at the purely mental tests. I am better at the mathematical tests and, but I am not good with figures or shapes usually I confuse them but that's about it.' TB20, SO

The only measure that had a negative response from participants was the 'Supermarket task', This is a tablet based cognitive measure that evaluates Visual Spatial memory (Tu et al., 2015). Participants reported that the aim was unclear and that it made them feel frustrated.

'Yes, I don't think I realized what I was meant to be doing. Cause You start at the entrance and then I think u said go down right left and then you had to say how do you get back to the beginning. Now my sense of direction is pretty poor anyway, when I'm driving so, I am not the greatest in terms of that, so I found it frustrating that I forgot which way.' GB13, CO

'I don't think that my spatial awareness is very good, and I found it really, really difficult and confusing to do.' MS19, SO

Furthermore, the participants became agitated while completing the task as it felt long and repetitive. There were 9 of 31 (30%) participants at baseline who refused to finish the task and stopped the task half-way through.

'There was one you did before in which you're in the supermarket. I found that one stressful.' TT10, CO

'I was a bit, A bit discouraged. The Thing you know it is confusing.' MS19, SO

The graphics of the task along with the bright colours made it challenging for participants, especially those who were not familiar with technology and using digital devices.

'I think paper based are easier as the colours were irritating.' JI4, CO

'Well although the plan was shown in the first place you were put in random places, and I found it difficult to remember how many isles there were to go back out and such. I thought I was quite good at things like that, but it seems I am not.' VG30, CO

As the tests at 6 months were conducted virtually, it was not possible to conduct the supermarket task assessment and some participants expressed their relief at not having to re-do the test.

'I did find the one on the computer more difficult but as you say we won't do it today.' GB13, CO

'I am glad we are not doing the iPad one today.' TT10, CO

ii) Views of Genetic Testing:

As described in chapter 4 section 4.6, it was intended to conduct an Apolipoprotein E4 genetic test planned to screen for APO E4 genotype in study participants. The test relies on a buccal swab sample. However, it was not possible to conduct the test at the time of the study due to Covid-19 restrictions. However, as part of this feasibility study, participants were asked about their willingness to do the test as part of future research.

Participants reported frustration upon not having the Apo E4 genotype test completed as they were interested in finding out the outcome of the test. They were looking forward to having the test and are willing to do it in the future if possible.

'Missing the APO test is disappointing, but you know, it was just not possible.' RP18, CO

'I would like to know the results of the genetic test that you were going to do Regarding if I have the gene. Yeah, that would be interesting.' JI4, CO

'It is unfortunate that the pandemic has prevented the blood test from happening and the genetic test.' MS19, SO

Theme 2 Incorporation of oil into diet

As reported in section 4.1.5 of this chapter, most participants 23 out of 28 (82%) at 3 months and 20 out of 28 (71%) at 6 months) managed to adhere to consuming the oils in both groups. During the interview, participants were asked about their opinion on the amount of oil they were asked to consume. Some participants reported that 30 mls of oil per day was too much for them, as they normally tried to follow a low-fat diet.

'I cooked with the oil, but 30 mls was a lot of oil per day.' JD3, SO

'At first found it too much but after dropping to half dose, I have managed quite well. I am taking it on my morning cereal.' CS17, CO

'I shouldn't think that I used 30 mls/day for a second because I did say to you previously, I would almost have to drink it to take that much, which is a lot.' PO9, SO

a) Incorporating oil into normal diet:

There were 22 out of 28 (78%) of participants (see section 5.1.6) who reported being able to incorporate the oil into their normal diet once they got used to it. This was reflected in the interviews.

'I have noticed about not using more oil than we usually did. I didn't have to change my diet to accommodate the oil.' TB20, SO

'Well, I was a bit warry about having to take it every day but once I got used to it that worked well, I just found a way I could take it.' GB13, CO

Most participants cooked with both the CO and SO, however participants taking the SO reported increasing their intake of fried food to accommodate using all the required amount of 30mls each day. Participants did not comment in the recipes they were provided with, instead they tried to incorporate the oil into their normal diet.

'I prefer not using SO in salad dressing, so I only used it when frying food.' PH12; SO

'I cook with it. I am now eating more fried food than usual.' MS19, SO

'Using it for frying, thus I am eating more fried food than before.' AS2, SO

However, participants in the CO group did not report an increased intake of fried food as they reported using it on their cereal, bread or in drinks.

'I used it mostly with coffee because CO is quite a strong taste for frying or using it in cooking. I do use some CO in some of my baking, which I did before the study. So yeah, I find it really easy to use.' LC27, CO

'I used it sometimes on bread instead of butter.' MF5, CO

'I had it with my cereal each morning.' CS17, CO

b) Issues taking the oil:

Most of the participants (78%) managed to incorporate both the CO and SO into their diet without any problems (see section 5.1.6). Participants in the SO group did not report any

issues or concerns related to the oil intake. However, participants in the CO groups reported struggling with the texture of the oil as it was solid at room temperature, which made it more difficult to use.

'The only issue that I had was that it is not easy, and it is not easily practical to use the oil because the oil doesn't flow as easily as butter does for example, that's the only issue that I had.' PP38, CO

'I tried to Heat it Say for instance I was dieting and I

I had lots of salads. And so, I put the oil on the salad. But that was a disaster.' JI4, CO

Thus, participants preferred to use the oil with hot beverages or porridge, so that it melts easier. Furthermore, participants reported struggling with measuring 30 mls of coconut oil per day as the oil was solid at room temperature.

'Because it didn't flow, it was very difficult to use the coconut oil. I tried hard to scrap the top of the oil to get some.' PF37, CO

One participant overcame the issue by freezing 30 ml portions of the oil and used the portions in food daily.

'I froze the right amount in portions to ensure I got the right amount every day. I put it in porridge, and it melted into it.' MG11, CO

Furthermore, as presented in section 5.1.4, some participants reported minor side effects e.g., gastrointestinal disturbances following consumption of the CO at the beginning of the study. However, they managed to overcome these issues by consuming the oil in smaller amounts.

'Had an upset tummy at first when I was using too much.' RP18, CO

One participant reported being worried about the potential effect of CO intake on cholesterol; another participant withdrew from the study due to an elevation in blood cholesterol concentration. Refer to section 5.1.4. for further details.

"The downside of the coconut oil has been the cholesterol." DS31, CO

c) Willingness to continue taking the oil after the study:

When asked about their willingness to continue taking the oil after the 6 months study, 9 of 28 (32 %) participants said that they are willing to continue taking the oil if it proves effective in improving memory and delaying cognitive decline.

'I would keep taking coconut oil anyways because I like it.' MG11, CO

'If you if you were to say to me, you must carry on taking coconut oil I'm not sure I'd be very happy about. I would certainly think about it, because if it's beneficial and I'd be crazy not to give serious consideration and will probably take it.' CS17, CO

'If there is anything in the research that was positive then we have got to take it on board and use it really.' MH7, SO

However, one participant reported that consuming 30 mls of the oil each day was challenging, and it would be easier to take it as a pill instead if it proves efficient.

'I would say turn it into something like you have cod liver oil tablets and have Sunflower oil tablets because that is much easier to take on regular basis than try to incorporate the oil in the food every day.' MH7, SO

Theme 3: Limited improvement in health

All the participants were asked if they felt any changes in their memory or cognitive abilities as a result of consuming the oil.

Twenty of the 28 (71%) participants reported feeling no change in their memory or their abilities related to the study.

'I had thought about it occasionally, but I don't think it has had that much of an effect on me. But it may have, I don't know.' PO9, SO

'I can't honestly say my memory has improved or got worse from having eaten or cooking with coconut oil.' MD32, CO

Three of the 15 participants (20%) from the CO group reported an improvement in their memory that they attributed to the oil intake.

'It certainly improved my recall and I think I have improved my memory during the time that I have taken it. I could recall facts that I know instead of struggling like I used to. Umm like I do general knowledge crosswords and quizzes on the TV, and I seem to be doing much better with those except for popstar one's and yeah, I find the puzzles not quite as testing as they used to be. It certainly improved my mental state anyway.' VG30, CO

'Yeah, it's so different, I wish I could measure it and I can't I think I think it did help me. I felt more comfortable doing things on my own… I could see I was not remembering recent things that well now I don't I have had less of that kind of problem.' CS17, CO

'I would say that my memory has held up since the first time I met you. I even improved since the use of it. So, I would be positive about coconut oil.' MF5, CO

Two of the 13 (15%) participants from the SO group reported feeling an improvement in their memory after taking the oil. However, they were unsure if this observation was attributable to consuming the SO. Both participants who reported an improvement in their memory due to SO, had a confirmed diagnosis of MCI.

'For the first time in years, I don't feel that I have MCI anymore; I still forget things, but they do come back to me. I feel much brighter and aware.' JD3, SO

'My memory has improved whether it is the sunflower oil or just the different circumstances that we find ourselves in during lockdown I don't know.' AS2, SO

However, participants also mentioned that the impact on memory whether an improvement or decline could be attributed to the exceptional circumstances associated with the Covid-19 lockdown. Participants acknowledged that the changes in their everyday life associated with the lockdown reduced the burden on them by setting a strict routine or made their memory worse due to isolation.

'I feel active, and I don't know fresher but that could be from lockdown, and it certainly had different demands on me, and I have coped really well but I can't say whether it was due to oil or not.' MA8, SO

'I must say I haven't been exposed to the same kind of situations as pre-lockdown so it's difficult to try and quantify or put a measure to it. But I do, I do think I'm better with it than I was before.' CS17, CO

'I feel that the routine that I have now with the isolation helped me focus more which made things easier.' JD3, SO

'No, nothing to do with the study but my memory has definitely gone worse. Probably because of the lockdown.' MG11, CO

Theme 4 Positive experiences of participation

a) Satisfaction:

To inform the process evaluation of the intervention, participants were asked about their overall experience in the study. Participants were asked what worked well for them, what were the barriers and challenges they faced in the study and how they overcame them and recommendations for any alterations in the study design and procedures of a future trial. All 28 participants reported being satisfied with the study process and that they were happy to be involved in the study and had no issues. Overall, the participants were satisfied with the study design and procedures.

'I am very very happy to have done the study and satisfaction to me is quite high, maybe 9/10.' PP38, CO

'I have enjoyed it all. It's been a nice experience obviously the experience in itself. And I think it's given me more. I feel I'm okay. So, it's giving me a bit more confidence in You know, in my ability. Yeah. Yeah. So, the whole experience has been good.' DF25, CO

20 of the 28 (71 %) participants expressed their willingness to take part in the same study or similar studies in the future.

'I mean you know, maybe, maybe the best thing I can say is if somebody was to ask me to do it again or do a study again in the light of what I've already done I'd be quite happy to say yes.' CS17, CO

'If you do anything in the future I would be interested to maybe participate.' TT10, CO

b) Supported by Contact:

This section presents participant perceptions regarding the support they received and amount of contact time they had with the study researcher, either via visits, emails, or phone calls. There were 20 of the 28 (71 %) participants who reported that the researcher managed to clarify the study process, procedure, and expectations to them. Furthermore, having regular monthly contact helped ease their concerns while taking part in the study.

'All the contact was informative or helpful or I had to reply. I find it really easy all the way through. I didn't have any problems with contact or anything. I find it quite easy.' LC27, CO

The initial visit was very helpful to explain the study and inform the participants what to expect from the study. Out of 28 participants, 19 (67%) reported that they felt the researcher was supportive, flexible, and easy to be contacted via email or phone if they had any questions.

'Well, you have been flexible, and we met at times that was appropriate for me and that was fine.' PO9, SO

Two of the 28 (7%) participants felt that more face-to-face contact would have been beneficial. However, they understood that some changes were necessary due to the Covid-19 restrictions. The participants appreciated the flexibility and ability to continue the study despite the lockdown measures in place at the time.

> *'I think the way you did it under the circumstances because we were living in a very difficult environment you carried on and did it and you used zoom and because of that I think you were still able to go ahead and carry on and get your results. I think that was a good thing.' PP38, CO*

> *'This whole covid thing. You can't expect it to work according to the way it was designed to work in the first place that after two weeks or six weeks or whatever it is something's going to happen, because this is not going to happen, like that, but I was very happy I expected there to be disruptions in terms of us being able to talk and those kinds of things. But I think you know, bearing in mind all the circumstances, I think it went very well.' CS7, CO*

The telephone calls with participants provided an opportunity for informal conversations and helped participants stay in touch with the researcher and ask any questions they might have had. Participants reported that they felt that there were always answers to queries and advice available when needed either through phone calls or emails. As such, they felt re-assured that in case of any problems they could directly contact someone.

> *'Your prompt replies, your quick replies I appreciated because I didn't want to do it wrong, and you always came back really quickly.' MG11, CO*

Some participants mentioned that the phone calls helped them stay positive and motivated throughout the study.

> *'The coronavirus did interrupt the thing. But everything else you know you supplied the extra coconut oil. You listen to our wants and needs, so to speak in other words, what was motivating us, and you responded to those wants and needs. I felt that we were on the same page and same wavelength.' MF5, CO*

c) Overcoming barriers and challenges:

This section describes some of the challenges that the participants reported facing during the intervention and ways that helped them overcome them.

The concept of having to consume 30 mls of the oil per day caused pressure on one participant and caused some distress. However, after reaching out to the study researcher for support, they were reassured that they could be more flexible with consuming the oil (using oil in smaller amounts throughout the day, not consuming the whole 30 mls of oil every day), and they managed to complete the study.

> *"I found either your flexibility helpful Because when I when I first sent you that I couldn't swear to take two tablespoons you said don't worry be more flexible by allowing me to do that I was able to carry on participate in the study, but I also it also over that period of time I've seen how I have changed my attitude with using the oil."*
>
> *DS31, CO*

Of the 31 participants, 3 (9%) participants reported gastrointestinal symptoms including stomach aches and runny stool due to the oil intake (refer to section 5.1.4) about adverse events). However, they reduced their oil intake on such days and that helped alleviate these symptoms.

Nine of the 28 (32 %) participants reported problems with measuring 30 mls of the CO as a solid at room temperature. However, one participant overcame the issue by freezing 30 mls portions of the oil and using one portion each day. Other participants relied on scraping oil from the jar or heating the oil to help measure out smaller quantities.

Four participants consuming SO, reported struggling with consuming 30 mls of oil per day if they were not frying food. As an alternative approach, they introduced food items that contained SO such as Tuna in SO, Flora with SO, SO biscuits and sunflower spread. However, this created issues for the researcher in calculating the amount of SO consumed by the participants. As the content of SO differs between the different food items which makes it harder to estimate the exact amount used.

> *'No real difficulties but we don't use a lot of oil we tend to eat without oil most of the time except anything I buy processed in tins or whatever if there is an option. I buy it*

with sunflower oil. So, for example, if I have sardines I have them with sunflower oil and we only use sunflower spread but apart from that we don't cook a lot with oil. When we do use it, we use SO, it is by the cooker my wife uses it religiously.' TB20, SO

d) Recommendations and Factors to consider in a future trial:

Two of the 28 (7%) participants suggested the inclusion of monitoring blood cholesterol concentrations through-out the study as they were worried about this during the study (see section 5.1.4).

'I feel it would have been beneficial to have a cholesterol test at the beginning of the test, halfway through & at the end to see if there was any correlation. When I spoke to 2 medical practitioners about the project, they both asked if a cholesterol was incorporated.' DS31, CO

However, two other participants (7%) reported being satisfied with the study and had no further recommendations for future trials.

'I can't think of anything that really wasn't good that could be improved.' MS19, SO

'I was quite happy with everything that was done.' PF37, CO

5.19. Summary:

In this chapter, findings related to recruitment, retention and data collection methods were presented. As this is a feasibility study, adherence and perceived acceptability of the intervention were reported based on results of open-ended questionnaires and interviews. The design aspects of the intervention regarding acceptability, randomisation and processes for data collection were also considered. This chapter reported on results related to the outcome measures and design aspects of the study which informs evaluating the feasibility of the intervention.

Chapter 6: Discussion

6.1. Introduction

This chapter discusses the results of the study presented in chapter 5. The aim of the study was to evaluate the feasibility of the dietary intervention in the older adults and adults with MCI. This chapter brings together the discussions around the outcomes of the study and reports on the process evaluation of the intervention based on the MRC complex interventions framework (Craig et al., 2008, Skivington et al., 2018).

6.2. Assessing the feasibility of conducting a future trial

This section discusses the feasibility evaluation of the intervention and demonstrated how the study aim was achieved based on the study objectives (see chapter 2, section 2.6) and considers the design for a future study. In the first section, outcomes relating to objectives 1 and 2 will be discussed.

Objective 1 and 2:

1. To test the procedures of the intervention (estimate recruitment and retention rates, recording and monitoring of adverse events, study procedures, to refine the selection of outcome measures in preparation for an RCT that would test the effectiveness of the intervention).
2. To assess adherence rate of participants to consuming dietary vegetable oils (coconut and sunflower oils)

6.2.1. Screening process/ Recruitment

The inclusion and exclusion criteria form an important part of the screening process and it is key to consider if they are too broad or restrictive (Tickle-Degnen, 2013). The ability to recruit people to research is dependent on ensuring the recruitment criteria is feasible

(Tickle-Degnen, 2013, Bell et al., 2018). At the beginning of this study (October 2019-January 2020), the target population was adults with a confirmed diagnosis of MCI within the last year. However, recruiting participants with MCI proved harder than expected (refer to Chapter 5, section 5.1.2). This could be attributed to the widespread variation in the rates of MCI diagnosis across UK memory services (Dunne et al., 2021, Richardson et al., 2019). Some memory services rarely if ever diagnose the condition, whereas other services' diagnosis rates may be 20% or more (Dunne et al., 2021). MCI recruitment challenges were also reported by trials in Ireland, Germany, and Netherlands as recruitment was slow and difficult (Sanders et al., 2018, McGrattan et al., 2021). A Mediterranean diet trial in Ireland attributed this to multiple factors including: inappropriate patient referrals by primary services for timely MCI diagnosis, difficulty in promotion of the trail in memory clinic due to workloads issues, competing demands from multiple MCI studies with a limited target population group (McGrattan et al., 2021). Sanders and colleagues suggest that non-medical settings and research communities can facilitate the recruitment of MCI patients for large studies (Sanders et al., 2018).

Recruitment rates at the beginning of the study demonstrated that the recruitment of MCI patients directly through memory clinics might not be a feasible approach. Including individuals with cognitive impairments in clinical trials is important so that consideration of the cognitive impairments that prevent full participation or adherence in an intervention can be understood (Cadilhac et al., 2016, Jefferson et al., 2008). The present research has shown that recruiting participants with MCI helps gain insights into their acceptability of the intervention. In addition, the study has demonstrated the challenges of recruiting participants with MCI. In future trials, the findings would suggest screening for MCI as part of the study procedures, instead of screening for people with a confirmed diagnosis due to disparities in diagnosing MCI across the different trusts in the UK (Dunne et al., 2021, Richardson et al., 2019). Currently, there is no NICE guidance on MCI thus there is no guidance as to how MCI cases seen in UK memory clinics should be investigated, diagnosed and managed (Dunne et al., 2021). Leading to a variation in clinical practice affecting the diagnosis and management of these patients. Furthermore, an MCI diagnosis can lead to emotional distress and social stigma which might affect patients willingness to screen for MCI if cognitive decline hasn't impacted their daily life (Richardson et al., 2019).

Furthermore, the recruitment for ketogenic diet studies in older-adults can be difficult; which was also demonstrated in a study conducted by Taylor and colleagues (Taylor, 2018).

Adapting the inclusion criteria to include older adults helped increase the reach for potential participants who could be recruited into the study. Including older adults with AD could have also increased the participant pool. However, the feasibility of the intervention might differ between people with MCI whose impairment does not generally affect their everyday life in comparison to people with AD whose daily activities are impacted. The ability to cook for oneself and utilise the oil was essential and would have been reduced in people with AD in comparison to OA or those with MCI. Furthermore, evidence on the effect of DK or CO on the reduction of cognitive decline is recommended for earlier stages of cognitive impairment before major neuronal damage occurs, as the main mechanism of action relies on providing fuel to neurons to prevent damage and cognitive decline rather than restoration of damage neurons. The inclusion criteria were adapted to include older adults over the age of 65 irrespective of their cognitive functions. However, despite utilising different ways to recruit over one year (October 2019, October 2020) the target of recruiting 60 participants was not met. The effect of Covid-19 pandemic due to lockdown restrictions and shielding disrupted recruitment as it was difficult to engage with the community and identify potential participants.

Engaging with Join Dementia Research helped raise awareness of the study and allowed access to greater numbers of potential participants who met the inclusion criteria. Furthermore, this platform allowed the researcher to initiate engagement which helped increase recruitment rates through a conversation The participants were more likely to ask for further details about the study once approached by the researcher rather than from finding about the study via newspaper or magazine (Patel et al., 2003, Obeid et al., 2017). Furthermore, participants who were identified through JDR and Bournemouth University's ADRC, were more likely to engage with research as they were already interested in taking part in ageing and dementia related research.

The present research has shown that recruiting older adults is more feasible through databases of people who have already provided consent to contact which supports previous observations (Grady et al., 2019). This approach narrows the participant pool into people who are interested and willing to take part in research. However, it also presents issues with

recruitment bias as people who tend to consent to participate in future research tend to be more educated and health conscious than other groups of people within the same group (Grady et al., 2019). This presents an issue with the actual efficacy of the intervention in the overall population, as the recruited participants might represent a select health conscious group (Patel et al., 2003).

In the present study, it was also important to consider if people who consented to participate in this study were different from those who did not and therefore establish if there is any recruitment bias (Patel et al., 2003). The presence of any factors that affected recruitment must also be considered and the potential bias it produced (Patel et al., 2003). The reasons for participating in a study could have been attributed to individual's personality, their interests and availability (Grill et al., 2014). Especially that in the interviews some participants *(n 18)* mentioned being interested in dementia research due to having a family member struggling with dementia or being worried about it themselves.

Despite, not collecting any data about ethnicity for the study, all the study participants were white which reflects the local demographics. Previous studies have shown ethnicity and cultural background of participants might impact their willingness to alter their eating behaviour, especially affecting their willingness to incorporate a foreign food item into their ever day diet (Mora and Golden, 2017, Nierkens et al., 2013). It is important for future trails to utilise methods to increase diversity in study participants, to better understand the need for cultural adaptations for the intervention (Nierkens et al., 2013, Barrera Jr et al., 2013).

6.2.2. Adverse Events

The need for a risk assessment when using dietary and food-based interventions has been highlighted (Lucey et al., 2016).The current study monitored adverse events and the dietary intake of study participants. None of the adverse events were serious *(n 3*) and were similar to those reported by other researchers e.g., Gastrointestinal tract issues (Henderson et al., 2009, Rebello et al., 2015).

i. Coconut Oil & Cholesterol

Findings from interviews with participants demonstrated the importance of measuring blood cholesterol concentrations. Of the 28 participants, one withdrew from the study due to an increase in blood cholesterol and another reported feeling worried about the effect of oil intake on blood cholesterol.

Previous studies have investigated the effect of dietary coconut oil (CO) intake on blood cholesterol concentrations (Khaw et.al, 2018, Chinwong et al., 2017, Boemeke et al., 2015). The research demonstrates that CO intake does not significantly increase blood cholesterol concentration in adults. However, it was associated with an increase in High Density Lipo-protein in comparison to other vegetable oils (Liau et al., 2011, Chinwong et al., 2017, Boemeke et al.,2015). An increase in HDL, is considered to have an atheroprotective effect; as it is associated with a reduced risk of cardiovascular disease (Tran-Dinh et al., 2013, Ng et al., 2013, Hovingh et al., 2015). However, there has been a recent debate on the positive effect of high HDL concentrations on health (de Boer and Brunzell, 2014, Xiang et al., 2019). For a future trial, it would be recommended to include assessment of blood cholesterol concentration levels (High Density Lipoprotein and Low-Density Lipoproteins) as part of the study procedures to better understand the effect of the intervention on blood lipid levels in older adults.

6.2.3. Study procedures

i. Location of Study sessions

Participants chose the timing and location for testing (i.e., at university or at home) to ensure accessibility and flexibility for the present study. Based on data from interviews, participants appreciated the flexibility provided by the study design regarding the location of data collection. Of the 28 participants; the majority (68%) participants preferred their baseline testing in the comfort of their own homes. At 6 months, nearly half (13 of 18, 46%) of the testing was conducted virtually at home. However, it meant that some participants were using “Zoom” to undergo the testing procedures which might have affected the quality of data collection. The change in location and circumstances (virtually or face-to-face) of the session might have affected the results of the cognitive measures. However a study

conducted by Martin-Khan and colleagues (2007) (Martin-Khan et al., 2007) showed no difference in results between face-to-face and virtually conducted battery of cognitive measures. In contrast, familiarity of the surrounding may affect the outcomes of some cognitive measures (Bechtel et al., 2015, Overton et al., 2016). In a future trial a more standardised approach could be adopted to ensure consistency in the approach for data collection. However, this may result in poorer attrition and completion rates as participants appreciated the flexibility of the study design.

Part 2:

In the second section, findings from quantitative and qualitative outcome measures are presented to address study objectives 3 and 4

3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future RCT.
4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.

6.3. Outcome Measures:

The key factors that determined whether participants completed the adherence, dietary and cognitive outcome measures included accountability and the opportunity to be monitored and assessed. Monitoring is an important aspect in the management of interventions (Santacroce et al., 2004). In this study participants felt accountable to the researcher which supported the timely completion of questionnaires and outcome measures.

a. Adherence

The MRC process evaluation guidance advocates that the quantity of an intervention implemented (the dose) is assessed (Moore et al. 2015). DICe intervention encouraged people to consume 30 mls of the oils per day. The monthly phone logs with participants recorded 70% adherence to both CO and SO oil intake in general. These results are encouraging given that there is evidence to support that one of the barriers to dietary

interventions inducing ketosis is adherence (refer to chapter 2, section 2.3.3). As studies conducted on the effect of DK on ketosis demonstrated high dropout rates and low adherence rates associated with Gastrointestinal side effects of MCT consumption and the restrictive nature of the ketogenic diet (Henderson et al., 2009, Krikorian et al., 2012a).

The phone logs provided quantitative data on adherence and the data from the open-ended questionnaires and interviews complemented and qualified this data. This data provides insights into the incorporation of oil into the diet and feasibility of the dietary intervention. In the present study participants completed a 4-day diary at the baseline and post intervention. In contrast participants were asked to complete a food diary every day for 8 weeks (Krikorian et al., 2012a) to assess adherence to a ketogenic diet intervention. However, completing a food diary daily for the entire 6 month period could have been burdensome for study participants in the present study (Cantwell et al., 2006).The use of phone logs every month, allowed participants to self-monitor and motivated them to engage with the intervention.

The phone logs therefore played an important role in the assessment of adherence to the intervention. Further aspects of adherence were also explored in the open-ended questionnaire and the interviews. The combined results demonstrated that participants managed to incorporate the oil into their diet and during the interviews 9 participants mentioned their willingness to continue using the oil long term if it proves beneficial.

Adherence to the intervention was explored using different methods to keep participants engaged without increasing the study burden. Thus, the findings would suggest that 30 mls intake of CO and SO per day is a feasible intervention in older adults and adults with MCI.

b. Dietary Intake

Participants were asked to provide a 4-day food diary at baseline and post intervention. The food diary was used to assess the effect of the oil intake on dietary intake, especially fat intake of participants.

The data showed that at baseline, dietary energy and macronutrient intake of the participants was consistent with intakes for older adults, based on national UK survey data

(NDNS, 2019). Thus, the findings would suggest that the participants did not appear to have unusual dietary habits that might have influenced their ability to incorporate the oil into their diet.

Some of the study participants reported feeling that they were consuming a higher amount of fat than usual, given the daily 30 mls oil intake. However, comparison of fat intake between baseline and post intervention demonstrated a statistically significant decrease in both dietary fat and saturated fatty acids intake in both CO and SO groups. This demonstrates that participants perception of fat intake does not match with actual intake measured using food diaries.

Cognitive Measures

In the present study a number of cognitive measures were utilised to evaluate the feasibility and validity of the measure in the target population.

The ACE III was used to evaluate the overall memory of the first study participant. However, after the session the participant reported feeling fatigued by the prolonged testing session that was 90 minutes. Thus, the ACE III was substituted by its shorter version m-ACE which reduced the testing time to 1 hour in total. Based on the feedback from participants regarding cognitive tests (refer to chapter 5, section 5.7), participants did not suggest that testing session was prolonged or exhausting. They reported feeling that the testing sessions were thorough and not burdensome to participants.

Findings from the present study showed that participants reported struggling with the “The Supermarket Task” which is an assessment of visual spatial memory in a virtual supermarket environment (Tu et al., 2015).

The supermarket task test was completed by only 7 of 28 (25%) participants, due to technical errors and the participants being agitated with the test. Participants reported having issues with completing the task, due to unfamiliarity of using an iPad and issues with the colours of the game on the iPad (Refer to chapter 5, section 5.7). The test was not conducted during the post intervention session as it was not possible to deliver it virtually. These observations are in contrast to data from previous studies that demonstrated the feasibility of the conduction of cognitive tests using an iPad (Rentz et al., 2016, Canini et al.,

2014). However, there is evidence that some older adults are less willing to use technology for tasks when they are unfamiliar with them (Vaportzis et al., 2017, Heinz et al., 2013). The findings suggest that for future trials, the paper-based supermarket task can be used to assess visuospatial memory, where possible in-person.

No further issues were reported in any of the other tests (m-ACE, Trail Making, Verbal & Category fluency, ADCS-MCI-ADL, Digit span and Digit coding) that were conducted. Participants completed all other cognitive measures. They reported enjoying the variety of undertaking different measures as they helped them identify their strength and weaknesses with regards to memory. Some participants *(n 11)* reported feeling more comfortable with letter and word-based measures while others preferred numerical measures. Overall, the participants preferred in-person testing sessions rather than virtual ones; however, they did not struggle with completing the measures virtually.

c. Anthropometric, dietary ad blood ketone measurements

In the present study, participants did not report any problems with anthropometric, dietary and blood ketone measures in the interviews. In case sessions were conducted virtually some of the measures were not collected, such as the blood ketone measure. However, participants were willing to undergo the assessment if needed.

d. Genetic Screening

Due to Covid-19 restrictions and social distancing measures, it was not possible to conduct APO E4 screening in the present study. It was the intention to conduct screening to assess the feasibility of the genetic screening in older adults because APO E4 affects the metabolism of ketones in the body. Thus, it is a factor that could influence the findings in a future study. A survey conducted on adults reported the potential unwillingness of people to undergo APO E4 testing due to its association with an increased risk of Alzheimer's disease (Cutler et al., 2003). However, another study that compares the perceptions of family caregivers and lay people on APO E4 testing demonstrated that there isn't a conclusive stance that is pro or anti testing (Alpinar-Sencan et al., 2020); views differ among different individuals. Despite not conducting the genetic tests, participants expressed their

willingness to undergo the tests on another occasion. Participants even expressed their disappointment to not undergoing the test (Refer to chapter 5, section 5.7). As part of the process for study consent, the participants were given the option to be informed of the test results; however, only one participant opted out.

Summary

Given high completion rates, as well as positive experiences of participants based on the data from the interviews, the findings from the present study suggest that the participants found the outcome measures acceptable with the exception of the Supermarket Task. The results suggest that the data collection processes and outcome measures in this study were feasible and have potential to be transferred to a larger future trial. The third and fourth objectives were to calculate preliminary effect sizes and estimates of SDs to inform the sample size for future trial. The outcome measures were used to assess their feasibility and calculate preliminary estimates of effect size. The results of the intervention suggest a positive effect in the direction of benefit following the CO intake. It demonstrated some positive changes in cognitive functions in participants taking CO in comparison to those taking SO. A larger sample size, with 16 participants in each arm is required to further test the effectiveness of the intervention. However, with a larger sample size the practicalities of study co-ordination would need to be considered to ensure that the administration procedures and monitoring are carried out according to the protocol.

6.4. Participants Feedback

Objective five gathered feedback from participants about their experiences during the study. In depth qualitative data can provide insights regarding how the intervention ran in the pilot study to identify issues that may need to be addressed for a full-scale trial (Moore et al 2015). The use of qualitative methods to capture participants' experiences of the intervention at two time points at 3 and 6 months provided insights into the longer-term use of the oil (Moore et al 2015).

The qualitative data from this study showed that participants accepted their allocation to the oil group as part of the research process. Participants were interested in both oil groups and did not show any objection with the group they were allocated to in the study. No randomisation contamination was reported in the study as none of the participants tried to use the other oil despite the ease in accessibility of both oils in supermarkets (Howe et al., 2007, Keogh-Brown et al., 2007). They understood that group allocation was part of the study procedures and were happy to be involved. Participants in the present study generally had an altruistic view of being involved in research with a view of helping others who are living with dementia. They stated they were happy to be involved in the study, to be part of research that could support those with dementia.

Participants appreciated the flexibility in the times and location of the study and did not report any fatigue from study procedures. Although, a previous study has shown that timing is an important factor with more fatigue experienced by participants if testing is conducted later in the day (Overton et al., 2016). Furthermore, the location of the sessions might have influenced cognitive measures as familiarity of environment impacts the results (Bechtel et al., 2015). As for participants who undertook the measures in their own houses might have had better results in comparison to those who undertook them in an unfamiliar environment on Bournemouth University campus.

In summary, the design of the feasibility study was perceived as acceptable to participants, and they did not report any major issues. Overall participants reported high satisfaction level in the study design and procedures.

6.5. Feasibility and acceptability of DICe study

The approach used to engage and motivate participants in the DICe study to improve their adherence will be discussed and recommendations made for the refinement of a future trial in this section.

It will discuss the components of the intervention as described in the TIDieR template (appendix 14) in the context of the participant's views of the DICe intervention.

I. Rationale for DICe:

DICe draws upon glucose hypometabolism and behavioural change theory. A novel food based dietary intervention has been used to induce ketosis which might reduce age related cognitive decline.

Food based interventions have higher positive nutrition-related outcomes in community-dwelling older adults than other interventions (Bandayrel et al., 2011). Food based approaches require long-term commitments, but are more likely to be sustainable for longer (Demment et al., 2003, Smitasiri et al., 2007) as they overcome some of the barriers that medical or clinical dietary interventions have (Bandayrel et al., 2011, Demment et al., 2003). This was one of the main drivers for the DICe study, it provides a non-restrictive, simple, food-based intervention with minimal side effects in comparison to other DK inducing diets or supplements.

II. Resource material:

This section includes a discussion regarding the DICe study materials provided to participants. The participants were provided with leaflets and recipes to help them incorporate the oil into their diet.

Recipes:

All study participants were provided with a leaflet and a range of recipes to support them incorporate the oil into their diet. The recipes were different for the intervention groups but all the participants within each group received the same recipes. The recipes provided included multiple easy to prepare and nutrient dense meals to help the participants utilise the oil; especially if they have never used it before participating in the study. It also ensured that all participants received the same level of support.

However only 2 of the 28 participants reported using the recipes. The other participants reported incorporating the oil into their meals and using it in different ways (i.e., Adding to coffee or porridge, roasting, frying). This demonstrates that participants relied more on the oil incorporation leaflet than the recipes. As food based dietary interventions aim at changing habits (Wood et al., 2016), the present study has shown that in this group of participants, the incorporation of oil into everyday diet would be a better approach to

support sustainability in the long term. As the incorporation of oil would allow to habitual changes in dietary intake and the potential to long term adherence to the change (Wood et al., 2016). The findings show that participants used the oil in a variety of ways and indicates the need to provide a range of resources to support participants. This data provides insights about how participants engaged with the study resources, and what support they felt were more important to support their adherence to the intervention. The data from the interviews suggest that participants managed to overcome the barriers to using the oil either by seeking help from the researcher or applied their own problem-solving skills. These findings reflect similar findings from DK interventions that provided education and support to participants to adhere to DK diet or CO intake (Krikorian et al., 2012a, Krikorian et al., 2014, Taylor, 2018)

In the present study, the provision of advice directly from the researcher during the initial session or through the resource materials were valued by the participants. The provision on information regarding how an individual can make lifestyle changes is an important behavioural change technique in intervention studies (Lara et al., 2014, Timlin et al., 2020).

III. DICe Processes and procedures

The present study has shown the feasibility of conducting an intervention using CO on older adults. It demonstrated the acceptance of participants to the subsets of cognitive measures on older adults rather than the full test-set and their acceptance of dietary and anthropometric measures. The study processes and procedures were evaluated to assess feasibility of the intervention and inform the design of a future trial. The study design and intervention model (refer to figure 1) were evaluated to test participant's acceptance of the intervention.

The DICe initial sessions were conducted to discuss the study with participants and elevate any worries related to the dietary change, oil consumption and study outcome measures. People who previously used CO were more interested in incorporating the oil into their diet, however, those who never used it before had more stress related to risks and worries about its side effects. Thus, those participants used that session to alleviate their worries and allowed the researcher to explain the different methods in which the oil can be incorporated into their diet.

During the interview, participants reported having no problem with the study sessions and the outcome measures used. They reported their acceptance for the use of different measures to test different aspect of memory. They reported that the study sessions were not prolonged and that they did not feel fatigue afterwards. This demonstrates the feasibility of conducting the cognitive measures in older adults. Similar cognitive measures were used in previous studies and participants reported their acceptance of the methods (Krikorian et al., 2014, Abe et al., 2017)

IV. DICe mode of delivery:

This section discusses the role of the DICe study researcher. The findings from the study showed that all the participants were satisfied with the support they received from the researcher. The participants valued the amount of advice and support provided.

Ongoing advice, support and monthly monitoring of adherence were provided via email or telephone calls. The monthly telephone calls offered individualised advice, encouragement, and support for overcoming barriers to incorporating the oil. This support encouraged participants to develop problem solving skills. The support offered by the researcher received positive feedback from participants, but the time required to provide that level of support needs to be taken into account for the design of future studies to consider the cost implications. These may include conducting initial sessions in groups, instead of one-to-one sessions. A section of frequently asked questions could be included in the study resources, especially questions regarding the texture and physical state of the CO.

A key motivation for adhering to the oil that emerged from the interviews with participants was a sense of 'accountability'. This accountability could be to the research study, researcher, oneself, or a combination of all. For example, at the start of the study, some participants reported consuming the oil to please the researcher, but overtime came to like it and enjoyed adding it to their food. However, some participants described a sense of guilt or pressure if they had not been able to consume all 30 mls of the oil every day. In such instances, the researcher needed to provide reassurance to the participants and allowed them to be more flexible with their intake.

Accountability is inherent in the social interactions between patients and health care professionals which impacts some patient's motivation to adhere to the treatment (Oussedik et al., 2019). Accountability refers to the expectation of an individual to having to explain an action or inaction (Oussedik et al., 2019).

Research shows that human support improves adherence to an intervention due to accountability felt towards the healthcare provider (Oussedik et al., 2019) . This is due to seeing the provider as a trustworthy expert. The effect of accountability can be impacted by personal motivation. The more intrinsically motivated a person is the less support they need to adhere. Intrinsic motivation refers to self-determined action that come from the need to engage or work towards a goal or behaviour (Michalak et al., 2004). It arises from a person's psychological needs do something (Michalak et al., 2004). While extrinsic motivation refers to anytime of motivation that arises due to external factors (Michalak et al., 2004). Research shows that changes that rely on extrinsic motivation alone are unstable as the change might stop when the extrinsic motivator is removed. To cultivate long term change, intrinsic motivation should be the sole driver of change (Mohr et al., 2011).

There was a fine line between accountability being a motivator and becoming an unhelpful pressure. Therefore, it is essential to consider internal motivation and how to maximise the impact of intervention by potentially including behaviour change techniques without adding pressure on participants.

V. DICe participants:

Some participants mentioned using either CO or SO before the study, but that did not affect their acceptance to the oil group they were allocated to. None of the participants who have previously used CO were using it when recruited for the study; thus, it did not affect the baseline data. However, participants who have previously used CO managed to adapt faster to the oil and easily incorporated it into their diet. Some participants *(n 8)* were aware of the potential negative and positive effects of CO in relation to other diseases (e.g., general health, cholesterol, weight loss) but none of the participants reported the potential benefits of consuming CO in relation to memory. Thus, the participant group can be considered were treatment naïve as they were not aware of the potential effect of CO on memory. One of

the participants created different recipes using the CO, despite never using it before the study. This demonstrates the potential of co-production of approaches by participants to incorporate oil into the diet to guide future studies.

Tailoring:

The findings showed that participants managed to incorporate the oil into their diet using the incorporation leaflet that allowed them to tailor the incorporation method based on their individual needs. The incorporation of oil into the diet offered a person-centred approach that accommodated individual preferences. From the interviews, participants reported different methods that they utilised to adhere to the intervention and tailor it based on their usual dietary intake (i.e., adding oil to coffee or oatmeal, cooking, roasting).

Participants with MCI did not require additional support or contact suggesting that the intervention does not need to be tailored to support those with memory impairments.

a) Adherence:

Adherence was measured via open ended questionnaires, phone logs and pictures. The monthly phone calls and the pictures had a dual purpose as a measure of adherence for the intervention and a way to facilitate self-monitoring. Based on the findings, adherence rate to the intervention were high as 81% (n 23) adhered at 3 months and 70% (n 20) at 6 months was recorded. The adherence rate is better than that reported in other DK studies (Henderson et al., 2009) and the drop-out rate in the study (9%) is lower than that reported in previous DK interventions which ranged between 5-33% (Henderson et al., 2009, Rebello et al., 2015, Ota et al., 2016, Taylor, 2018).

b) Phone calls support:

The support and resources provided by the researcher helped to increase participant's confidence and autonomy in using the oil. Telephone calls were easy and brief if participant wasn't having any issues with oil consumption. They were also used to reassure participants if they were feeling guilty while still encouraging accountability. Developing a rapport and supportive relationship with participants was an important factor for motivating them to adhere to the intervention.

VI. Modifications:

The Covid-19 pandemic and associated lockdown impacted the delivery and implementation of the dietary intervention. The study protocol was adapted to reduce disruptions to the delivery of the intervention as much as possible during the pandemic. When assessing study fidelity it is essential to assess any changes in the intervention content or delivery (Castro et al., 2004).

6.6. Fidelity

Promoting fidelity (the extent to which the intervention was delivered as intended) (Hasson, 2010) in the developmental phase of the current study involved creating the detailed DICe recipes, methods to incorporate oil into the diet and study flowchart. One of the objectives of these resources was to standardise the delivery of the intervention.

Study fidelity is defined as the degree to which an implementation of a particular program follows a protocol (Hasson, 2010). Fidelity is a measure for the degree if which an intervention was implemented as intended (Dusenbury et al., 2003). Fidelity was assessed from interviews with participants and data collected from monthly phone calls and adherence questionnaires.

There are subcategories that help assess the fidelity of the delivery of an intervention (Hasson, 2010):

Content: The content aspect represents changes related to omitting, modifying, or adding intervention components. The genetic test and blood ketone measures were omitted from the intervention during the lockdown. A risk assessment was conducted during the Covid-19 pandemic, and it was deemed unsafe to collect salivary samples from participants at that time, as UK government recommended maintaining 1 metre distance between people to reduce risk of infection. Thus, APO E4 test was omitted from the study procedure. Furthermore, due to the lockdown some third- and sixth-months study sessions were conducted virtually via zoom; in that case blood ketone level was not measured and the test was omitted from the study procedures.

Frequency: Per study protocol, the researcher contacted participant's monthly to ask about their adherence to the oil intake. Furthermore, no changes were made to the study visits as

they were conducted virtually instead of face to face in case of the lockdown. All study participants met the researcher either virtually or face to face 3 times during the study.

Duration: All participants completed the 6 months intervention and there was no difference in duration between participants.

Timeliness: Study visits were planned within one week time period of the cut-off point for all participants. Thus, there was no difference in the study time frame between participants.

These are the essential components of the intervention and demonstrate that it was delivered with high fidelity. The Covid-19 pandemic impacted the delivery of the study; however, it did not affect the fidelity of the implementation of the intervention as the study procedures were adapted to allow the continuation of the intervention and reduce disruptions. Per protocol, participants were contacted once a month by the researcher and received their allocated oil in time to ensure adherence to the intervention. Virtual meetings were used to allow the collection of cognitive, dietary, and qualitative data from participants. However, collection of physical measures was omitted from the intervention to ensure adherence to PHE recommendations regarding social distancing and reduce Covid-19 infection risk.

6.7. Logic Model

Logic models are assigned the role, in process evaluations, of representing the underlying theory of interventions in simple, diagrammatical form (Kellogg, 2004, O'Cathain et al., 2019). The findings of the current study helped in the development of the intervention's logic model; focusing on how the intervention would be expected to work in a future study. The feasibility aspect of the study helped inform multiple components of the model that would aid in the future when the intervention is applied on a bigger scale and potentially in a multi-centre aspect were the intervention is delivered by multiple people. The logic model was developed based on the findings from the literature review and the feasibility study to inform the design of a future study.

The review of available literature (refer to chapter 2) helped in identifying the potential mechanisms of action, target population and outcome measures. In the present study, the

mechanism of action was based on the potential effect of coconut oil intake on inducing dietary ketosis which may improve cognition by bypassing the effect of age-related cerebral glucose hypometabolism (refer to chapter 2, section 2.4). This provided the rationale for the intervention which targeted older adults to combat the age-related cognitive decline associated with glucose hypometabolism. The scoping review on DK and cognition in older adults identified the importance of reducing side effects of DK inducing interventions (refer to chapter 2, section 2.3) in order to facilitate long term adherence to the intervention. The review also identified key uncertainties e.g., barriers to adherence to intervention, side effects off using MCT's, wide range of cognitive measures used (overall cognition and specific tests). Thus, the logic model of the study focused on the feasibility of the intervention using coconut oil intake to improve cognitive functions and quality of life of older adults and adults with MCI. Table 6.1 provides a logic model of the components for the dietary intervention.

Table 6.1. Logic model components in DICe study

Problem	Evidence Base	Target Population	Study Outcomes	Full trial outcome
Relation between age related cerebral glucose hypometabolism and cognitive decline later in life.	DK can help bypass glucose hypometabolism and reduce age related cognitive decline. Potential effect of CO in inducing DK in the body.	Older Adults Adults with a confirmed MCI diagnosis	Adherence to CO intake. Potential improvements in cognitive measures in participants consuming CO. DICe successfully evaluated the feasibility of the intervention in preparation for a future trial.	Ability of CO intake to induce DK in older adults and adults with MCI. Improvement in cognitive functions in older adults and adults with MCI consuming CO.

It is recommended to use the components of this logic model in the design of a future RCT to document the expected outcomes of the intervention on cognition and quality of life and how it aims at achieving them (Moore et al. 2015).

- **IMB Model:**

DICe study aimed at changing dietary intake of participants by encouraging them to incorporate CO and SO into their everyday diet. Based on the findings from the thematic analysis (refer to chapter 5, section 5.6), participants reported on their experience in the intervention, especially focusing on their motivation for participation, adherence, and completion of the study. The data from the results was used to determine the best behavioural change model that could be used to illicit change in dietary habits in the target group. Most participants reported that their motivation to be involved in dementia research

affected their participation and completion of the study focused on the detailed information and researcher support as the reason behind their adherence to the intervention and change in dietary habits. Thus, the information, motivation and behavioural skills (IMB) model was the best fit for the dietary intervention (Fisher et al., 2003).The model proposes that behaviour changes occurs when individuals are well informed, highly motivated and have the skills necessary to perform the behaviour.

Information: This aspect of the IMB model can be supported through providing essential information to participants to aid in behaviour change (Fisher et al., 2003). The resources provided to participant who took part in the DICe intervention included leaflets and documents explaining the intervention. The recipes and the oil diet incorporation leaflets helped the participants in adding the oil into their everyday diet. It provided them with the necessary skills that allowed them to consume the oil and adhere to the intervention.

Motivation: Study participants were motivated to take part in the study intervention and follow the study procedures with the researcher's support. Furthermore, the constant contact with study participants and advice they received from the study researcher aided in maintaining their motivation and willingness to use the oil throughout the intervention.

Behaviour: The behaviour change of participants was assessed by evaluating the adherence of participants to the oil intake and their ability to incorporate the oil into their diet. The adherence results demonstrate that participants managed to incorporate oil into their daily diet. Furthermore, some participants expressed their willingness to continue using the oil after the study as they found it useful and enjoyable.

6.9. Strengths & limitations:

6.9.1. Strengths

i. A strength of this study is the systematic nature of its investigation into the acceptability and feasibility of the intervention. The study benefited from drawing upon the complex intervention framework (Skivington et al., 2018, Craig et al.,2008)

and other relevant literature in order to contribute to the cycle of complex intervention development.

ii. The intervention was developed and modelled based on the current evidence, it drew upon the available literature (Levac et al., 2010).

iii. Healthcare is complex and acknowledges the need for different perspectives to build a whole picture for interventions. This randomised controlled pilot study incorporated a mixed method, quantitative and qualitative along with patient and public involvement throughout. A mixed methods approach enables quantitative findings to be qualified by qualitative data, giving a depth of understanding on the feasibility of the intervention (Craig et al., 2008).

iv. The study incorporated a food-based intervention that is novel as previous interventions that aimed at inducing DK utilised specific nutritional elements (i.e., Medium Chain Triglyceride oils, Medium Chain Fatty Acids) or restrictive ketogenic diets (refer to Chapter 2, section 2.3.2). Food based interventions have higher positive nutrition-related outcomes in community-dwelling older adults than other interventions (Bandayrel et al., 2011). Food based approaches require long-term commitments, but are more likely to be sustainable for longer (Demment et al., 2003, Smitasiri et al., 2007) as they overcome some of the barriers that medical or clinical dietary interventions have (Bandayrel et al., 2011, Demment et al., 2003). This was one of the main drivers for the DICe study, it provides a non-restrictive, simple, food-based intervention with minimal side effects in comparison to other DK inducing diets or supplements.

6.9.2. Limitations

i. An important limitation of this study is the potential for bias. Due to the nature of this doctoral research, the researcher was involved in all stages of the research including initial meeting, delivering of the intervention, and the post-intervention interview. This may have led to a potential bias in data gathered at the interview, in that participants may not have wanted to give critical feedback (Loftin et al., 2011, Edwards and Chalmers, 2002). The researcher managed to build a personal

relationship with study participants over the 6 months period; thus, this relationship could have impacted the participants ability to critique the study procedures when discussing it with the researcher.

ii. Covid-19 caused some disruption in the study process and procedures. The lockdown might have had positive or negative impact on the results; especially as the national lockdown could have potentially affected the mental health of study participants subsequently affecting their motivation, quality of life and cognitive measures. Participants reacted differently to the lockdown and reported how it affected them and potentially their quality of life (refer to chapter 5, section 5.6). Thus, the impact of the intervention on participants might have been affected by the circumstances.

iii. Covid-19 also caused some disruption to data collection methods and some of the missing data especially the lack of measure of blood ketone concentration levels is a limitation of the study. One of the objectives of the study was to evaluate the impact of 30 ml coconut oil intake on blood ketone levels. However, Covid-19 rendered it impossible to test ketone at 3 and 6 months; thus, it remains unknown whether study participants consuming CO achieved ketosis.

iv. A limitation of this study was the lack of diversity in the participant group. Recruitment strategies for attracting a more diverse population needs to be considered in a future study. As ethnicity and different genetic makeup impacts fatty acid metabolism in the body, which means different groups would react differently to the intervention. Furthermore, the cultural aspect of food would impact the acceptance of participants from different backgrounds to the dietary intervention (refer to chapter 6, section 6.6 for further details).

v. Recruiting patients with MCI into the study demonstrated the challenges of recruiting participants with MCI. The findings demonstrated that it is not feasible to recruit MCI patients through memory assessment clinics. For future trials, it would be recommended to screen for MCI as part of the study procedures instead of screening for people with a confirmed diagnosis due to the disparities in diagnosing MCI across the different trusts in the UK (Dunne et al., 2021, Richardson et al., 2019).

6.10. Reflexivity

Reflexivity in the research process refers to the examination of the researcher's own beliefs, judgments and practices and how these could have influenced the research (Finlay, 1998). Reflexivity is "acknowledging the central position of the researcher in the construction of knowledge" (Bannister et al., 1994).

This section discusses the impact that the researcher may have had in this study. My role as the researcher may have had an influence on the research process. It is important to understand the researcher's own beliefs to be able to understand their potential influences on the study (Banister et al., 2011, Guillemin and Gillam, 2004). Failure in recognising the researcher's assumptions could results in data collection and study design bias long before data is interpreted (Korstjens and Moser, 2018). When working with people, the researcher needs to acknowledge the potential impact of their own views on the study participants to prevent potential bias(Guillemin and Gillam, 2004).

The study was not double blinded and due to my knowledge of the group allocation of participants to the control and intervention group. I already had some assumptions on the potential results of some of the measures on participants in the different groups. In order to prevent these views from being a source of bias an awareness of these assumptions was required. Thus, I used a diary to keep track of my research journey and note problems with the study processes and the reasons behind them. I also kept a log of all of my interactions with study participants to minimise bias and ensure that the support I provide was not biased towards the intervention group. This allowed me to critically report any key issues to the multi-disciplinary study supervisory team. The discussions I had with my supervisory team allowed me to reflect on my own assumptions and their impact on the study procedures and potential results. This helped me maintain an objective point of view and reduced my influence on the study procedures.

As previously mentioned, I managed to build a personal relationship with all the study participants which might have impacted their level of motivation and adherence to the study. This needs to be acknowledged as in a future trial with a bigger sample size it would be impractical to build personal relations with all study participants. Unfortunately, due to

the nature of this doctoral study; I was involved in all aspects of the study and was in continuous contact with study participants which allowed these relations to develop over the six months period. Especially, in the case of participants who were living alone during lockdown as for two of them I was the only human interaction they had for months. These relationships might have cause participants to feel accountable to me which might have influenced their adherence to the study. It also helped build a relation of trust and honesty in which they felt confident to report back non-adherence to the oil intake. Thus, these relations might have influenced the data and some of the study results as participants were more motivated to adhere to the study due to a sense of accountability to me rather than to the study itself. It might not be feasible to develop such relations in a future study with a bigger sample size, thus there should be more focus on improving the participant's internal motivation to adherence.

Reflexivity also looks into the influence of the research on the researcher (Banister et al., 2011). As a doctoral student and being involved in all aspects of the research project impacted my way of thinking about intervention design and applications in the community. It allowed me to develop new skills in the area of cognition as I learnt how to administer and interpret the results of different cognitive measures. It also helped me learn a lot about the bigger picture of interventions and especially lifestyle interventions as it made me realise the importance of using a person-centred approach even in a standardised community intervention.

During my doctoral journey, I have gained skills and knowledge in intervention development, implementation, and process evaluation. This research gave me the opportunity to improve my research skills and develop new skills in clinical trial management, clinical intervention development and collaboration a multi-disciplinary team.

6.11. Summary

In summary, the DICe study enabled participants to feel confident about incorporating the oil into their everyday diet. In general, participants gave positive feedback about the study design and resources provided. Participant feedback is of value to gain understanding of how people engaged with the intervention to inform the ongoing development for a future trial. The results of this study show that a randomised trial is feasible. The results of the pilot

testing show preliminary estimates of small effect sizes for cognitive measures in direction of benefit for the CO group. This study provided important information in relation to the feasibility of a dietary intervention using coconut oil and the appropriateness of the outcome measures used.

Chapter 7: Conclusion

The final chapter concludes this thesis by summarising the key findings and contributions to knowledge of the study and providing recommendations for future research. The first section considers the aims of the study and summarises the key findings related to the study objectives. The second section examines the contributions to knowledge of the present study while the third section provides recommendations for future research.

7.1. Thesis aim & key findings

This mixed methods study aimed at evaluating the feasibility of a dietary intervention using CO to contribute to the evidence base on the relation of dietary ketosis on cognition and quality of life in older adults and adults with MCI. To the researcher's knowledge, DICe is the first food-based intervention to test the feasibility of a 6-month dietary intervention using CO in older adults and adults with MCI in the community. Intervention development feasibility studies are important in order to systematically prepare for larger trials (Craig et al., 2011, Skivington et al., 2018). Initial studies will inform researchers about decisions, directions, and practical considerations for future trials. The intervention was developed using a rigorous approach following the MRC framework for complex interventions This study incorporated the experience of the participants which helped to understand their perspective of the intervention from a user perspective. This thesis presents data that aimed to inform the design and minimise error in a future trial. (Morris et al., 2015a)

This study has successfully piloted and evaluated the feasibility of DICe for a future RCT in older adults. Good adherence rate (70% overall) showed that the dietary intervention is feasible and applicable in the target population. Using a food-based intervention with minimal side effects (restrictiveness of Ketogenic diet, Gastro-intestinal side effects of MCT intake) helped overcome some of the adherence issues reported in previous DK related studies. The present study demonstrated that recruitment of adults with MCI might not be feasible in the community due to disparities in diagnosis across different trusts. Gaining consent to contact databases of participants in research centres and platforms offered the

most successful way in recruitment of older adults in the community. Retention rate in the study was high (91%) in comparison to DK interventions (67-95%) (Henderson et al., 2009, Rebello et al., 2015, Ota et al., 2016, Taylor, 2018) despite the effect of Covid-19 pandemic. No serious adverse events were recorded in the study, however, minor GI discomfort that was later alleviated with changes in the approach used to consume oil was reported by three study participants. For a future trial, it is recommended to measure blood cholesterol concentrations as it was a concern reported by two study participants.

The processes for data collection and outcome measures were acceptable for participants. Participants reported that they enjoyed the battery of cognitive measures used in the study, apart from the visual spatial memory assessment "supermarket task" and found it difficult to complete the measure. There were no difficulties reported for undertaking the dietary and anthropometric outcome measures.

Covid-19 and its associated lockdown measures occurred during the recruitment and data collections phases of the study. It caused delays to the study procedures and impacted some of the data collection methods. Most of the second and third study sessions (at 3 and 6 months cut off points) were conducted virtually and some measures were not collected (i.e., blood ketone measure, APO E4 genetic test).

Participants accepted the randomisation process as part of research and were happy to be allocated to their intervention group. Participants reported that they had altruistic motivation to get involved in the study with a view of helping people with dementia. They expressed their willingness to take part in a similar study in the future.

Feedback from participants provided insights on how the oil was used and whether it was incorporated into their habitual diet. They provided examples on how they consumed the oil and integrated it into their diet. For instance, the majority of participants added CO to their coffee or porridges as they struggled with the solid state of the oil at room temperature. Despite the addition of oil into the diet and participants reporting that they feel that they were consuming more fat, a significant decrease in fat intake was recorded in study participants after the intervention. Telephone calls and virtual sessions were accepted by participants however they reported valuing face to face sessions more. Overall, the study demonstrated the feasibility and applicability of the intervention.

Key concluding points:

- DICe was developed and successfully piloted to evaluate its feasibility and inform the design of a future RCT to assess the effect of coconut oil induced DK on cognition in older adults and adults with MCI
- DICe offers an acceptable and practical food-based intervention that might induce ketosis and potentially prevent cognitive decline in older adults and those with MCI.
- The effectiveness of DICe requires further evaluation with a larger sample size.

Figure 7.1. Summary of DICe study key concluding points

7.2. Contribution to knowledge

The current study has tested the feasibility and acceptability etc of a novel food-based intervention that has potential to improve cognitive functions and quality of life in older adults.

This development and feasibility assessment phase of the intervention is an important aspect for the development of the intervention before testing its effectiveness in a future trial (Skivington et al., 2021). The results from this study will provide information on the feasibility of this intervention and similar dietary and food interventions in this population. It demonstrated the acceptability of study participants to the dietary intervention and the cognitive measures used. It also showed that older adults prefer paper based cognitive measures in comparison to virtual based ones. The findings provide insights into the challenges encountered in nutrition interventions on cognition, especially during ageing. It also showed the challenges of recruiting participants with MCI in the community. However, it showed that providing a flexible food-based intervention that can be tailored based on individual needs to enhance adherence to the intervention. Thus, the results can be used to inform the design of future research in the field of nutrition and cognition, especially due to the lack of feasibility studies in the area.

Thus, the findings from this feasibility study can inform the design of a full-scale trial to evaluate the effectiveness of an intervention and has potential to information on a non-pharmaceutical intervention that could potentially delay cognitive decline, reducing risk of dementia and improving quality of life for longer.

7.3. Recommendations for future research

Together the findings from this study from both qualitative and quantitative data indicate that the dietary intervention is feasible and acceptable to older adults and adults with MCI. As such, this study demonstrates that DICe offers a promising intervention for older adults and adults with MCI. However, the study highlighted a number of opportunities for future research. These are discussed in the following section.

The information gathered in this mixed methods feasibility study addressed important procedural, methodological and clinical uncertainties. Larger sample sizes, or multi-site studies would allow statistical exploration of quantitative outcome measures, to test the effect of the dietary intervention on cognition and quality of life in the target population.

For a future trial, thorough and diverse recruitment strategies need to be applied especially when targeting people with MCI. Due to disparities in MCI diagnosis between trusts in the UK, it is recommended that future studies use cognitive measures to assess cognitive abilities and MCI risk instead of targeting participants with a confirmed diagnosis. A limitation of the study was the recruitment of participants from diverse ethnic and socioeconomic communities. It is recommended for a future intervention to recruit participants from diverse ethnic and cultural backgrounds, as ethnicity and culture play an important role in dietary habits and behaviour of individuals. As previous studies have shown ethnicity and cultural background of participants might impact their willingness to alter their eating behaviour, especially affecting their willingness to incorporate a foreign food item into their ever day diet (Mora and Golden, 2017, Nierkens et al., 2013). Another limitation of the study was the absence of measurement of CO intake on blood ketone levels. Therefore, it is recommended that future studies address the relation between both and asses the effect of CO intake on blood ketone levels.

Based on the qualitative findings the intervention was feasible. However, peer support might be a useful addition to the intervention resources in the future, but further research is needed to understand the impact of peer support in dietary interventions (Toobert et al., 2005, McEvoy et al., 2018, Moore et al., 2019). Participants mentioned appreciating the support they received from the researcher, as it made them feel accountable and improved their adherence to the study. This level of support might not be possible on a larger scale, so

a peer support system through a website or social media groups might be a useful alternative on a bigger scale. The first introductory session could be conducted in a group setting, to allow participants to meet and form a community of support. A website or social media group would offer opportunities for support, encouragement, answers and sharing of recipes.

Furthermore, the cost of the intervention was not evaluated as part of this study. The updated MRC complex interventions framework emphasizes the need to evaluate the cost of the intervention and its economic implications (Skivington et al., 2021). Thus, a future study, needs to evaluate the cost of the interventions and the impact on the economic health burden on the provision of health and care services for older adults.

The present studies showed that the intervention is feasible in older adults. However, it is recommended that blood cholesterol concentrations (HDL and LDL) are measured in a future trial to assess the effects of CO intake on lipid profile and minimise any health risks to study participants. As scientists still debate the effect of CO intake on lipid profile and its potential effect on increasing HDL and total cholesterol without increasing LDL concentrations (Tran-Dinh et al., 2013, Ng et al., 2013, Hovingh et al., 2015). A future study should consider using a paper based cognitive measure of visuospatial memory instead of virtual based one as this might be more effective in older adults. As participants struggled with completing the virtual based “Supermarket Task”.

Chapter 8: References

ABE, S., EZAKI, O. & SUZUKI, M. 2017. Medium-Chain Triglycerides in Combination with Leucine and Vitamin D Benefit Cognition in Frail Elderly Adults: A Randomized Controlled Trial. *Journal of Nutritional Science and Vitaminology,* 63**,** 133-140.

ACQUISTAPACE, S., PATEL, L., PATIN, A., FORBES-BLOM, E., CUENOUD, B., WOOSTER, T. J. J. F. & FUNCTION 2019. Effects of interesterified lipid design on the short/medium chain fatty acid hydrolysis rate and extent (in vitro). 10**,** 4166-4176.

ALPINAR-SENCAN, Z., LOHMEYER, L., SCHICKTANZ, S. J. N. G. & SOCIETY 2020. Planning later life with dementia: comparing family caregivers' perspectives on biomarkers with laypersons' attitudes towards genetic testing of dementia prediction. 39**,** 52-79.

ALZHEIMER'S DISEASE INTERNATIONAL 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. London.

ANDERSON, R. T., ORY, M., COHEN, S. & MCBRIDE, J. S. 2000. Issues of Aging and Adherence to Health Interventions. *Controlled Clinical Trials,* 21**,** S171-S183.

ANDREU-REINÓN, M. E., CHIRLAQUE, M. D., GAVRILA, D., AMIANO, P., MAR, J., TAINTA, M., ARDANAZ, E., LARUMBE, R., COLORADO-YOHAR, S. M., NAVARRO-MATEU, F., NAVARRO, C. & HUERTA, J. M. 2021. Mediterranean Diet and Risk of Dementia and Alzheimer's Disease in the EPIC-Spain Dementia Cohort Study. *Nutrients,* 13**,** 700.

ARAIN, M., CAMPBELL, M. J., COOPER, C. L. & LANCASTER, G. A. J. B. M. R. M. 2010. What is a pilot or feasibility study? A review of current practice and editorial policy. 10**,** 1-7.

ARKSEY, H. & O'MALLEY, L. 2005. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology,* 8**,** 19-32.

ARPON, A., RIEZU-BOJ, J. I., MILAGRO, F., MARTI, A., RAZQUIN, C., MARTÍNEZ-GONZÁLEZ, M., CORELLA, D., ESTRUCH, R., CASAS, R. & FITÓ, M. 2016. Adherence to Mediterranean diet is associated with methylation changes in inflammation-related genes in peripheral blood cells. *Journal of physiology and biochemistry,* 73**,** 445-455.

ASCHERIO, A. J. T. A. J. O. M. 2002. Epidemiologic studies on dietary fats and coronary heart disease. 113**,** 9-12.

ASSUNÇÃO, M. L., FERREIRA, H. S., DOS SANTOS, A. F., CABRAL, C. R. & FLORÊNCIO, T. M. M. T. 2009. Effects of Dietary Coconut Oil on the Biochemical and Anthropometric Profiles of Women Presenting Abdominal Obesity. *Lipids,* 44**,** 593-601.

ATKINS, S., ODENDAAL, W., LEON, N., LUTGE, E. & LEWIN, S. 2015. Qualitative process evaluation for complex interventions. *Complex Interventions in Health.* Routledge (London).

AUGUSTIN, K., KHABBUSH, A., WILLIAMS, S., EATON, S., ORFORD, M., CROSS, J. H., HEALES, S. J., WALKER, M. C. & WILLIAMS, R. S. 2018. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. *The Lancet Neurology,* 17**,** 84-93.

B. ALLÈS , C. S., C. FÉART , M.-A. JUTAND, D. LAURIN AND P. BARBERGER-GATEAU 2012. Dietary patterns: a novel approach to examine the link between nutrition and cognitive function in older individuals. *Nutrition Research Reviews,* 25**,** 207–222.

BANDAYREL, K., WONG, S. J. J. O. N. E. & BEHAVIOR 2011. Systematic literature review of randomized control trials assessing the effectiveness of nutrition interventions in community-dwelling older adults. 43**,** 251-262.

BANERJEE, S., SMITH, S., LAMPING, D., HARWOOD, R., FOLEY, B., SMITH, P., MURRAY, J., PRINCE, M., LEVIN, E. & MANN, A. 2006. Quality of life in dementia: more than just cognition. An analysis

of associations with quality of life in dementia. *Journal of Neurology, Neurosurgery & Psychiatry,* 77**,** 146-148.
BANISTER, P., BUNN, G. & BURMAN, E. 2011. *Qualitative methods in psychology: A research guide: A research guide*, McGraw-Hill Education (UK).
BANNISTER, P., BURMAN, E., PARKER, I., TAYLOR, M. & TINDALL, C. 1994. Qualitative Methods in psychology. Buckingham. OUP.
BARNARD, N. D., BUNNER, A. E. & AGARWAL, U. 2014. Saturated and trans fats and dementia: a systematic review. *Neurobiology of aging,* 35**,** S65-S73.
BARRERA JR, M., CASTRO, F. G., STRYCKER, L. A., TOOBERT, D. J. J. J. O. C. & PSYCHOLOGY, C. 2013. Cultural adaptations of behavioral health interventions: a progress report. 81**,** 196.
BAXTER, S. K., BLANK, L., WOODS, H. B., PAYNE, N., RIMMER, M. & GOYDER, E. J. B. M. R. M. 2014. Using logic model methods in systematic review synthesis: describing complex pathways in referral management interventions. 14**,** 1-9.
BEARD, J. R., OFFICER, A., DE CARVALHO, I. A., SADANA, R., POT, A. M., MICHEL, J.-P., LLOYD-SHERLOCK, P., EPPING-JORDAN, J. E., PEETERS, G. G. & MAHANANI, W. R. 2016. The World report on ageing and health: a policy framework for healthy ageing. *The lancet,* 387**,** 2145-2154.
BECHTEL, C., REMINGTON, R., BARTON, B., BARASAUSKAS, C. & SHEA, T. B. J. B. R. N. 2015. Cognitive testing for dementia is adversely affected by administration in a foreign location. 8**,** 1-4.
BELL, M. L., WHITEHEAD, A. L. & JULIOUS, S. A. J. C. E. 2018. Guidance for using pilot studies to inform the design of intervention trials with continuous outcomes. 10**,** 153.
BENCH, S., DAY, T. & METCALFE, A. J. N. R. 2013. Randomised controlled trials: An introduction for nurse researchers. 20.
BENLLOCH, M., LÓPEZ-RODRÍGUEZ, M. M., CUERDA-BALLESTER, M., DREHMER, E., CARRERA, S., CERON, J. J., TVARIJONAVICIUTE, A., CHIRIVELLA, J., FERNÁNDEZ-GARCÍA, D. & DE LA RUBIA ORTÍ, J. E. 2019. Satiating effect of a ketogenic diet and its impact on muscle improvement and oxidation state in multiple sclerosis patients. *Nutrients,* 11**,** 1156.
BLATCH-JONES, A. J., PEK, W., KIRKPATRICK, E. & ASHTON-KEY, M. J. B. O. 2018. Role of feasibility and pilot studies in randomised controlled trials: a cross-sectional study. 8**,** e022233.
BONELL, C., FLETCHER, A., MORTON, M., LORENC, T., MOORE, L. J. S. S. & MEDICINE 2012. Realist randomised controlled trials: a new approach to evaluating complex public health interventions. 75**,** 2299-2306.
BORDA, M. G., AYALA COPETE, A. M., TOVAR-RIOS, D. A., JARAMILLO-JIMENEZ, A., GIIL, L. M., SOENNESYN, H., GOMEZ-ARTEAGA, C., VENEGAS-SANABRIA, L. C., KRISTIANSEN, I. & CHAVARRO-CARVAJAL, D. A. 2021. Association of malnutrition with functional and cognitive trajectories in people living with dementia: a five-year follow-up study. *Journal of Alzheimer's Disease,* 79**,** 1713-1722.
BOWER, P., BRUETON, V., GAMBLE, C., TREWEEK, S., SMITH, C. T., YOUNG, B. & WILLIAMSON, P. J. T. 2014. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. 15**,** 1-9.
BOWLING, A. 2014. *Research methods in health: investigating health and health services*, McGraw-hill education (UK).
BRAGDON, J. & KARMEN, A. 1960. The fatty acid composition of chylomicrons of chyle and serum following the ingestion of different oils. *Journal of Lipid Research,* 1**,** 167-170.
BRANDT, J. & MANNING, K. J. 2009. Patterns of word-list generation in mild cognitive impairment and Alzheimer's disease. *Clin Neuropsychol,* 23**,** 870-9.
BRAUN, V. & CLARKE, V. J. Q. R. I. P. 2006. Using thematic analysis in psychology. 3**,** 77-101.
BUCHMAN, A. & BENNETT, D. A. 2013. Cognitive frailty. *The journal of nutrition, health & aging,* 17**,** 738.
BURNS, A. 2009. Alzheimer's disease: on the verges of treatment and prevention. *The Lancet. Neurology,* 8**,** 4-5.

CADILHAC, D. A., KILKENNY, M. F., SRIKANTH, V., LINDLEY, R. I., LALOR, E., OSBORNE, R. H. & BATTERBSY, M. J. I. J. O. S. 2016. Do cognitive, language, or physical impairments affect participation in a trial of self-management programs for stroke? 11**,** 77-84.

CALLAHAN, C. M., FOROUD, T., SAYKIN, A. J., SHEKHAR, A. & HENDRIE, H. C. 2014. Translational research on aging: clinical epidemiology as a bridge between the sciences. *Translational Research,* 163**,** 439-445.

CALVO-OCHOA, E. & ARIAS, C. 2015. Cellular and metabolic alterations in the hippocampus caused by insulin signalling dysfunction and its association with cognitive impairment during aging and Alzheimer's disease: studies in animal models. *Diabetes/metabolism research and reviews,* 31**,** 1-13.

CAMPBELL, N. C., MURRAY, E., DARBYSHIRE, J., EMERY, J., FARMER, A., GRIFFITHS, F., GUTHRIE, B., LESTER, H., WILSON, P. & KINMONTH, A. L. 2007. Designing and evaluating complex interventions to improve health care. *BMJ,* 334**,** 455.

CANEVELLI, M., LUCCHINI, F., QUARATA, F., BRUNO, G. & CESARI, M. 2016. Nutrition and Dementia: Evidence for Preventive Approaches? *Nutrients,* 8**,** 144-144.

CANINI, M., BATTISTA, P., DELLA ROSA, P. A., CATRICALÀ, E., SALVATORE, C., GILARDI, M. C., CASTIGLIONI, I. J. C. & MEDICINE, M. M. I. 2014. Computerized neuropsychological assessment in aging: testing efficacy and clinical ecology of different interfaces. 2014.

CANTWELL, M. M., MILLEN, A. E., CARROLL, R., MITTL, B. L., HERMANSEN, S., BRINTON, L. A. & POTISCHMAN, N. J. T. J. O. N. 2006. A debriefing session with a nutritionist can improve dietary assessment using food diaries. 136**,** 440-445.

CARDOL, C. K., BOSLOOPER-MEULENBELT, K., VAN MIDDENDORP, H., MEULEMAN, Y., EVERS, A. W. M. & VAN DIJK, S. 2022. Psychosocial barriers and facilitators for adherence to a healthy lifestyle among patients with chronic kidney disease: a focus group study. *BMC Nephrology,* 23**,** 205.

CASAS, R., SACANELLA, E., URPÍ-SARDÀ, M., CORELLA, D., CASTANER, O., LAMUELA-RAVENTOS, R.-M., SALAS-SALVADÓ, J., MARTÍNEZ-GONZÁLEZ, M.-A., ROS, E. & ESTRUCH, R. 2016. Long-term immunomodulatory effects of a mediterranean diet in adults at high risk of cardiovascular disease in the PREvención con DIeta MEDiterránea (PREDIMED) randomized controlled trial. *The Journal of nutrition,* 146**,** 1684-1693.

CASTELLANO, C.-A., NUGENT, S., PAQUET, N., TREMBLAY, S., BOCTI, C., LACOMBE, G., IMBEAULT, H., TURCOTTE, E., FULOP, T. & CUNNANE, S. C. 2015. Lower brain 18F-fluorodeoxyglucose uptake but normal 11C-acetoacetate metabolism in mild Alzheimer's disease dementia. *Journal of Alzheimer's Disease,* 43**,** 1343-1353.

CASTRO, F. G., BARRERA, M. & MARTINEZ, C. R. J. P. S. 2004. The cultural adaptation of prevention interventions: Resolving tensions between fidelity and fit. 5**,** 41-45.

CHAKRABARTI, S., MUNSHI, S., BANERJEE, K., THAKURTA, I. G., SINHA, M. & BAGH, M. B. 2011. Mitochondrial dysfunction during brain aging: role of oxidative stress and modulation by antioxidant supplementation. *Aging and disease,* 2**,** 242.

CHATTERJEE, P., FERNANDO, M., FERNANDO, B., DIAS, C. B., SHAH, T., SILVA, R., WILLIAMS, S., PEDRINI, S., HILLEBRANDT, H., GOOZEE, K., BARIN, E., SOHRABI, H. R., GARG, M., CUNNANE, S. & MARTINS, R. N. 2020. Potential of coconut oil and medium chain triglycerides in the prevention and treatment of Alzheimer's disease. *Mechanisms of Ageing and Development,* 186**,** 111209.

CHENG, S.-T., LAM, L. C., CHAN, L. C., LAW, A. C., FUNG, A. W., CHAN, W.-C., TAM, C. W. & CHAN, W.-M. 2011. The effects of exposure to scenarios about dementia on stigma and attitudes toward dementia care in a Chinese community. *International Psychogeriatrics,* 23**,** 1433-1441.

CHINWONG, S., CHINWONG, D. & MANGKLABRUKS, A. 2017. Daily consumption of virgin coconut oil increases high-density lipoprotein cholesterol levels in healthy volunteers: a randomized crossover trial. *Evidence-Based Complementary and Alternative Medicine,* 2017.

CHIU, C.-C., SU, K.-P., CHENG, T.-C., LIU, H.-C., CHANG, C.-J., DEWEY, M. E., STEWART, R. & HUANG, S.-Y. 2008. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: A preliminary randomized double-blind placebo-controlled study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 32**,** 1538-1544.

CIAVARDELLI, D., PIRAS, F., CONSALVO, A., ROSSI, C., ZUCCHELLI, M., DI ILIO, C., FRAZZINI, V., CALTAGIRONE, C., SPALLETTA, G. & SENSI, S. L. 2016. Medium-chain plasma acylcarnitines, ketone levels, cognition, and gray matter volumes in healthy elderly, mildly cognitively impaired, or Alzheimer's disease subjects. *Neurobiology of Aging,* 43**,** 1-12.

CLARK, S., JUNG, S. & LAMSAL, B. 2014. *Food processing: principles and applications*, John Wiley & Sons (USA).

COELHO-JÚNIOR, H. J., TRICHOPOULOU, A. & PANZA, F. 2021. Cross-sectional and longitudinal associations between adherence to Mediterranean diet with physical performance and cognitive function in older adults: A systematic review and meta-analysis. *Ageing Research Reviews,* 70**,** 101395.

COSTANTINI, L. C., BARR, L. J., VOGEL, J. L. & HENDERSON, S. T. 2008. Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neuroscience,* 9**,** 1-9.

CRAFT, S., ASTHANA, S., SCHELLENBERG, G., BAKER, L., CHERRIER, M., BOYT, A. A., MARTINS, R. N., RASKIND, M., PESKIND, E. & PLYMATE, S. 2000. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. *Ann N Y Acad Sci,* 903.

CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I. & PETTICREW, M. J. M. R. C., UK 2011. Developing and evaluating complex interventions (UK).

CRESWELL, J. W. 2003. A framework for design Research design: Qualitative, quantitative,

mixed methods approaches 9-11.

CRESWELL, J. W. 2009. Mapping the field of mixed methods research. SAGE publications Sage CA: Los Angeles, CA.

CROTEAU, E., CASTELLANO, C. A., FORTIER, M., BOCTI, C., FULOP, T., PAQUET, N. & CUNNANE, S. C. 2017. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Experimental Gerontology*.

CUNNANE, S., NUGENT, S., ROY, M., COURCHESNE-LOYER, A., CROTEAU, E., TREMBLAY, S., CASTELLANO, A., PIFFERI, F., BOCTI, C., PAQUET, N., BEGDOURI, H., BENTOURKIA, M., TURCOTTE, E., ALLARD, M., BARBERGER-GATEAU, P., FULOP, T. & RAPOPORT, S. I. 2011. Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition,* 27**,** 3-20.

CUNNANE, S. C., TRUSHINA, E., MORLAND, C., PRIGIONE, A., CASADESUS, G., ANDREWS, Z. B., BEAL, M. F., BERGERSEN, L. H., BRINTON, R. D. & DE LA MONTE, S. 2020. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. *Nature Reviews Drug Discovery,* 19**,** 609-633.

CUTLER, S. J., HODGSON, L. G. J. A. J. O. A. S. D. & DEMENTIAS®, O. 2003. To test or not to test: Interest in genetic testing for Alzheimer's disease among middle-aged adults. 18**,** 9-20.

DAVID, D. C., HAUPTMANN, S., SCHERPING, I., SCHUESSEL, K., KEIL, U., RIZZU, P., RAVID, R., DRÖSE, S., BRANDT, U. & MÜLLER, W. E. 2005. Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L tau transgenic mice. *Journal of Biological Chemistry,* 280**,** 23802-23814.

DAYRIT, F. M., DIMZON, I. K. D., VALDE, M. F., SANTOS, J. E. R., GARROVILLAS, M. J. M. & VILLARINO, B. J. 2011. Quality characteristics of virgin coconut oil: comparisons with refined coconut oil. *Pure and Applied Chemistry,* 83**,** 1789-1799.

DAYRIT, F. M. J. J. O. T. A. O. C. S. 2015. The properties of lauric acid and their significance in coconut oil. 92**,** 1-15.

DE BOER, I. H. & BRUNZELL, J. D. 2014. HDL in CKD: how good is the "good cholesterol?". Am Soc Nephrol.
DE LA RUBIA ORTÍ, J. E., SÁNCHEZ ÁLVAREZ, C., SELVI SABATER, P., BUENO CAYO, A. M., SANCHO CASTILLO, S., ROCHINA, M. J. & HU YANG, I. 2017. How does coconut oil affect cognitive performance in alzheimer patients? *Nutricion Hospitalaria,* 34**,** 352-356.
DEAN C DELIS, E. K., JOEL H KRAMER. 2001. *Delis-Kaplan Executive Function System™ (D-KEFS™)* [Online]. Available: https://www.pearsonclinical.co.uk/Psychology/AdultCognitionNeuropsychologyandLanguage/AdultAttentionExecutiveFunction/Delis-KaplanExecutiveFunctionSystem(D-KEFS)/Delis-KaplanExecutiveFunctionSystem(D-KEFS).aspx [Accessed].
DEL SOLE, A., CLERICI, F., CHITI, A., LECCHI, M., MARIANI, C., MAGGIORE, L., MOSCONI, L. & LUCIGNANI, G. 2008. Individual cerebral metabolic deficits in Alzheimer's disease and amnestic mild cognitive impairment: an FDG PET study. *European journal of nuclear medicine and molecular imaging,* 35**,** 1357-1366.
DEMMENT, M. W., YOUNG, M. M. & SENSENIG, R. L. J. T. J. O. N. 2003. Providing micronutrients through food-based solutions: a key to human and national development. 133**,** 3879S-3885S.
DENT, E., LIEN, C., LIM, W. S., WONG, W. C., WONG, C. H., NG, T. P., WOO, J., DONG, B., DE LA VEGA, S. & POI, P. J. H. 2017. The Asia-Pacific clinical practice guidelines for the management of frailty. *Journal of the American Medical Directors Association,* 18**,** 564-575.
DUFOUIL, C., SESHADRI, S. & CHENE, G. 2014. Cardiovascular risk profile in women and dementia. *Journal of Alzheimer's Disease,* 42**,** S353-S363.
DUNNE, R. A., AARSLAND, D., O'BRIEN, J. T., BALLARD, C., BANERJEE, S., FOX, N. C., ISAACS, J. D., UNDERWOOD, B. R., PERRY, R. J., CHAN, D. J. A. & AGEING 2021. Mild cognitive impairment: the Manchester consensus. 50**,** 72-80.
DUSENBURY, L., BRANNIGAN, R., FALCO, M. & HANSEN, W. B. J. H. E. R. 2003. A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. 18**,** 237-256.
EDWARDS, M. & CHALMERS, K. 2002. Double agency in clinical research. *Canadian Journal of Nursing Research Archive*. CJNR Vol 34 Issue 1, 131-142.
ELDRIDGE, S. M., CHAN, C. L., CAMPBELL, M. J., BOND, C. M., HOPEWELL, S., THABANE, L. & LANCASTER, G. A. 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Bmj,* 355**,** i5239.
FARQUHAR, M. C., EWING, G. & BOOTH, S. 2011. Using mixed methods to develop and evaluate complex interventions in palliative care research. *Palliative Medicine,* 25**,** 748-757.
FERNANDO, W. M. A. D. B., MARTINS, I. J., GOOZEE, K. G., BRENNAN, C. S., JAYASENA, V. & MARTINS, R. N. 2015. The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action. *British Journal of Nutrition,* 114**,** 1.
FERNIHOUGH, A. & MCGOVERN, M. E. 2015. Physical stature decline and the health status of the elderly population in England. *Economics & Human Biology,* 16**,** 30-44.
FINLAY, L. J. B. J. O. O. T. 1998. Reflexivity: an essential component for all research? 61**,** 453-456.
FISHER, W. A., FISHER, J. D., HARMAN, J. J. S. P. F. O. H. & ILLNESS 2003. The information-motivation-behavioral skills model: A general social psychological approach to understanding and promoting health behavior. *Social psychological foundations of health and illness* 22**,** 82-106 (USA).
FLICK, U. 2004. Triangulation in qualitative research. *A companion to qualitative research,* 3**,** 178-183. Sage Publications (London).
FOLSTEIN, M. F., FOLSTEIN, S. E. & MCHUGH, P. R. J. J. O. P. R. 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. 12**,** 189-198.
FORTIER, M., CASTELLANO, C. A., ST-PIERRE, V., MYETTE-CÔTÉ, É., LANGLOIS, F., ROY, M., MORIN, M. C., BOCTI, C., FULOP, T. & GODIN, J. P. 2021. A ketogenic drink improves cognition in mild cognitive impairment: Results of a 6-month RCT. *Alzheimer's & Dementia,* 17**,** 543-552.

FRACKOWIAK, R., POZZILLI, C., LEGG, N. D., BOULAY, G. H., MARSHALL, J., LENZI, G. & JONES, T. 1981. REGIONAL CEREBRAL OXYGEN SUPPLY AND UTILIZATION IN DEMENTIA: A CLINICAL AND PHYSIOLOGICAL STUDY WITH OXYGEN-15 AND POSITRON TOMOGRAPHY A CLINICAL AND PHYSIOLOGICAL STUDY WITH OXYGEN-15 AND POSITRON TOMOHRAPHY. *Brain,* 104**,** 753-778.

FRANCIS, H. M. & STEVENSON, R. J. 2018. Potential for diet to prevent and remediate cognitive deficits in neurological disorders. *Nutrition Reviews,* 76**,** 204.

FREEMAN, J. M. & KOSSOFF, E. H. 2010. Ketosis and the Ketogenic Diet, 2010: Advances in Treating Epilepsy and Other Disorders. *Advances in Pediatrics,* 57**,** 315-329.

FREEMANTLE, E., VANDAL, M., TREMBLAY-MERCIER, J., TREMBLAY, S., BLACHÈRE, J.-C., BÉGIN, M. E., THOMAS BRENNA, J., WINDUST, A. & CUNNANE, S. C. 2006. Omega-3 fatty acids, energy substrates, and brain function during aging. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA),* 75**,** 213-220.

FRIEDMAN, A. N. 2004. High-protein diets: potential effects on the kidney in renal health and disease. *American journal of kidney diseases,* 44**,** 950-962.

GALASKO, D., BENNETT, D., SANO, M., ERNESTO, C., THOMAS, R., GRUNDMAN, M., FERRIS, S. J. A. D. & DISORDERS, A. 1997. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease.

GERSHUNI, V. M., YAN, S. L. & MEDICI, V. 2018. Nutritional ketosis for weight management and reversal of metabolic syndrome. *Current nutrition reports,* 7**,** 97-106.

GILBERT, D. L., PYZIK, P. L. & FREEMAN, J. M. 2000. The ketogenic diet: seizure control correlates better with serum β-hydroxybutyrate than with urine ketones. *Journal of child neurology,* 15**,** 787-790.

GRADY, K., GIBSON, M. & BOWER, P. J. B. M. R. M. 2019. Can a 'consent to contact'community help research teams overcome barriers to recruitment? The development and impact of the 'Research for the Future'community. 19**,** 1-7.

GRIFFITHS, P. & NORMAN, I. J. I. J. O. N. S. 2012. Qualitative or quantitative? Developing and evaluating complex interventions: time to end the paradigm wars.

GRILL, J. D., GALVIN, J. E. J. A. D. & DISORDERS, A. 2014. Facilitating Alzheimer's disease research recruitment. 28**,** 1.

GRILLO, C., PIROLI, G., HENDRY, R. & REAGAN, L. 2009. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. *Brain research,* 1296**,** 35-45.

GROOT, P., SCHOLTE, H. & HÜLSMANN, W. 1976. Fatty acid activation: specificity, localization, and function. *Advances in lipid research.* Elsevier.

GU, Y., NIEVES, J. W., STERN, Y., LUCHSINGER, J. A. & SCARMEAS, N. 2010. Food combination and Alzheimer disease risk: a protective diet. *Archives of neurology,* 67**,** 699-706.

GUILLEMIN, M. & GILLAM, L. J. Q. I. 2004. Ethics, reflexivity, and "ethically important moments" in research. 10**,** 261-280.

HASSELBALCH, S. G., MADSEN, P. L., HAGEMAN, L. P., OLSEN, K. S., JUSTESEN, N., HOLM, S. & PAULSON, O. B. 1996. Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *American Journal of Physiology-Endocrinology And Metabolism,* 270**,** E746-E751.

HASSON, H. J. I. S. 2010. Systematic evaluation of implementation fidelity of complex interventions in health and social care. 5**,** 1-9.

HEINZ, M., MARTIN, P., MARGRETT, J. A., YEARNS, M., FRANKE, W., YANG, H.-I., WONG, J. & CHANG, C. K. J. J. O. G. N. 2013. Perceptions of technology among older adults. 39**,** 42-51.

HENDERSON, S. T. 2008. Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics,* 5.

HENDERSON, S. T., MORIMOTO, B. H., CUMMINGS, J. L., FARLOW, M. R. & WALKER, J. 2020. A placebo-controlled, parallel-group, randomized clinical trial of AC-1204 in mild-to-moderate Alzheimer's disease. *Journal of Alzheimer's Disease,* 75**,** 547-557.

HENDERSON, S. T. & POIRIER, J. 2011. Pharmacogenetic analysis of the effects of polymorphisms in APOE, IDE and IL1B on a ketone body based therapeutic on cognition in mild to moderate Alzheimer's disease; a randomized, double-blind, placebo-controlled study. *BMC Medical Genetics,* 12**,** 137-137.

HENDERSON, S. T., VOGEL, J. L., BARR, L. J., GARVIN, F., JONES, J. J. & COSTANTINI, L. C. 2009. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutrition & Metabolism,* 6**,** 31.

HENEKA, M. T., CARSON, M. J., EL KHOURY, J., LANDRETH, G. E., BROSSERON, F., FEINSTEIN, D. L., JACOBS, A. H., WYSS-CORAY, T., VITORICA, J. & RANSOHOFF, R. M. 2015. Neuroinflammation in Alzheimer's disease. *The Lancet Neurology,* 14**,** 388-405.

HERTZ, L., CHEN, Y. & WAAGEPETERSEN, H. S. 2015. Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, β-amyloid toxicity, and astrocyte function. *Journal of Neurochemistry,* 134**,** 7-20.

HIGGINS JPT, T. J., CHANDLER J, CUMPSTON M, LI T, PAGE MJ, WELCH VA (EDITORS). 2019. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0* [Online]. Available: www.training.cochrane.org/handbook. [Accessed].

HOFFMANN, T. C., GLASZIOU, P. P., BOUTRON, I., MILNE, R., PERERA, R., MOHER, D., ALTMAN, D. G., BARBOUR, V., MACDONALD, H. & JOHNSTON, M. J. B. 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. 348.

HOLLIDAY, M. 1971. Metabolic rate and organ size during growth from infancy to maturity and during late gastation and early infancy. *Pediatrics,* 47**,** Suppl 2: 169+-Suppl 2: 169+.

HOVINGH, G. K., RADER, D. J. & HEGELE, R. A. J. C. O. I. L. 2015. HDL re-examined. 26**,** 127-132.

HOWE, A., KEOGH-BROWN, M., MILES, S. & BACHMANN, M. J. M. E. 2007. Expert consensus on contamination in educational trials elicited by a Delphi exercise. 41**,** 196-204.

HOWIESON, D. B. & LEZAK, M. D. 1995. Separating memory from other cognitive problems. In A. D. Baddeley, B. A. Wilson, & F. N. Watts (Eds.), *Handbook of memory disorders* (pp. 411–426). John Wiley & Sons (USA).

HOWLETT, N., SCHULZ, J., TRIVEDI, D., TROOP, N. & CHATER, A. J. J. O. H. P. 2019. A prospective study exploring the construct and predictive validity of the COM-B model for physical activity. 24**,** 1378-1391.

HOYER, S. 1992. Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. *Mol Chem Neuropathol,* 16.

HSIEH, S., MCGRORY, S., LESLIE, F., DAWSON, K., AHMED, S., BUTLER, C. R., ROWE, J. B., MIOSHI, E. & HODGES, J. R. 2015. The Mini-Addenbrooke's Cognitive Examination: A New Assessment Tool for Dementia. *Dementia and Geriatric Cognitive Disorders,* 39**,** 1-11.

HUANG, L., GAO, L. & CHEN, C. 2021. Role of Medium-Chain Fatty Acids in Healthy Metabolism: A Clinical Perspective. *Trends in Endocrinology & Metabolism,* 32**,** 351-366.

HURT, C. S., BANERJEE, S., TUNNARD, C., WHITEHEAD, D., TSOLAKI, M., MECOCCI, P., KŁOSZEWSKA, I., SOININEN, H., VELLAS, B. & LOVESTONE, S. 2010. Insight, cognition and quality of life in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry,* 81**,** 331-336.

IKEDA, M., BROWN, J., HOLLAND, A. J., FUKUHARA, R. & HODGES, J. R. 2002. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry,* 73**,** 371-376.

ISHII, H., ISHIKAWA, H., MEGURO, K., TASHIRO, M. & YAMAGUCHI, S. 2009. Decreased cortical glucose metabolism in converters from CDR 0.5 to Alzheimer's disease in a community: the Osaki-Tajiri Project. *International psychogeriatrics,* 21**,** 148-156.

IWAGAMI, M., QIZILBASH, N., GREGSON, J., DOUGLAS, I., JOHNSON, M., PEARCE, N., EVANS, S. & POCOCK, S. 2021. Blood cholesterol and risk of dementia in more than 1· 8 million people over two decades: a retrospective cohort study. *The Lancet Healthy Longevity,* 2**,** e498-e506.

JACK JR, C. R., KNOPMAN, D. S., JAGUST, W. J., PETERSEN, R. C., WEINER, M. W., AISEN, P. S., SHAW, L. M., VEMURI, P., WISTE, H. J. & WEIGAND, S. D. 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *The Lancet Neurology,* 12**,** 207-216.

JACKSON, J., MANDEL, D., BLANCHARD, J., CARLSON, M., CHERRY, B., AZEN, S., CHOU, C.-P., JORDAN-MARSH, M., FORMAN, T. & WHITE, B. 2009. Confronting challenges in intervention research with ethnically diverse older adults: the USC Well Elderly II trial. *Clinical Trials,* 6**,** 90-101.

JEFFERSON, A. L., LAMBE, S., MOSER, D. J., BYERLY, L. K., OZONOFF, A. & KARLAWISH, J. H. J. J. O. T. A. G. S. 2008. Decisional capacity for research participation in individuals with mild cognitive impairment. 56**,** 1236-1243.

JENNINGS, A., CUNNANE, S. C. & MINIHANE, A. M. 2020. Can nutrition support healthy cognitive ageing and reduce dementia risk? *bmj,* 369.

JEUKENDRUP, A. E. & ALDRED, S. 2004. Fat supplementation, health, and endurance performance. *Nutrition,* 20**,** 678-688.

JEZEK, P., GARLID, K. D., OROSZ, D. E., MODRIANSKÝ, M. & VASSANELLI, S. 1996. On the mechanism of fatty acid-induced proton transport by mitochondrial uncoupling protein. *Journal of Biological Chemistry,* 271**,** 2615-2620.

JOHNSTONE, B., ERDAL, K. & STADLER, M. A. 1995. The relationship between the Wechsler Memory Scale—revised (WMS-R) attention index and putative measures of attention. *Journal of Clinical Psychology in Medical Settings,* 2**,** 195-204.

JURICK, S. M., EGLIT, G. M. L., DELIS, D. C., BONDI, M. W. & JAK, A. J. 2022. D-KEFS trail making test as an embedded performance validity measure. *Journal of Clinical and Experimental Neuropsychology,* 44**,** 62-72.

KAI, K., HASHIMOTO, M., AMANO, K., TANAKA, H., FUKUHARA, R. & IKEDA, M. 2015. Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease. *Plos One,* 10**,** e0133666-e0133666.

KANIKARLA-MARIE, P. & JAIN, S. K. 2016. Hyperketonemia and ketosis increase the risk of complications in type 1 diabetes. *Free Radical Biology and Medicine,* 95**,** 268-277.

KATAN, M. B., ZOCK, P. L. & MENSINK, R. P. 1994. Effects of fats and fatty acids on blood lipids in humans: an overview. *The American journal of clinical nutrition,* 60**,** 1017S-1022S.

KEARNEY, A., WILLIAMSON, P., YOUNG, B., BAGLEY, H., GAMBLE, C., DENEGRI, S., MUIR, D., SIMON, N. A., THOMAS, S. & ELLIOT, J. T. 2017. Priorities for methodological research on patient and public involvement in clinical trials: A modified Delphi process. *Health Expectations,* 20**,** 1401-1410.

KELLOGG, W. K. 2004. Using logic models to bring together planning, evaluation, and action: logic model development guide. *Michigan: WK Kellogg Foundation*.

KENNEDY, A. M., FRACKOWIAK, R. S., NEWMAN, S. K., BLOOMFIELD, P. M., SEAWARD, J., ROQUES, P., LEWINGTON, G., CUNNINGHAM, V. J. & ROSSOR, M. N. 1995. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neuroscience letters,* 186**,** 17-20.

KENT, D. M. & KITSIOS, G. J. T. 2009. Against pragmatism: on efficacy, effectiveness and the real world. 10**,** 1-3.

KEOGH-BROWN, M., BACHMANN, M., SHEPSTONE, L., HEWITT, C., HOWE, A., RAMSAY, C. R., SONG, F., MILES, J., TORGERSON, D. & MILES, S. 2007. Contamination in trials of educational interventions.

KESSELS, R. P. C., MOLLEMAN, P. W. & OOSTERMAN, J. M. 2011. Assessment of working-memory deficits in patients with mild cognitive impairment and Alzheimer's dementia using Wechsler's Working Memory Index. *Aging Clinical and Experimental Research,* 23**,** 487-490.

KORSTJENS, I. & MOSER, A. J. E. J. O. G. P. 2018. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. 24**,** 120-124.
KOSSOFF, E. H. & HARTMAN, A. L. 2012. Ketogenic diets: new advances for metabolism-based therapies. *Current opinion in neurology,* 25**,** 173.
KRIKORIAN, R., BOESPFLUG, E. L., DUDLEY, J. A., NORRIS, M. M., CHU, W.-J., SUMMER, S. S. & ELIASSEN, J. C. 2014. Enhanced cerebral bioenergetics with dietary ketosis in Mild Cognitive Impairment. *Nutrition & Aging,* 2**,** 223.
KRIKORIAN, R., SHIDLER, M. D., DANGELO, K., COUCH, S. C., BENOIT, S. C. & CLEGG, D. J. 2012a. Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiology of Aging,* 33**,** 425-425.
KRIKORIAN, R., SHIDLER, M. D., DANGELO, K., COUCH, S. C., BENOIT, S. C. & CLEGG, D. J. 2012b. Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiology of Aging,* 33**,** 425.e19-425.e27.
KRISHNA, A. G., GAURAV, R., SINGH, B. A., KUMAR, P. P. & PREETI, C. J. I. C. J. 2010. Coconut oil: chemistry, production and its applications-a review. 53**,** 15-27.
KURT, P., YENER, G. & OGUZ, M. 2011. Impaired digit span can predict further cognitive decline in older people with subjective memory complaint: A preliminary result. *Aging & Mental Health,* 15**,** 364-369.
LAM, L. C., CHAU, R. C., WONG, B. M., FUNG, A. W., TAM, C. W., LEUNG, G. T., KWOK, T. C., LEUNG, T. Y., NG, S. P. & CHAN, W. M. 2012. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. *Journal of the American Medical Directors Association,* 13**,** 568. e15-568. e20.
LAM, L. C. W. & CHENG, S. T. 2013. Maintaining long-term adherence to lifestyle interventions for cognitive health in late life. *International Psychogeriatrics,* 25**,** 171-173.
LANCASTER, G. A., DODD, S. & WILLIAMSON, P. R. J. J. O. E. I. C. P. 2004. Design and analysis of pilot studies: recommendations for good practice. 10**,** 307-312.
LANGE, K. W., LANGE, K. M., MAKULSKA-GERTRUDA, E., NAKAMURA, Y., REISSMANN, A., KANAYA, S. & HAUSER, J. 2017. Ketogenic diets and Alzheimer's disease. *Food Science and Human Wellness,* 6**,** 1-9.
LARA, J., EVANS, E. H., O'BRIEN, N., MOYNIHAN, P. J., MEYER, T. D., ADAMSON, A. J., ERRINGTON, L., SNIEHOTTA, F. F., WHITE, M. & MATHERS, J. C. J. B. M. 2014. Association of behaviour change techniques with effectiveness of dietary interventions among adults of retirement age: a systematic review and meta-analysis of randomised controlled trials. 12**,** 1-12.
LEE, Y.-J., HAN, S. B., NAM, S.-Y., OH, K.-W. & HONG, J. T. 2010. Inflammation and Alzheimer's disease. *Archives of pharmacal research,* 33**,** 1539-1556.
LEIJON, M. E., FASKUNGER, J., BENDTSEN, P., FESTIN, K. & NILSEN, P. 2011. Who is not adhering to physical activity referrals, and why? *Scandinavian journal of primary health care,* 29**,** 234-240.
LEVAC, D., COLQUHOUN, H. & O'BRIEN, K. K. 2010. Scoping studies: advancing the methodology. *Implementation Science,* 5**,** 69.
LEWIS, F., KARLSBERG SCHAFFER, S., SUSSEX, J., O'NEILL, P. & COCKCROFT, L. 2014. The trajectory of dementia in the UK-making a difference. *Office of Health Economics Consulting Reports*.
LILAMAND, M., PORTE, B., COGNAT, E., HUGON, J., MOUTON-LIGER, F. & PAQUET, C. 2020. Are ketogenic diets promising for Alzheimer's disease? A translational review. *Alzheimer's Research & Therapy,* 12**,** 42.
LIM, W.-S., CANEVELLI, M. & CESARI, M. 2018. Dementia, frailty and aging. *Frontiers in medicine,* 5**,** 168.
LOFTIN, C., CAMPANELLA, H. & GILBERT, S. 2011. Ethical issues in nursing education: the dual-role researcher. *Teaching and Learning in Nursing,* 6**,** 139-143.

LOUDON, K., TREWEEK, S., SULLIVAN, F., DONNAN, P., THORPE, K. E. & ZWARENSTEIN, M. J. B. 2015. The PRECIS-2 tool: designing trials that are fit for purpose. 350.

LUCEY, A., HENEGHAN, C. & KIELY, M. 2016. Guidance for the design and implementation of human dietary intervention studies for health claim submissions. Wiley Online Library.

LYING-TUNELL, U., LINDBLAD, B., MALMLUND, H. & PERSSON, B. 1981. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids: II. PRESENILE DEMENTIA AND NORMAL-PRESSURE HYDROCEPHALUS. *Acta Neurologica Scandinavica,* 63**,** 337-350.

MAGISTRETTI, P. J. & PELLERIN, L. 1996. Cellular bases of brain energy metabolism and their relevance to functional brain imaging: evidence for a prominent role of astrocytes. *Cerebral cortex,* 6**,** 50-61.

MAGISTRETTI, P. J. & PELLERIN, L. 1999. Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences,* 354**,** 1155-1163.

MAHLEY, R. W., WEISGRABER, K. H. & HUANG, Y. J. P. O. T. N. A. O. S. 2006. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. 103**,** 5644-5651.

MANCZAK, M., PARK, B. S., JUNG, Y. & REDDY, P. H. 2004. Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease. *Neuromolecular medicine,* 5**,** 147-162.

MARINA, A., MAN, Y. C. & AMIN, I. 2009. Virgin coconut oil: emerging functional food oil. *Trends in Food Science & Technology,* 20**,** 481-487.

MARTEN, B., PFEUFFER, M. & SCHREZENMEIR, J. 2006. Medium-chain triglycerides. *International Dairy Journal,* 16**,** 1374-1382.

MARTIN-KHAN, M., VARGHESE, P., WOOTTON, R. & GRAY, L. 2007. Successes and failures in assessing cognitive function in older adults using video consultation. 13**,** 60-62.

MARTIN, K. A., BOWEN, D. J., DUNBAR-JACOB, J. & PERRI, M. G. J. C. C. T. 2000. Who will adhere? Key issues in the study and prediction of adherence in randomized controlled trials. 21**,** S195-S199.

MATTEI, J., SOTOS-PRIETO, M., BIGORNIA, S. J., NOEL, S. E. & TUCKER, K. L. 2017. The Mediterranean diet score is more strongly associated with favorable cardiometabolic risk factors over 2 years than other diet quality indexes in Puerto Rican adults. *The Journal of nutrition,* 147**,** 661-669.

MAYNARD, S. D. & GELBLUM, J. 2013. Retrospective case studies of the efficacy of caprylic triglyceride in mild-to-moderate Alzheimer's disease. *Neuropsychiatric Disease And Treatment,* 9**,** 1629-1635.

MCEVOY, C. T., MOORE, S. E., APPLETON, K. M., CUPPLES, M. E., ERWIN, C., KEE, F., PRIOR, L., YOUNG, I. S., MCKINLEY, M. C. & WOODSIDE, J. V. 2018. Development of a peer support intervention to encourage dietary behaviour change towards a Mediterranean diet in adults at high cardiovascular risk. *BMC Public Health,* 18**,** 1194.

MCEWEN, B. S. & REAGAN, L. P. 2004. Glucose transporter expression in the central nervous system: relationship to synaptic function. *European journal of pharmacology,* 490**,** 13-24.

MCGRATTAN, A. M., MCEVOY, C. T., VIJAYAKUMAR, A., MOORE, S. E., NEVILLE, C. E., MCGUINNESS, B., MCKINLEY, M. C. & WOODSIDE, J. V. 2021. A mixed methods pilot randomised controlled trial to develop and evaluate the feasibility of a Mediterranean diet and lifestyle education intervention 'THINK-MED' among people with cognitive impairment. *Pilot and Feasibility Studies,* 7**,** 3.

MCGRATTAN, A. M., MCGUINNESS, B., MCKINLEY, M. C., KEE, F., PASSMORE, P., WOODSIDE, J. V. & MCEVOY, C. T. 2019. Diet and Inflammation in Cognitive Ageing and Alzheimer's Disease. *Current Nutrition Reports,* 8**,** 53-65.

MCLAUGHLIN, A. C., WHITLOCK, L. A., LESTER, K. L. & MCGRAW, A. E. 2015. Older adults' self-reported barriers to adherence to dietary guidelines and strategies to overcome them. *Journal of Health Psychology,* 22**,** 356-363.

MCPHERSON, P. A. C. & MCENENY, J. 2012. The biochemistry of ketogenesis and its role in weight management, neurological disease and oxidative stress. *Journal of physiology and biochemistry,* 68**,** 141-151.

MICELI, G., CALTAGIRONE, C., GAINOTTI, G., MASULLO, C., SILVERI, M. J. J. O. C. & NEUROPSYCHOLOGY, E. 1981. Neuropsychological correlates of localized cerebral lesions in non-aphasic brain-damaged patients. 3**,** 53-63.

MICHALAK, J., KLAPPHECK, M. A. & KOSFELDER, J. 2004. Personal goals of psychotherapy patients: The intensity and the "why" of goal-motivated behavior and their implications for the therapeutic process. *Psychotherapy Research,* 14**,** 193-209.

MIHALKO, S. L., BRENES, G. A., FARMER, D. F., KATULA, J. A., BALKRISHNAN, R. & BOWEN, D. J. J. C. C. T. 2004. Challenges and innovations in enhancing adherence. 25**,** 447-457.

MILLER, S. A. & FORREST, J. L. 2001. Enhancing your practice through evidence-based decision making: PICO, learning how to ask good questions. *Journal of Evidence Based Dental Practice,* 1**,** 136-141.

MOHR, D. C., CUIJPERS, P. & LEHMAN, K. 2011. Supportive Accountability: A Model for Providing Human Support to Enhance Adherence to eHealth Interventions. *J Med Internet Res,* 13**,** e30.

MOLINA-AZORIN, J. F., BERGH, D. D., CORLEY, K. G. & KETCHEN JR, D. J. 2017. Mixed methods in the organizational sciences: Taking stock and moving forward. Sage Publications Sage CA: Los Angeles, CA.

MOORE, G. F., AUDREY, S., BARKER, M., BOND, L., BONELL, C., HARDEMAN, W., MOORE, L., O'CATHAIN, A., TINATI, T., WIGHT, D. & BAIRD, J. 2015. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ : British Medical Journal,* 350**,** h1258.

MOORE, S. E., MCMULLAN, M., MCEVOY, C. T., MCKINLEY, M. C. & WOODSIDE, J. V. 2019. The effectiveness of peer-supported interventions for encouraging dietary behaviour change in adults: a systematic review. *Public health nutrition,* 22**,** 624-644.

MORA, N. & GOLDEN, S. H. J. C. D. R. 2017. Understanding cultural influences on dietary habits in Asian, Middle Eastern, and Latino patients with type 2 diabetes: a review of current literature and future directions. 17**,** 1-12.

MORRIS, M. C. & TANGNEY, C. C. 2014. Dietary fat composition and dementia risk. *Neurobiology of aging,* 35**,** S59-S64.

MORRIS, M. C., TANGNEY, C. C., WANG, Y., SACKS, F. M., BARNES, L. L., BENNETT, D. A. & AGGARWAL, N. T. 2015a. MIND diet slows cognitive decline with aging. *Alzheimer's & dementia,* 11**,** 1015-1022.

MORRIS, M. C., TANGNEY, C. C., WANG, Y., SACKS, F. M., BARNES, L. L., BENNETT, D. A., AGGARWAL, N. T. J. A. S. & DEMENTIA 2015b. MIND diet slows cognitive decline with aging. 11**,** 1015-1022.

MORRIS, M. C., TANGNEY, C. C., WANG, Y., SACKS, F. M., BENNETT, D. A. & AGGARWAL, N. T. 2015c. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's & Dementia,* 11**,** 1007-1014.

MORRIS, M. C., TANGNEY, C. C., WANG, Y., SACKS, F. M., BENNETT, D. A., AGGARWAL, N. T. J. A. S. & DEMENTIA 2015d. MIND diet associated with reduced incidence of Alzheimer's disease. 11**,** 1007-1014.

NDNS 2019. National Diet and Nutrition Survey Rolling programme Years 9 to 11 (2016/2017 to 2018/2019).

NESTLE, M. 2016. Corporate Funding of Food and Nutrition Research: Science or Marketing? *JAMA Internal Medicine,* 176**,** 13-14.

NEVIN, K. & RAJAMOHAN, T. J. C. B. 2004. Beneficial effects of virgin coconut oil on lipid parameters and in vitro LDL oxidation. 37**,** 830-835.

NEWMAN, J. C. & VERDIN, E. 2017. β-Hydroxybutyrate: A Signaling Metabolite. *Annual Review of Nutrition,* 37**,** 51-76.
NEWPORT, M. T., VANITALLIE, T. B., KASHIWAYA, Y., KING, M. T. & VEECH, R. L. 2015. A new way to produce hyperketonemia: Use of ketone ester in a case of Alzheimer's disease. *Alzheimer's & Dementia,* 11**,** 99-103.
NG, D. S., WONG, N. C. & HEGELE, R. A. J. N. R. E. 2013. HDL—is it too big to fail? 9**,** 308-312.
NIERKENS, V., HARTMAN, M. A., NICOLAOU, M., VISSENBERG, C., BEUNE, E. J., HOSPER, K., VAN VALKENGOED, I. G. & STRONKS, K. J. P. O. 2013. Effectiveness of cultural adaptations of interventions aimed at smoking cessation, diet, and/or physical activity in ethnic minorities. A systematic review. 8**,** e73373.
NORDLUND, A., ROLSTAD, S., HELLSTRÖM, P., SJÖGREN, M., HANSEN, S. & WALLIN, A. 2005. The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition. *Journal of Neurology, Neurosurgery & Psychiatry,* 76**,** 1485-1490.
NOTKOLA, I.-L., SULKAVA, R., PEKKANEN, J., ERKINJUNTTI, T., EHNHOLM, C., KIVINEN, P., TUOMILEHTO, J. & NISSINEN, A. J. N. 1998. Serum total cholesterol, apolipoprotein E {FC12} e4 allele, and Alzheimer's disease. 17**,** 14-20.
NUGENT, S. 2014. Brain energy metabolism in older adults : implications for the risk of age-related cognitive decline. *Métabolisme énergétique du cerveau chez les personnes âgées : implications pour le risque de déclin cognitif lié au vieillissement.*
NUTRITICS 2019. Research Edition (V5.09). Dublin.
NVIVO 2020. QSR International Pty Ltd. 12 ed.
O'CATHAIN, A., CROOT, L., DUNCAN, E., ROUSSEAU, N., SWORN, K., TURNER, K. M., YARDLEY, L. & HODDINOTT, P. 2019. Guidance on how to develop complex interventions to improve health and healthcare. *BMJ open,* 9**,** e029954.
O'CATHAIN, A., MURPHY, E. & NICHOLL, J. 2007. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. *BMC Health Services Research,* 7**,** 85.
OBEID, J. S., BESKOW, L. M., RAPE, M., GOURIPEDDI, R., BLACK, R. A., CIMINO, J. J., EMBI, P. J., WENG, C., MARNOCHA, R., BUSE, J. B. J. J. O. C. & SCIENCE, T. 2017. A survey of practices for the use of electronic health records to support research recruitment. 1**,** 246-252.
OCLOO, J. E. & FULOP, N. J. 2012. Developing a 'critical'approach to patient and public involvement in patient safety in the NHS: learning lessons from other parts of the public sector? *Health Expectations,* 15**,** 424-432.
OHNUMA, T., TODA, A., KIMOTO, A., TAKEBAYASHI, Y., HIGASHIYAMA, R., TAGATA, Y., ITO, M., OTA, T., SHIBATA, N. & ARAI, H. 2016. Benefits of use, and tolerance of, medium-chain triglyceride medical food in the management of Japanese patients with Alzheimer's disease: a prospective, open-label pilot study. *Clinical Interventions In Aging,* 11**,** 29-36.
OLSSON, E., KARLSTRÖM, B., KILANDER, L., BYBERG, L., CEDERHOLM, T. & SJÖGREN, P. 2015. Dietary patterns and cognitive dysfunction in a 12-year follow-up study of 70 year old men. *Journal of Alzheimer's Disease,* 43**,** 109-119.
ORSAVOVA, J., MISURCOVA, L., AMBROZOVA, J. V., VICHA, R. & MLCEK, J. 2015. Fatty acids composition of vegetable oils and its contribution to dietary energy intake and dependence of cardiovascular mortality on dietary intake of fatty acids. *International journal of molecular sciences,* 16**,** 12871-12890.
ORSMOND, G. I., COHN, E. S. J. O. O., PARTICIPATION & HEALTH 2015. The distinctive features of a feasibility study: Objectives and guiding questions. 35**,** 169-177.
OTA, M., MATSUO, J., ISHIDA, I., HATTORI, K., TERAISHI, T., TONOUCHI, H., ASHIDA, K., TAKAHASHI, T. & KUNUGI, H. 2016. Effect of a ketogenic meal on cognitive function in elderly adults: potential for cognitive enhancement. *Psychopharmacology,* 233**,** 3797-3802.
OUSSEDIK, E., CLINE, A., SU, J. J., MASICAMPO, E. J., KAMMRATH, L. K., IP, E. & FELDMAN, S. R. 2019. Accountability in patient adherence. *Patient Prefer Adherence,* 13**,** 1511-1517.

OVERTON, M., PIHLSGÅRD, M. & ELMSTÅHL, S. J. C. P. 2016. Test administrator effects on cognitive performance in a longitudinal study of ageing. 3**,** 1260237.
OWEN, O., MORGAN, A., KEMP, H., SULLIVAN, J., HERRERA, M. & CAHILL, G. J. 1967. Brain metabolism during fasting. *The Journal of clinical investigation,* 46**,** 1589-1595.
PAN, J. W., ROTHMAN, D. L., BEHAR, K. L., STEIN, D. T. & HETHERINGTON, H. P. 2000. Human brain β-hydroxybutyrate and lactate increase in fasting-induced ketosis. *Journal of Cerebral Blood Flow & Metabolism,* 20**,** 1502-1507.
PATEL, M. X., DOKU, V. & TENNAKOON, L. J. A. I. P. T. 2003. Challenges in recruitment of research participants. 9**,** 229-238.
PERKINS, M., WOLF, A. B., CHAVIRA, B., SHONEBARGER, D., MECKEL, J. P., LEUNG, L., BALLINA, L., LY, S., SAINI, A., JONES, T. B., VALLEJO, J., JENTARRA, G. & VALLA, J. 2016. Altered Energy Metabolism Pathways in the Posterior Cingulate in Young Adult Apolipoprotein E ε4 Carriers. *Journal of Alzheimer's disease : JAD,* 53**,** 95-106.
PETERS, R., PETERS, J., BOOTH, A. & ANSTEY, K. J. 2020. Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review. *The British Journal of Psychiatry,* 216**,** 16-28.
PHE 2016. Government recommendations for energy and nutrients for males and females aged 1 – 18 years and 19+ years.
PHE 2018. National Diet and Nutrition Survey: Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016). *In:* HEALTH, P. (ed.). PHE publications.
PHELPS, M. E., HUANG, S., HOFFMAN, E., SELIN, C., SOKOLOFF, L. & KUHL, D. E. 1979. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18) 2-fluoro-2-deoxy-D-glucose: validation of method. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 6**,** 371-388.
PHILLIPS, M. C., DEPREZ, L. M., MORTIMER, G., MURTAGH, D. K., MCCOY, S., MYLCHREEST, R., GILBERTSON, L. J., CLARK, K. M., SIMPSON, P. V. & MCMANUS, E. J. 2021a. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. *Alzheimer's research & therapy,* 13**,** 1-12.
PHILLIPS, M. C. L., DEPREZ, L. M., MORTIMER, G. M. N., MURTAGH, D. K. J., MCCOY, S., MYLCHREEST, R., GILBERTSON, L. J., CLARK, K. M., SIMPSON, P. V., MCMANUS, E. J., OH, J.-E., YADAVARAJ, S., KING, V. M., PILLAI, A., ROMERO-FERRANDO, B., BRINKHUIS, M., COPELAND, B. M., SAMAD, S., LIAO, S. & SCHEPEL, J. A. C. 2021b. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. *Alzheimer's Research & Therapy,* 13**,** 51.
PIROLI, G. G., GRILLO, C. A., REZNIKOV, L. R., ADAMS, S., MCEWEN, B. S., CHARRON, M. J. & REAGAN, L. P. 2007. Corticosterone impairs insulin-stimulated translocation of GLUT4 in the rat hippocampus. *Neuroendocrinology,* 85**,** 71-80.
RAFTERY, J., YOUNG, A., STANTON, L., MILNE, R., COOK, A., TURNER, D. & DAVIDSON, P. J. H. T. A. 2015. Clinical trial metadata: defining and extracting metadata on the design, conduct, results and costs of 125 randomised clinical trials funded by the National Institute for Health Research Health Technology Assessment programme. 19**,** 1-166.
REBELLO, C. J., KELLER, J. N., LIU, A. G., JOHNSON, W. D. & GREENWAY, F. L. 2015. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. *BBA Clinical,* 3**,** 123-125.
REED, B., VILLENEUVE, S., MACK, W., DECARLI, C., CHUI, H. C. & JAGUST, W. J. J. N. 2014. Associations between serum cholesterol levels and cerebral amyloidosis. 71**,** 195-200.
REGER, M. A., HENDERSON, S. T., HALE, C., CHOLERTON, B., BAKER, L. D., WATSON, G. S., HYDE, K., CHAPMAN, D. & CRAFT, S. 2004. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiology of Aging,* 25**,** 311-314.
RENTZ, D. M., DEKHTYAR, M., SHERMAN, J., BURNHAM, S., BLACKER, D., AGHJAYAN, S. L., PAPP, K. V., AMARIGLIO, R. E., SCHEMBRI, A. & CHENHALL, T. J. T. J. O. P. O. A. S. D. 2016. The feasibility of at-home iPad cognitive testing for use in clinical trials. 3**,** 8.

RICHARD, C., COUTURE, P., OOI, E. M., TREMBLAY, A. J., DESROCHES, S., CHAREST, A., LICHTENSTEIN, A. H. & LAMARCHE, B. 2014. Effect of Mediterranean diet with and without weight loss on apolipoprotein B100 metabolism in men with metabolic syndrome. *Arteriosclerosis, thrombosis, and vascular biology,* 34**,** 433-438.

RICHARDSON, C., STEPHAN, B. C. M., ROBINSON, L., BRAYNE, C., MATTHEWS, F. E., COGNITIVE, F. & AGEING STUDY, C. 2019. Two-decade change in prevalence of cognitive impairment in the UK. *European Journal of Epidemiology,* 34**,** 1085-1092.

ROSEN, W. G., MOHS, R. C. & DAVIS, K. L. J. T. A. J. O. P. 1984. A new rating scale for Alzheimer's disease.

SAMIERI, C., GRODSTEIN, F., ROSNER, B. A., KANG, J. H., COOK, N. R., MANSON, J. E., BURING, J. E., WILLETT, W. C. & OKEREKE, O. I. 2013. Mediterranean diet and cognitive function in older age: results from the Women's Health Study. *Epidemiology (Cambridge, Mass.),* 24**,** 490.

SAMPSON, E. L. 2012. Frailty and dementia: common but complex comorbidities. Taylor & Francis.

SÁNCHEZ-CUBILLO, I., PERIÁÑEZ, J. A., ADROVER-ROIG, D., RODRÍGUEZ-SÁNCHEZ, J. M., RÍOS-LAGO, M., TIRAPU, J. & BARCELÓ, F. 2009. Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society,* 15**,** 438-450.

SÁNCHEZ-IZQUIERDO, M. & FERNÁNDEZ-BALLESTEROS, R. 2021. Cognition in healthy aging. *International journal of environmental research and public health,* 18**,** 962.

SANDERS, M. L., STUCKENSCHNEIDER, T., DEVENNEY, K. E., LAWLOR, B., SCHNEIDER, S., OLDE RIKKERT, M. G. M. & ON BEHALF OF THE NEUROEXERCISE STUDY, G. 2018. Real World Recruiting of Older Subjects with Mild Cognitive Impairment for Exercise Trials: Community Readiness is Pivotal. *Journal of Alzheimer's Disease,* 62**,** 579-581.

SANTACROCE, S. J., MACCARELLI, L. M. & GREY, M. J. N. R. 2004. Intervention fidelity. 53**,** 63-66.

SCARMEAS, N., ANASTASIOU, C. A. & YANNAKOULIA, M. 2018. Nutrition and prevention of cognitive impairment. *The Lancet Neurology,* 17**,** 1006-1015.

SCARMEAS, N., STERN, Y., TANG, M. X., MAYEUX, R. & LUCHSINGER, J. A. 2006. Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 59**,** 912-921.

SCHIFFMAN, S. S. 1997. Taste and smell losses in normal aging and disease. *JAMA,* 278**,** 1357-1362.

SCHOLTE, H. & GROOT, P. 1975. Organ and intracellular localization of short-chain acyl-CoA synthetases in rat and guinea-pig. *Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism,* 409**,** 283-296.

SCHÖNFELD, P. & WOJTCZAK, L. J. J. O. L. R. 2016. Short-and medium-chain fatty acids in energy metabolism: the cellular perspective. 57**,** 943-954.

SHEEHAN, J. P., SWERDLOW, R. H., MILLER, S. W., DAVIS, R. E., PARKS, J. K., PARKER, W. D. & TUTTLE, J. B. 1997. Calcium homeostasis and reactive oxygen species production in cells transformed by mitochondria from individuals with sporadic Alzheimer's disease. *Journal of Neuroscience,* 17**,** 4612-4622.

SIERVO, M., SHANNON, O. M., LLEWELLYN, D. J., STEPHAN, B. C. M. & FONTANA, L. 2021. Mediterranean diet and cognitive function: From methodology to mechanisms of action. *Free Radical Biology and Medicine,* 176**,** 105-117.

SILVA, D. F., SELFRIDGE, J. E., LU, J., E, L., ROY, N., HUTFLES, L., BURNS, J. M., MICHAELIS, E. K., YAN, S. & CARDOSO, S. M. 2013. Bioenergetic flux, mitochondrial mass and mitochondrial morphology dynamics in AD and MCI cybrid cell lines. *Human molecular genetics,* 22**,** 3931-3946.

SILVA, D. F., SELFRIDGE, J. E., LU, J., LEZI, E., CARDOSO, S. M. & SWERDLOW, R. H. 2012. Mitochondrial abnormalities in Alzheimer's disease: possible targets for therapeutic intervention. *Advances in pharmacology,* 64**,** 83-126.

SIMPSON, I. A., CHUNDU, K. R., DAVIES-HILL, T., HONER, W. G. & DAVIES, P. 1994. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with

Alzheimer's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 35**,** 546-551.
SIMS, N. R., BLASS, J. P., MURPHY, C., BOWEN, D. M. & NEARY, D. 1987. Phosphofructokinase activity in the brain in Alzheimer's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 21**,** 509-510.
SKIVINGTON, K., MATTHEWS, L., CRAIG, P., SIMPSON, S. & MOORE, L. J. T. L. 2018. Developing and evaluating complex interventions: updating Medical Research Council guidance to take account of new methodological and theoretical approaches. 392**,** S2.
SKIVINGTON, K., MATTHEWS, L., SIMPSON, S. A., CRAIG, P., BAIRD, J., BLAZEBY, J. M., BOYD, K. A., CRAIG, N., FRENCH, D. P. & MCINTOSH, E. J. B. 2021. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *bmj,* 374.
SMALL, S. A., NAVA, A. S., PERERA, G. M., DELAPAZ, R. & STERN, Y. 2000. Evaluating the function of hippocampal subregions with high-resolution MRI in Alzheimer's disease and aging. *Microscopy research and technique,* 51**,** 101-108.
SMITASIRI, S., UAUY, R. J. F. & BULLETIN, N. 2007. Beyond recommendations: implementing food-based dietary guidelines for healthier populations. 28**,** S141-S151.
SOKOLOFF, L. 1999. Energetics of functional activation in neural tissues. *Neurochemical research,* 24**,** 321-329.
SOLFRIZZI, V., PANZA, F., FRISARDI, V., SERIPA, D., LOGROSCINO, G., IMBIMBO, B. P. & PILOTTO, A. 2011. Diet and Alzheimer's disease risk factors or prevention: the current evidence. *Expert Review of Neurotherapeutics,* 11**,** 677-708.
STANFIELD, C. L. 2012. *Principles of human physiology*, Pearson Higher Ed.
STOLBERG, H. O., NORMAN, G. & TROP, I. J. A. J. O. R. 2004. Randomized controlled trials. 183**,** 1539-1544.
SWERDLOW, R. H. 2011. Role and treatment of mitochondrial DNA-related mitochondrial dysfunction in sporadic neurodegenerative diseases. *Current pharmaceutical design,* 17**,** 3356.
SWERDLOW, R. H. 2012. Mitochondria and cell bioenergetics: increasingly recognized components and a possible etiologic cause of Alzheimer's disease. *Antioxidants & redox signaling,* 16**,** 1434-1455.
SWERDLOW, R. H., BURNS, J. M. & KHAN, S. M. 2010. The Alzheimer's disease mitochondrial cascade hypothesis. *Journal of Alzheimer's Disease,* 20**,** S265-S279.
SWERDLOW, R. H., BURNS, J. M. & KHAN, S. M. 2014. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease,* 1842**,** 1219-1231.
SWERDLOW, R. H. & KHAN, S. M. 2004. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Medical hypotheses,* 63**,** 8-20.
SWERDLOW, R. H., KOPPEL, S., WEIDLING, I., HAYLEY, C., JI, Y. & WILKINS, H. M. 2017. Mitochondria, Cybrids, aging, and Alzheimer's disease. *Progress in molecular biology and translational science,* 146**,** 259-302.
SWERDLOW, R. H. & NEWELL, K. L. 2012. "Untangling" the relationship between Alzheimer disease and dementia with Lewy bodies. AAN Enterprises.
TANG, E. Y. H., HARRISON, S. L., ALBANESE, E., GORMAN, T. J., RUTJES, A. W. S., SIERVO, M. & STEPHAN, B. 2015. Dietary interventions for prevention of dementia in people with mild cognitive impairment. *Cochrane Database of Systematic Reviews*.
TANGNEY, C. C., LI, H., WANG, Y., BARNES, L., SCHNEIDER, J. A., BENNETT, D. A. & MORRIS, M. C. 2014. Relation of DASH-and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology,* 83**,** 1410-1416.
TASHAKKORI, A., TEDDLIE, C. & TEDDLIE, C. B. 1998. *Mixed methodology: Combining qualitative and quantitative approaches*, Sage (USA).

TAYLOR, M. K. 2018. *Influence of diet in Alzheimer's Disease: The role of carbohydrate intake and ketogenic therapy.* 78, ProQuest Information & Learning.
TEDDLIE, C. & TASHAKKORI, A. J. R. I. T. S. 2006. A general typology of research designs featuring mixed methods. 13**,** 12-28.
THABANE, L., MA, J., CHU, R., CHENG, J., ISMAILA, A., RIOS, L. P., ROBSON, R., THABANE, M., GIANGREGORIO, L. & GOLDSMITH, C. H. J. B. M. R. M. 2010. A tutorial on pilot studies: the what, why and how. 10**,** 1-10.
THOMAS, K. R., EPPIG, J., EDMONDS, E. C., JACOBS, D. M., LIBON, D. J., AU, R., SALMON, D. P. & BONDI, M. W. 2018. Word-list intrusion errors predict progression to mild cognitive impairment. *Neuropsychology,* 32**,** 235-245.
THORPE, K. E., ZWARENSTEIN, M., OXMAN, A. D., TREWEEK, S., FURBERG, C. D., ALTMAN, D. G., TUNIS, S., BERGEL, E., HARVEY, I. & MAGID, D. J. J. J. O. C. E. 2009. A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. 62**,** 464-475.
THURMOND, V. A. 2001. The point of triangulation. *Journal of nursing scholarship,* 33**,** 253-258.
TICKLE-DEGNEN, L. J. A. J. O. O. T. 2013. Nuts and bolts of conducting feasibility studies. 67**,** 171-176.
TIMLIN, D., MCCORMACK, J. M., KERR, M., KEAVER, L. & SIMPSON, E. E. J. B. P. H. 2020. Are dietary interventions with a behaviour change theoretical framework effective in changing dietary patterns? A systematic review. 20**,** 1-18.
TOOBERT, D. J., STRYCKER, L. A., GLASGOW, R. E., BARRERA, M. & ANGELL, K. 2005. Effects of the mediterranean lifestyle program on multiple risk behaviors and psychosocial outcomes among women at risk for heart disease. *Annals of Behavioral Medicine,* 29**,** 128-137.
TRAN-DINH, A., DIALLO, D., DELBOSC, S., VARELA-PEREZ, L. M., DANG, Q., LAPERGUE, B., BURILLO, E., MICHEL, J., LEVOYE, A. & MARTIN-VENTURA, J. J. B. J. O. P. 2013. HDL and endothelial protection. 169**,** 493-511.
TREWEEK, S. & ZWARENSTEIN, M. J. T. 2009. Making trials matter: pragmatic and explanatory trials and the problem of applicability. 10**,** 1-9.
TRICCO, A. C., LILLIE, E., ZARIN, W., O'BRIEN, K. K., COLQUHOUN, H., LEVAC, D., MOHER, D., PETERS, M. D., HORSLEY, T. & WEEKS, L. 2018. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of internal medicine,* 169**,** 467-473.
TU, S., WONG, S., HODGES, J. R., IRISH, M., PIGUET, O. & HORNBERGER, M. J. C. 2015. Lost in spatial translation–A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. 67**,** 83-94.
TUNIS, S. R., STRYER, D. B. & CLANCY, C. M. J. J. 2003. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. 290**,** 1624-1632.
TURAN, S., OMAR, A. & BEREKET, A. J. A. D. 2008. Comparison of capillary blood ketone measurement by electrochemical method and urinary ketone in treatment of diabetic ketosis and ketoacidosis in children. 45**,** 83-85.
UNITED NATIONS 1982. Provisional guidelines on standard international age classifications. *statistical papers.* United Nations.
VANDENBERGHE, C., ST-PIERRE, V., FORTIER, M., CASTELLANO, C.-A., CUENOUD, B. & CUNNANE, S. C. 2020. Medium Chain Triglycerides Modulate the Ketogenic Effect of a Metabolic Switch. *Frontiers in Nutrition,* 7.
VANZELLA, L. M., ROUSE, V., AJWANI, F., DEILAMI, N., POKOSH, M., OH, P. & GHISI, G. L. D. M. 2021. Barriers and facilitators to participant adherence of dietary recommendations within comprehensive cardiac rehabilitation programmes: a systematic review. *Public Health Nutrition,* 24**,** 4823-4839.
VAPORTZIS, E., GIATSI CLAUSEN, M. & GOW, A. J. J. F. I. P. 2017. Older adults perceptions of technology and barriers to interacting with tablet computers: a focus group study. 8**,** 1687.
VARTIAINEN, E., LAATIKAINEN, T., PELTONEN, M., JUOLEVI, A., MÄNNISTÖ, S., SUNDVALL, J., JOUSILAHTI, P., SALOMAA, V., VALSTA, L. & PUSKA, P. 2009. Thirty-five-year trends in cardiovascular risk factors in Finland. *International journal of epidemiology,* 39**,** 504-518.

VAUZOUR, D., CAMPRUBI-ROBLES, M., MIQUEL-KERGOAT, S., ANDRES-LACUEVA, C., BÁNÁTI, D., BARBERGER-GATEAU, P., BOWMAN, G. L., CABERLOTTO, L., CLARKE, R. & HOGERVORST, E. 2017. Nutrition for the ageing brain: towards evidence for an optimal diet. *Ageing research reviews,* 35**,** 222-240.

VIERA, A. J. & BANGDIWALA, S. I. 2007. Eliminating bias in randomized controlled trials: importance of allocation concealment and masking. *FAMILY MEDICINE-KANSAS CITY-,* 39**,** 132.

WASAN, A. D. 2014. Efficacy vs Effectiveness and Explanatory vs Pragmatic: Where Is the Balance Point in Pain Medicine Research? *Pain Medicine,* 15**,** 539-540.

WECHSLER, D. 2010. *Wechsler Adult Intelligence Scale - Fourth UK Edition (WAIS-IV UK)* [Online]. Available: https://www.pearsonclinical.co.uk/Psychology/AdultCognitionNeuropsychologyandLanguage/AdultGeneralAbilities/WechslerAdultIntelligenceScale-FourthUKEdition(WAIS-IVUK)/WechslerAdultIntelligenceScale-FourthUKEdition(WAIS-IVUK).aspx [Accessed].

WEIR, C. B. & JAN, A. 2019. BMI classification percentile and cut off points.

WESTMAN, E. C., FEINMAN, R. D., MAVROPOULOS, J. C., VERNON, M. C., VOLEK, J. S., WORTMAN, J. A., YANCY, W. S. & PHINNEY, S. D. 2007. Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr,* 86.

WESTMAN, E. C., MAVROPOULOS, J., YANCY, W. S. & VOLEK, J. S. 2003. A review of low-carbohydrate ketogenic diets. *Current Atherosclerosis Reports,* 5**,** 476-483.

WHO 2017. Global action plan on the public health response to dementia 2017–2025.

WILKINS, H. M., CARL, S. M. & SWERDLOW, R. H. 2014. Cytoplasmic hybrid (cybrid) cell lines as a practical model for mitochondriopathies. *Redox biology,* 2**,** 619-631.

WILLIAMS, M. S. & TUROS, E. 2021. The Chemistry of the Ketogenic Diet: Updates and Opportunities in Organic Synthesis. *International Journal of Molecular Sciences,* 22**,** 5230.

WILLIAMSON, J. R., BROWNING, E. & OLSON, M. 1968. Interrelations between fatty acid oxidation and the control of gluconeogenesis in perfused rat liver. *Advances in enzyme regulation,* 6**,** 67-100.

WŁODAREK, D. 2019. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). *Nutrients,* 11**,** 169.

WOOD, W., NEAL, D. T. J. B. S. & POLICY 2016. Healthy through habit: Interventions for initiating & maintaining health behavior change. 2**,** 71-83.

WU, L. & SUN, D. 2017. Adherence to Mediterranean diet and risk of developing cognitive disorders: an updated systematic review and meta-analysis of prospective cohort studies. *Scientific reports,* 7**,** 1-9.

XIANG, A. S., KINGWELL, B. A. J. T. L. D. & ENDOCRINOLOGY 2019. Rethinking good cholesterol: a clinicians' guide to understanding HDL. 7**,** 575-582.

XIAO, F., ZHOU, P., LYU, Y., ZHONG, X. & ZHANG, C. 2021. Nutritional status of elderly dementia patients in a memory clinic and analysis of related factors. *Chinese Journal of Geriatrics***,** 1368-1371.

Appendices:

Appendix 1: Study Protocol

Project summary:

Research has shown that neurodegeneration associated with ageing could be attributed to glucose hypo-metabolism by brain cells. Therefore, providing an alternative source of energy to the brain cells could reduce neurodegeneration and consequently, dementia in individuals with Mild Cognitive Impairment (MCI). The current study will investigate the use of an alternative energy source in the form of coconut oil, rich in medium chain fatty acids (MCFA) that are converted into ketone bodies in the human body. The process of ketogenesis to increase energy supply to the brain will be induced by consuming coconut oil in adults diagnosed with MCI.

Empirical evidence to date has demonstrated associations between nutrition and cognitive impairments in older adults specifically with the relation between glucose hypo-metabolism and neurodegeneration. Studies have suggested that interventions in the earliest stages of dementia such as in MCI, may delay the progression of the disease as MCI could represent the final point at which an intervention is effective. Previous studies have used Medium Chain Triglycerides (MCTs) as a source of ketone bodies to improve cognitive functions in older adults with MCI or Alzheimer's disease. However, the current study relies on the consumption of the whole food component (coconut oil) that is rich in MCFA, in adults with MCI.

Aim: A study evaluating the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in adults with MCI.

Objectives:

Primary Objectives:

1. To estimate the adherence rate of adults with MCI to dietary coconut oil intake.
2. To test the procedures of the intervention (accuracy of self-reported adherence, delivery of the intervention, recording and monitoring of adverse events, estimate recruitment and retention rates, and refine the selection of outcome measures in preparation for a Randomised Controlled Trial that would test the effectiveness of the intervention).
3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future Randomised Controlled Trial.
4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.

1. To determine the acceptability of randomisation and of the intervention in participants with MCI and obtain feedback about the study procedure from service users.

Secondary Objectives:

1. To provide preliminary estimates of the clinical effect of dietary coconut oil on cognitive functions in adults with MCI compared to the control group.
   Outcome measures to be considered:
   a. Difference in the cognitive executive measures in adults with MCI taking coconut oil. A composite measure can be calculated based on individual scores from the following tests: 1) Trail Making; 2) Verbal Fluency; 3) Category Fluency; 4) Digit Symbol; 5) Digit Span)
   b. Differences in overall cognitive measures in adults with MCI (Measured using the Addenbrookes Cognitive Examination (ACE- III or mACE)).
   c. Differences in memory measures in participants with MCI. (A composite measure can be calculated based on individual scores from the following tests: 1) verbal memory (Word List from the WMS-III); 2) Scores from the Super-market task and/or Sea-Hero Quest.)

2. To provide preliminary estimates of the potential effect of dietary coconut oil on quality of life in adults with MCI (by using Alzheimer's disease cooperative study- mild cognitive impairment- activities of daily life (ADCS-MCI-ADL) test).

3. To investigate the dietary energy and macronutrient (carbohydrate, fat, and protein) intake of adults with MCI.

Methodology: This will be a feasibility study that will follow a randomized clinical trial design. It will allow the unbiased evaluation of the adherence rate and effect of the dietary intervention on cognitive functions of adults with MCI. Mixed methods using quantitative and qualitative methodologies will be used in the study. Data collection methods will consist of questionnaires, focus groups/interviews, food records, cognitive tests (ACE III, trail making test, verbal fluency test, category fluency tests), quality of life questionnaire (ADCS-MCI-ADL), and finger prick blood tests (beta hydroxyl butyrate).

Outputs/impact: Results from this study could help determine whether such an intervention is applicable in adults with MCI. It will provide new knowledge relating to the feasibility of the implementation of such an intervention, to guide and inform the design of a randomised controlled trial (RCT) that is adequately powered, and evidence based. The RCT could provide a dietary intervention that might have the potential to improve cognitive functions and maintain quality of life for longer in people with MCI, by delaying the onset of dementia and reducing the progression from MCI to Alzheimer's Disease (AD) in adults.

FULL TITLE OF THE STUDY

A study evaluating the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in adults with Mild Cognitive Impairment.

SHORT STUDY TITLE / ACRONYM

The effect of vegetable oil on cognitive functions in MCI patients

DICe- Dietary intervention on cognitive functions

PROTOCOL VERSION NUMBER AND DATE

Version: V3

Date 25/09/2019

IRAS Number: 240254

Study Number: 1718/RASREZ/1

Key Study Contacts

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STUDY SUMMARY

Study Title	**A study evaluating the feasibility of undertaking an int looking into the effect of vegetable oils intake on cogn quality of life in adults with Mild Cognitive Impairment**
Internal ref. no. (or short title)	DICe
Study Design	Randomized Controlled Trial
Study Participants	Adults with Mild Cognitive Impairment
Planned Size of Sample (if applicable)	Sixty participants
Planned Study Period	Six months
Research Aim/ Questions:	**Aim:** Evaluating the feasibility of undertaking an int looking into the effect of vegetable oils intake on c and quality of life in adults with MCI. Can adults with MCI adhere to a dietary interventio coconut oil? Can older adults with MCI adhere to the randomisa dietary intervention? What are the views of adults with MCI on a dietary intervention using coconut oil?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**NON-FINANCIAL SUPPORT GIVEN** Support in identification of participants.
Dorset Healthcare University NHS Foundation Trust	Kimmeridge Court 71 Haven Road, Canford Cliffs, Poole, Dorset, BH13 7LN

ROLE OF STUDY SPONSOR AND FUNDER

The sponsor of the study is Bournemouth University; the University is funding the study and will be assuming overall responsibility for the initiation and management of the study.

The sponsor can be defined as the company, institution, or organisation assuming overall responsibility for the initiation and management of the study and is not necessarily the main funder. Identification of the study sponsor provides transparency and accountability. As sponsor for the study, Bournemouth University is the main data controller, and as such will own the data arising from the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Members from Bournemouth University have contributed to the development of the study protocol. The research study will be monitored by Governance staff from Bournemouth University to ensure that it is being conducted in accordance with the protocol, the UK Policy and Framework for Health and Social Care Research and GCP guidelines.

Patient Public Involvement:

A group of individuals with varying stages of dementia where approached by the researcher, during an event conducted by Dorset Healthcare University NHS Foundation Trust. Individuals were informed about the study and provided some feedback regarding their willingness to potentially participate in such a study.

Moreover, a summary of the study was sent to an individual with MCI, and feedback was provided regarding the study procedure and outcome measures.

Adverse events:

In case of any adverse events or accidents, the sponsor will be notified within 24 hours. The research team (supervisors and the researcher) will communicate with participant's GP to make a decision to withdraw said participant. In case of a pattern of events, decision will be made within the research team to stop the intervention. Bournemouth University holds Public liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University.

KEY WORDS:

MCI: Mild Cognitive Impairment

AD: Alzheimer's disease

MCT: Medium chain triglycerides

MCFA: Medium Chain Fatty Acids

STUDY PROTOCOL

The effect of vegetable oil on cognitive functions in MCI patients

Background:

With an ageing population, there is an increasing prevalence of dementia on both a national and international scale (Alzheimer'society 2011; WHO 2012). Currently in the UK there is an estimated 850,000 people living with dementia and this number is projected to increase to over 1 million by 2025, and to over 2 million by 2051 (Prince et al. 2013). Prevention and risk reduction of dementia are essential to reduce the impact and prevalence of this public health problem, and to improve quality of life, as there is no known cure for dementia. Multiple studies have been done on prevention and risk reduction of dementia, and there has been an increased interest in the relation between dementia and nutrition. Researchers have looked into the relation between whole diets (Mediterranean diet, Dietary Approaches to stop Hypertension (DASH) diet) and risk reduction (Solfrizzi et al. 2011; B. Allès 2012; Tang et al. 2015) while other studies focused on ketogenic diets due to the increased interest in understanding glucose and ketone metabolism in older adults (Freemantle et al. 2006; Ota et al. 2016). It has been proposed that dietary interventions in the earliest stages of dementia such as in MCI may delay its progression, as MCI could represent the final point at which an intervention is effective (Krikorian et al. 2012). Cognitive impairments that don't affect social functions or activities of daily life are considered mild cognitive impairments which are associated with an increased risk of progression to dementia (Petersen et al. 2001), and decreased quality of life (Tabert et al. 2002). Studies have demonstrated an association between nutrition and cognitive functions (Freemantle et al. 2006; Costantini et al. 2008; B. Allès 2012) through complex pathways which present opportunities for dietary interventions, as they suggest a relation between neurodegeneration and low glucose utilisation in the brain of older adults. Pre-symptomatic brain glucose hypo-metabolism occurs long before cognitive impairment symptoms are observed (Craft et al. 2000; Cunnane et al. 2011; Croteau et al. 2017), which means that it could potentially be the factor that contributes or progresses cognitive decline in older adults (Cunnane et al. 2011). The reduction of AD and its risk factors, rely on improving energy uptake by the brain. This could be achieved either by improving or bypassing systematic glucose metabolism in the brain by inducing ketosis to increase ketone availability for the brain cells (Cunnane et al. 2011). Ketones are the by-products of the breakdown of fatty acids in the body beta-hydroxybutyrate and acetoacetate are two forms of ketone bodies that can be used as a back-up fuel for the brain when glucose supply is insufficient (Sokoloff 1999).

Rationale:

Clinical trials have demonstrated that nutritional ketosis, that increases ketone availability to the brain, has beneficial cognitive effects in individuals with mild to moderate AD and MCI (Reger et al. 2004; Henderson et al. 2009; Krikorian et al. 2012; Rebello et al. 2015; De la Rubia Ortí et al. 2017). Nutritional ketosis can be achieved by high fat ketogenic diets or by the supplementation with Medium Chain triglycerides (MCT) or medium chain fatty acids (MCFA) that enhance the formation of ketones in the body (Krikorian et al. 2012). This study aims at using coconut oil which is a rich source of MCFA (62-70% of its composition) (Fernando et al., 2015) to increase ketone availability for brain cells. It is hoped that by using coconut oil, this might help reduce cognitive decline in patients with MCI and slow their progression into dementia.

Aim of research:

A study evaluating the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in adults with MCI.

Research Questions:

Can adults with MCI adhere to a dietary intervention using vegetable oil?

Can adults with MCI adhere to the randomisation of the dietary intervention?

What are the views of adults with MCI on a dietary intervention using vegetable oil?

Primary Objectives:

1. To estimate adherence rate of adults with MCI to dietary oil intake.
2. To test the procedures of the intervention (accuracy of self-reported adherence, delivery of the intervention, recording and monitoring of adverse events, estimate recruitment and retention rates, and refine the selection of outcome measures in preparation for an RCT that would test the effectiveness of the intervention).
3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future Randomised Control Trial.
4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.
5. To determine the acceptability of randomisation and of the intervention in participants with MCI and obtain feedback about the study procedure from study participants.

Secondary Objectives:

1. To provide preliminary estimates of the clinical effect of dietary coconut oil on cognitive functions in adults with MCI.
   Outcome measures to be considered:

a. Difference in the cognitive executive measures in adults with MCI taking coconut oil. (A composite measure can be calculated based on individual scores from the following tests: 1) Trail Making; 2) Verbal Fluency; 3) Category Fluency; 4) Digit Symbol; 5) Digit Span)
b. Differences in overall cognitive measures in adults with MCI (Measured using the Addenbrookes Cognitive Examination (ACE- III or mACE)).
c. Differences in memory measures in participants with MCI. (A composite measure can be calculated based on individual scores from the following test: 1) verbal memory (Word List from the WMS-III); 2) Scores from the Super-market task and/or Sea-Hero Quest.)

2. To provide preliminary estimates of the potential effect of dietary coconut oil on quality of life in adults with MCI (by using ADCS-MCI-ADL).

3. To investigate the dietary energy and macronutrient (carbohydrate, fat, and protein) intake of adults with MCI.

Study design/ Methodology:

Adults diagnosed with MCI will be recruited from memory clinics through Dorset Health Care University NHS Foundation Trust. Diagnosis should be based on a cognition assessment test (Montreal cognitive assessment test, the Addenbrookes Cognitive Examination) and should have been undertaken within the last year. Participants will be asked to provide fully informed consent through use of the informed consent form.

All participants will meet all of following inclusion but none of the following exclusion criteria:

Inclusion:

- Adults with a confirmed MCI diagnosis within the last year
- Patients above 18 years old.

Exclusion:

- Adults with AD diagnosis will be excluded from the study as the target is adults with MCI.
- Adults who have a confirmed diagnosis of Type I or Type II diabetes will be excluded from the study due to the risks of diabetic ketoacidosis resulting from the induction of ketosis in the body.
- For safety measures potential participants with a history of hypercholesterolemia will be excluded from the study. Coconut oil is rich in saturated fatty acids (Marina et al. 2009) which are associated with dyslipidaemia and cardiovascular diseases (Mensink and Katan 1992; Vartiainen et al. 2009). However, recent studies have shown that MCFA that make up the majority of the saturated fat content (70%) of coconut oil does not affect blood lipid levels (Marten et al. 2006; Assunçao et al. 2009; Fernando et al. 2015). As the absorption of MCFA in the body differs from the absorption of other fat sources; MCFA are directly absorbed from intestine into portal vein and sent directly to the liver. MCFA resists binding to fatty acid binding proteins which reduces their contribution to arterial fat deposits (Fernando et al. 2015). This reduces their impact on the cardiovascular system (Marten et al. 2006; Fernando et al. 2015).

- Adults with neurological disorders (other diagnosed disorders in addition to MCI) will be excluded. Since, neurological disorders affect cognitive functions and the results of cognitive tests used in the study.
- Adults who are unable to communicate in English or those with major physical disabilities (blind, deaf) or unable to use their dominant hand will be excluded. Since, the tests and interviews are all in English and require writing, reading, and understanding English language.
- Adults with coconut allergy.

Sample size:

Due to the feasibility nature of the study and the lack of clinical/statistical references for the cognitive tests used, and their significant effect in relation to ketosis (minimal clinically important difference), it was not possible to conduct a formal sample size calculation. One of the purposes of this study is to provide data for the sample size calculation for a future full-scale trial. The sample size calculation for the current feasibility study is based on estimations of adherence, recruitment and retention rates; along with estimation between subject variability (SD) and within-subject correlation, which are required to estimate the sample size for the future full-scale RCT. A total of 60 participants, with 30 participants in each group will allow the estimation of:

- An adherence rate in each group circa 80% with a 95% confidence interval +/- 14%.
- A recruitment rate circa 50% with a 95% confidence interval +/-9%.
- A retention rate circa 80% with 95% confidence interval +/-10%.
- A between subject standard deviation for a standardised outcome variable (i.e., SD=1) at baseline with 95% confidence interval of (0.85, 1.22).
- A moderate correlation of 0.5 between pre- and post-values would give a 95% CI of (0.38, 0.76), assuming 48 participants with both sets of data.

Study design:

This study will be a feasibility study that aims at evaluating the acceptance and adherence of participants to the intervention. A dietary intervention that relies on the administration of 30 ml of extra virgin coconut oil per day will be utilized in this study. Coconut oil administered will replace the cooking/vegetable oil usually used by the participants. Nutritional ketosis can be achieved by the supplementation of 20-70 g of MCT/day (Krikorian et al. 2012) as coconut oil is made of around 70% MCFA then 30 ml of oil a day will provide 21g/day MCFA.

. The coconut oil intake is consistent with the UK Government dietary recommendations of saturated fat intake which is 29 g/day for males and 23 g/day for females (PHE 2016). According to the National Diet and Nutrition Survey (NDNS), men aged 19-64 years old consume around 1974 kcal/day while those aged 65 and above consume an average of 1940 kcal/day (PHE 2018).

Women aged 19-64 years old consume an average of 1575 kcal/day which is higher than average energy intake of females aged 65 and above which is 1486 kcal/day (PHE 2018). Thus, 30 ml of coconut oil will provide 270 kcal which would contribute 13.6-14% of total fat intake in men (aged 19-64, 65 and above respectively) and 17-18% in women (aged 19-64, 65 and above respectively). According to the NDNS, fat intake in men contributes 32.6-33.7% to their total energy intake (aged 19-64, aged 65 and above respectively). While that of their female counterparts makes up 33.7-33.8 % of their total energy intake (PHE 2018). Thus, a 30 ml consumption of oil will remain within the recommended levels of daily dietary fat intake of adults.

The intervention will last for 6 months, during that time the intake of coconut oil will be determined by monitoring the amount of coconut oil used by the participant. Finger prick blood tests (beta hydroxybutyrate concentrations) will be used as biomarkers of adherence to demonstrate the level of ketone bodies in the blood (Gilbert et al. 2000). At each visit oil will be dispensed in excess of requirements. This will allow the measurement of the returned product, to estimate consumption and adherence levels. This will be done by measuring the returned product, as oil will be dispensed at each visit in excess of requirements and re-issued at every visit. Participants will be contacted by phone at random times during the intervention to check their adherence level (these calls will be documented).

Moreover, cognitive tests and interviews will be conducted during the study period to detect any changes in cognitive functions during the intervention. Cognitive tests will be conducted twice; at baseline before the intervention is initiated, and after 6 months. Focus groups/ interviews and questionnaires will be conducted within the third and sixth months of the intervention, so as to evaluate compliance and gain information on the study process.

Participants will be randomized in blocks of 2, 4 or 6, to the intervention and control groups by using an online randomisation software; Sealed envelope: (**https://www.sealedenvelope.com/**).

The control group will receive the same amount of sunflower oil, which was chosen based on its chemical and nutritional composition. Among vegetable oils, sunflower oil is among the few that are low in omega 3 fatty acids (0.2%) that have been linked to improved cognitive functions of adults (Chiu et al. 2008). Moreover, sunflower oil is low in saturated fats (10.1 %) that have been attributed to dyslipidaemia and cardiovascular diseases (Vartiainen et al. 2009).

The oils used are readily available in health shops and supermarkets. The coconut oil used in the study will be, Lucy Bee organic Extra Virgin Coconut Oil sold by multiple high street retailers. This specific oil was chosen because it is 100% raw and naturally, cold pressed. Moreover, it is suitable for vegetarians and vegans.

As for sunflower oil, the KTC sunflower oil sold by Sainsbury's was chosen since it is a commonly used cooking oil. It is made of 100% pure sunflower oil and suitable for vegetarians and vegans.

The study will also look into the effect of APO E4 genotype on the effects of the intervention. APO E4 screening will be conducted using a buccal swab sample. Results will be available 2 weeks after collection of the sample; the sample will be destroyed after analysis. In case the participants opted into knowing the result of the test; the researcher will arrange a meeting with them to provide them with the results and analysis report. In case they opted-out; they will not be contacted regarding the test after the sample is collected and will not be informed of the results. The results of the APO E4 test will be used in data analysis; to stratify the findings based on the APO E4 status of participants.

Outcome Measures:

Primary outcome measure:

Vegetable oil usage: monitoring the amount of oil used by individuals and the results of Beta hydroxyl butyrate tests will be used to investigate the adherence of participants to the oil consumed. The amount of oil used will be checked after 3 and 6 months, and at random times during the intervention through phone calls. Logs and records of the phone calls will be saved on a password protected computer.

Secondary outcome measures:

Blood samples (beta hydroxyl butyrate): will be collected using Abbott freestyle Optium Neo which is a blood ketone meter at baseline, and after 3 and 6 months of the initiation of the intervention, in order to measure plasma ketone bodies concentrations

Nutrient intake: Four-day food records will be used to explore the dietary energy and macronutrient intake of adults with MCI, at baseline and after 6 months; this will inform the exclusion criteria for the future study.

This will provide information on:

i) The proportion of the dietary fat intake that would be attributed to coconut oil consumption
ii) Participants with high total fat and saturated fat intakes
iii) Total carbohydrate intake which influences the production of ketosis in the body. [Increased carbohydrate intake (>50% of total energy intake) raises

i) blood glucose concentrations and consequently reduces ketosis in the body (Westman et al. 2003)].

Body Mass Index (BMI): Weight and height measurements will be used to calculate BMI of participants at each visit Weight will be measured using SECA Class III digital weight scale while height will be measured using Leicester Portable Height Measure.

Cognitive tests (ACE III, ADCS-MCI-ADL, trail making test, verbal fluency test, category fluency tests) will be used to assess the cognitive functions and quality of life of participants at baseline, and end of the intervention (6 months).

Focus groups/ interviews, questionnaires: will be conducted at the third- and sixth-month visits of the intervention, to gain feedback on the intervention (process, protocol, recruitment, and retention rates). The data will also provide information on participants' views on the outcome measures used and how meaningful they are to them.

Data Management and Analysis Plan:

Data produced from interviews will be thematically analysed using N-Vivo 11 software. Food records will be analysed using Nutritics software. A composite measure will be created for the different cognitive tests used; this would be used to evaluate cognitive function pre- and post-intervention. Data will be analysed using SPSS (Statistical Package for the Social Science) (v25.0). Analysis of covariance (which is a measure of how changes in one variable are associated with changes in a second variable) will be used to compare post intervention measure, while using baseline measure as a covariate.

A set of additional analysis will be conducted to compare some categories between the trial arms. These categories include:

- Dietary Carbohydrate Intake:
    - low (less than 5-10% of total energy intake)
    - normal (40-50% of total energy intake)
    - high (more than 50% of total energy intake)
- APO E4 status:
    - Carrier APO E4 gene (APO E 4 positive)
    - Not carrier of APO E4 gene (APO E4 negative)

Strength and Limitations:

Strength:

The randomization of the participants into the two groups improves the rigour of the study and reduces bias. It also provides a point of comparison between different participants, while demonstrating the difference in decline or progress in cognitive functions between the two groups.

The placebo effect is scientifically proven and could impact the results of the study. This effect would be reduced by providing the control group with sunflower oil that would have no effect on their cognitive functions. If significant improvement in cognitive functions is detected in the group taking coconut oil by the end of the trial, then participants in the control group will be provided with coconut oil.

Limitations:

The small sample size (n=60) reduces the generalizability and transferability of the data. However, this is a feasibility study that aims at exploring the intervention before a larger study is conducted with a much bigger sample size.

Another limitation would be the lack of an *accurate* method to measure the adherence of coconut oil intake. Monitoring of the participants intake through reading of volume of oil left between visits, does not ensure that the oil was used by the participants as it might be used by family members, relatives or even spilled. However, blood tests that measure beta hydroxyl butyrate will detect ketone bodies that result from consumption of coconut oil in the blood. Moreover, participants will be contacted randomly during the intervention period through phone calls to be asked about their intake. A record of these calls will be documented. Building a comfortable and trusting relationship between the researcher and the participant will also help in ensuring that participants are able to communicate any change in their intake or deviation from the intervention.

Ethical Considerations:

This human based study will be conducted in compliance with the protocol, Good Clinical Practice standards and associated regulations, and all applicable institutional research and ethical requirements. The researcher will seek ethical approval from HRA (Health Research Authority) and the NHS Research Ethics Committee to gain their approval and favourable opinion to use NHS sites to recruit individuals. All necessary approvals will be obtained before any study activity takes place. Moreover, the study will adhere to BU's Research Ethics Code of Practice.

In order to ensure that the study remains risk free and ethical, these risks were taken into consideration:

- The study requires working with people who have mild cognitive impairment that might get worse during the study. The possibility of such individuals losing their ability to consent during the study is rare (Jefferson et al. 2008), however, if there is any sign of accelerated progression, consent to continue the study will be sought either from the participant's carer or from a family member in accordance with the Mental Capacity Act (2005).

- Participants will be fully informed about the study and will be given a minimum of 24 hours to ask any questions or to raise any concerns before they are asked to provide informed consent to participate in the study. The ability of participants to consent will be assessed randomly by a registered psychologist during the study.

- Participants will also be made aware that they can withdraw from the study at any time with no disadvantage to them of any kind. Following this, participants will provide written informed consent to participate in the study by completing a consent form. Signed consent forms will be stored for 5 years from the final publication, in line with BU policy (or longer if required by the NHS) and then destroyed.

- All data collected will be stored on password protected computers and/or the BU server and will be handled in accordance with the General Data Protection Regulation 2018 and Data Protection Act 2018. Data will only be accessed by the investigator and the researcher, and the participant's identity will be pseudonymised using a coding system.

- In case of positive APO E4 test results, individuals with positive test results will be given the opportunity to be referred to genetic counselling services. This would help in reducing any emotional distress the test results might cause.

Health & safety issues

- A full risk assessment will be undertaken using the BU online Risk Assessment Tool, ensuring that risk is minimised against physical, mental, emotional, and social harm to the participants, and that the researcher is likewise protected.

- Stress may be induced during the qualitative interviews, focus groups and/or when completing the various psychological measures: The interviews are designed with sufficient breaks, however, when recounting some of the clinical history, participants may experience minimal stress. At any point, if any stress is noticed then they can choose not to answer the question, and/or take a break, and/or reschedule the session. They also would be reminded regularly; that they can choose to withdraw from the study at any point, without any explanation and their care would not be affected or compromised due to this study.

- Fatigue: The possibility of fatigue is often built into the study and there are sufficient breaks for the participants. However, if the participant does experience any fatigue, they could choose to take an additional break and/or continue the study at another time. They also would be reminded regularly; that they can choose to withdraw from

- the study at any point, without any explanation and their care would not be affected or compromised due to this decision.

- Finger prick tests will be used to measure blood ketone levels. Tests will be conducted in hygienic manner in accordance to health and safety training by the researcher. In summary, all equipment will only be used by trained individuals and for the purpose it is designed for. Any potential risks and discomforts will be communicated to participants prior to taking part in the study within the information sheet.

- In case of any adverse event due to the intervention, the sponsor will be informed within 24 hours.

- The researcher will be interviewing people in their homes to conduct the cognitive tests. To ensure the safety of the researcher, the guidelines of the lone working policies set by Bournemouth University and Dorset HealthCare University Foundation Trust will be used.

Contribution to knowledge:

This study would allow us to scientifically elicit the practicality of using coconut oil in people with MCI as an intervention and consequently enable the design of a full randomised controlled trial with larger participant numbers. Most previous studies in this area have used MCT supplementation and not the whole food component such as coconut oil (rich in MCFA), to provide ketones in individuals with dementia or MCI. The present study could provide evidence of the practicality of a simple and non-pharmaceutical dietary intervention. It will fill this gap to provide new knowledge to determine the effectiveness and applicability of such an intervention in adults living with MCI in the community.

Research Ethics Committee (REC) review & reports:

The Medicines and Healthcare products Regulatory Agency (MHRA), have confirmed that they do not need to review or issue a Clinical Trial Authorisation for this research study.

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained within study files and the Chief Investigator (CI) will produce the annual reports as required. The CI will also notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC that granted the favourable opinion.

If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Amendments:

A request for a substantial amendment (class A) to the protocol and study documents was submitted to the sponsor; research ethics committee and the Health Research Authority. The amendment covered changes in the inclusion/Exclusion criteria. The change specified that individuals who are carriers of the APO E4 gene would be included in the study while in Version 1 of the protocol these individuals were excluded. All documents and communications with the REC and HRA regarding the amendment were retained and stored within the study file.

Future amendments will be classed in accordance with the guidance from the Health Research Authority, by the CI, with the support of the sponsor. Applications for substantial amendments will be made to the REC that granted the favourable opinion, including supporting documents. The sponsor will submit a valid notice of amendment to the REC for consideration. The amendment will also be notified to the Health Research Authority, and Trust R&D.

In the case of non-substantial amendments, these will be sent to the HRA using their notification template. HRA processes will be followed.

Peer review:

The protocol was expertly peer reviewed by two academics from Bournemouth University. A Professor in Nutrition and a Doctor in Psychology both reviewed the protocol and approved it. They provided some feedback on the protocol and recommended some ammednments that helped in the development of the protocol. Moreover, consultation was sought from Bournemouth University's clinical governance advisor and the clinical research co-ordinator.

Protocol compliance:

Steps will be taken in order to minimise the risk of protocol deviations and non-compliance, Accidental protocol deviations can happen at any time, but if they do occur, they will be documented and reported to the CI and sponsor immediately.

Should the same deviation occur frequently, then immediate action will be taken, and the deviation accessed under the guidance surrounding serious breaches.

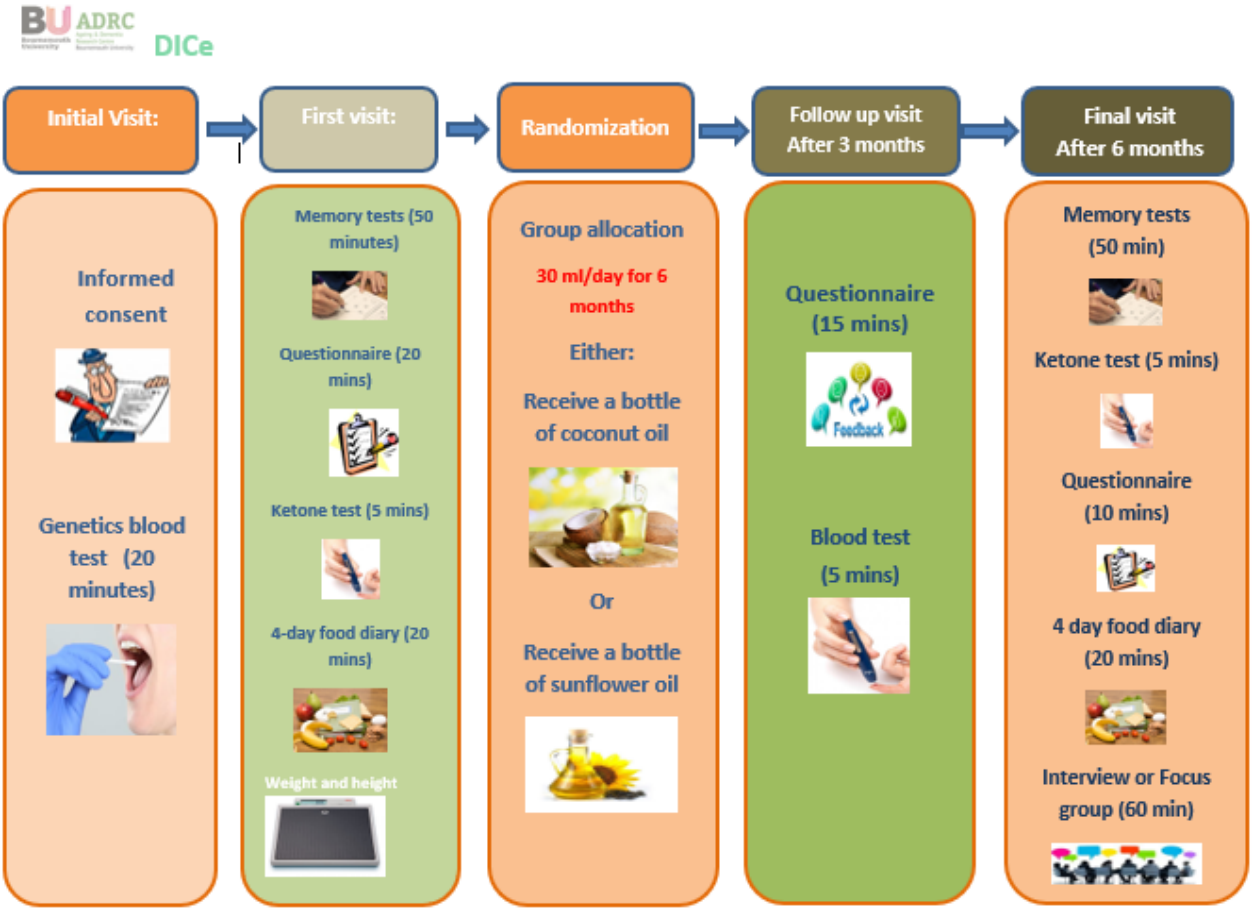
Indemnity:

Bournemouth University holds Public Liability insurance to cover the legal liability of the University as Research Sponsor, in the eventuality of harm to a research participant arising from management of the research by the University. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including the Trust's responsibility for Bournemouth University employees acting in connection with their NHS honorary appointments).Bournemouth University holds Professional Indemnity insurance to cover the legal liability of the University as Research Sponsor and/or as the employer of staff engaged in the research, for harm to participants arising from the design of the research, where the research protocol was designed by the University.
Bournemouth University's Public Liability and Professional Indemnity insurance policies provide an indemnity to employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including the Trust's responsibility for Bournemouth University employees acting in connection with their NHS honorary appointments).

Dissemination:

As sponsor for the study, Bournemouth University is the main data controller, and as such will own the data arising from the study. On completion of the study, the data will be analysed, and a final study report written. The results will be made available on clinicaltrials.gov and likewise results from the study will be disseminated in national and/or international conferences. Papers based on the results of the studies will be published in high quality peer reviewed journals.

Appendix 2: Study flowchart



Appendix 3: Participant Information Sheet

The effect of vegetable oil on cognitive functions in Mild Cognitive Impairment patients

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

Study Summary:

Research has shown that some forms of dementia associated with ageing can be linked to low levels of sugar in the brain. This can cause damage to the brain's nerve cells. The main source of fuel for the brain comes from sugar in the form of glucose. Providing an additional source of fuel to brain cells may reduce this damage and has the potential to prevent the risk of dementia in people with Mild Cognitive Impairment (MCI).

This study explores the possibility of using vegetable oils (coconut and sunflower oils) as an additional source of energy to people with MCI. The researchers will use different tests to evaluate if the study intervention is practical. Participants will be divided into two groups and will either receive 30 ml of coconut or sunflower oil to be consumed daily for six months. The researchers will visit participants in their homes over three occasions during the study to carry out the tests.

Results from this study will help show whether it is practical to use vegetable oils in people with MCI.

Who can take part in this study?

People with a confirmed diagnosis of mild cognitive impairment are invited to take part in this study; DICe (Dietary Intervention on Cognitive Functions) provided they meet a certain criterion. The criterion for participation is based on your medical history.

Do I have to take part?

Participation is voluntary. If you choose not to take part in the study, your care will not be affected in any way. If you decide to take part, you can choose to withdraw from the study at any time, without giving a reason for your withdrawal. If you do withdraw from the study at any stage, information collected about you during the study may still be used unless you ask for it not to be.

Please take time to read this information sheet carefully. Discuss it with your family, friends, or your doctor if you wish, and please ask if anything is not clear, or if you would like more information.

In case you lose your ability to give consent during the study, a consultee (a friend or a family member) will be approached and asked to provide advice on your continuation or withdrawal from the study while taking your best interest into consideration. A family member or a friend will be contacted if there is progression of cognitive impairment to a degree in which you won't be able to provide consent. In the event that you are unable to consent, the availability of a carer or a family member that would help you take the oil is essential for your continuation in the study. Despite continuing the intervention, you will be excluded from the interviews/focus groups in case you lose your ability to give consent. You will be withdrawn from the study if you show any signs of distress or disinterest during the study.

What will happen to me if I take part in the study?

After you give your consent for participation, the first part of the study would be to check if you fit the specific inclusion criteria. The researcher will arrange to meet with you at a convenient location. During this visit, the researcher will explain the study in full and answer any questions you have. You will be asked to sign an informed consent form to provide us with access to your medical history. After reviewing your medical notes, we might find that you are not suitable to participate in this study. If this is the case, the researcher will let you know.

In consent to take part in the study and you fit the eligibility criteria; the researcher will visit you three times during the study. You will also be asked to take an APO E4 genetic test. The genetic test is explained in detail in a separate fact sheet. We need to carry out this test to see if you are carrying a specific gene; an estimated 27% of the UK population are carriers of this gene. The results of the genetic test will be used in our data analysis by checking for links between APO E4 status and ketone metabolism. The test will be done by taking a saliva sample from you using a swab; it will be sent for analysis in the lab, and we will receive the results within 2 weeks. You can choose whether you want to be informed about the test results or not. You will

be provided with the option in the consent form, and you can change your choice at any point during the study. Based on that, the researcher will arrange a meeting with you to give you the result of the test. In case of a positive APO E4 positive test and if you request for you and your GP to be informed about the results, your GP will be contacted to request a referral to a genetic counselling service to further discuss the meaning of the results.

As for the study visits, the researcher will arrange to visit you at your home if this is preferred, or at another suitable location. During the first visit a saliva sample using a buccal swab kit will be collected for the genetic test. You will be asked to complete a questionnaire, four memory tests and a quality-of-life questionnaire. The level of ketones in your blood will be measured using a finger prick-test by a blood ketone-monitoring device. The used strips will be disposed of in a yellow incinerator bin that the researcher will be carrying. The researcher will also measure your weight and height using a portable scale and a height metre. You will also be asked to complete a 4-day food diary (which will take around 1 hour over a day to fill in). You can either send us the completed diary through the post by using the pre-paid envelopes that we will provide you. The researcher can also take them from you during the next visit. These results will allow the researcher to assess your memory and your dietary intake.

After that visit, you will be randomized (which is like flipping a coin), into one of two groups that offer different types of vegetable oils. Half of the people in the study will be allocated to the 'Coconut oil group' and the other half will be allocated to the 'Sunflower oil group'. You will receive a bottle of your allocated vegetable oil, and you will need to consume 30 mls (2 Tablespoons) of the vegetable oil a day. The oil can replace the oil you usually use while cooking. This falls within the UK Government's (Public Health England) recommended dietary fat intake for adults which is 35% of total energy intake. The researcher will explain the different ways you can incorporate the oil into your diet. You will be asked to use the allocated oil for 6 months, during which you will receive phone calls from the researcher to check how you are using the oil and how much has been consumed. Any data collected from these phone calls will be anonymised prior to their content being used in study publications.

The second visit will be after 3 months from the initial visit, at a convenient location. During this visit, you will be asked to fill a questionnaire to give your feedback of the study and will be asked to take the finger prick test again. Your weight will also be measured during the visit.

During the third and final visit (at 6 months post-the first visit), you will be asked to retake the memory tests, ketone blood test, weight measurement and fill another 4-day food record. You will also be invited to an interview or focus group that will be audiotaped to give your feedback about the study. Interviews will be carried out at home or at any convenient location and will take between 30 minutes and one hour. While focus groups will be carried out at a convenient location e.g.: memory café and will last for about an hour. The audio recordings will be transcribed and then destroyed. Data collected from the audio recordings will be anonymously transcribed before analysis. No other use will be made of them without your consent.

Which group will I be in?

A computer will 'decide' which group you are to be allocated to, so that the two groups are balanced and well-matched. This means that neither you nor the researcher will be able to choose which group you are allocated. You have an equal chance of being assigned to either coconut or sunflower oil. **If you want to take part in this study, it is important to realise that you won't be able to choose your group**. We need data from both groups in order to answer our question and so the data you provide is equally valuable to us, regardless of which group you are in.

What are the benefits of taking part?

We really do not know if vegetable oil will affect the health and wellbeing of people with mild cognitive impairment, so we cannot say with any certainty that you will benefit from taking part in this study. We are conducting this feasibility study to check the practicality of utilizing such an intervention in people with Mild Cognitive Impairment. Thus, you will certainly be helping us to answer a question, which might lead to improved treatment for people with mild cognitive impairment in the future.

What are the risks and disadvantages of taking part?

No ill effects are expected as a result of you taking either oil. If you are worried about your diet at any point, you can contact the research team that includes a Registered Dietitian (Professor Murphy) who will be happy to help answer any of your questions or concerns.

There is a small possibility that some people may find the questions or discussion during the interviews or focus groups distressing. As a result, you may come to the conclusion that you wish to withdraw yourself from the study.

If you feel any distress, you will be signposted to clinical services at Dorset Healthcare University NHS Foundation Trust to help you overcome this. We are

required to contact your GP for them to refer you to the right service. Moreover, you could also attend one of the support groups or memory cafés for people living with dementia supported by the Ageing and Dementia Research Centre at Bournemouth University.

In case of a positive result with the genetic test you will be signposted to a genetic counselling service to help you further understand the outcome of the test to help prevent any undue distress.

Additional information

Research studies are strictly regulated, and it is important that you fully understand all the implications of your participation. The following sections provide more detailed information, so please read through and contact us if you have any questions.

What if relevant new information becomes available?

If any new information that could affect your participation in the study becomes available, you will be informed. If the study is stopped for any reason, you will be told why.

What if there is a problem?

Complaints: If you have a concern about any aspect of this study, please speak to someone in the research team who will answer your questions. NHS complaints can be diverted to Dorset HealthCare University Foundation Trust's PALS department by FREEPHONE 0800 587 4997 or on dhc.pals@nhs.net. Further information regarding this service can be found here - https://www.dorsethealthcare.nhs.uk/patients-and-visitors/compliments-concerns-and-complaints/patient-advice-liaison-service-pals.

If you have any complaints regarding the conduct of the study by Bournemouth University, you may contact Professor Vanora Hundley, Deputy Dean for Research and Professional Practice, Faculty of Health and Social Sciences. You can contact her through email (researchgovernance@bournemouth.ac.uk).

Harm: We don't expect any harm to come to you as a result of participating in this study. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against your NHS Trust, but you may have to pay your legal costs.

Will my participation be kept confidential?

All information collected about you during the course of the study will be kept strictly confidential and in accordance with GDPR (General Data Protection Regulation) and the UK Data Protection Act 2018 that govern the processing of personal data.

Bournemouth University is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as one of the data controllers for this study. This means that we are responsible for looking after your information and using it properly. Bournemouth University will keep identifiable information about you until the study is completed.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

Your medical records will remain within the establishments which usually maintains them (your doctor or local hospital) but may be reviewed by members of the Bournemouth University research team to confirm your eligibility to take part in the study and to gather information regarding any blood tests or scans during the study period if needed. Your name and other identifying information will be removed from any study data before it is analyzed so that you cannot be identified from the data. Your contact details will be stored separately from the de-identified study information on secure password-protected computers, accessible only to authorized members of Bournemouth University. Paper-based information will be stored in in locked filing cabinets housed within secure offices and information kept on computers will be stored securely on a system maintained and password-protected by Bournemouth University.

Bournemouth University will use your contact details to contact you about the research study, making sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Bournemouth University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Dorset Healthcare University

NHS Foundation Trust will pass these details to Bournemouth University along with the information collected from you and your medical records. The only people in Bournemouth University who will have access to information that identifies you will be people who need to contact you to schedule a visit, or to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

Bournemouth University will keep identifiable information about you until the study is completed. Data collected during the study will be stored for 5 years after the last publication of the research results.

What happens when the research study stops? Will I find out the results?

When every participant has completed the study, we will prepare the study results (this normally takes several months) and send you a summary of the findings. The study results may be presented at national and international conferences and published in medical journals, but you will not be identified in any information included in any presentation or publication. If the results of this study indicate that it is feasible to conduct an intervention using vegetable oils in people with mild cognitive impairment, then a larger trial will be planned to further research this area.

Who is organizing and funding the research?

This is an educational project that is part of a post-graduate research studentship. The study is being conducted by Raysa EL Zein who is a PhD student at Bournemouth University and supervised by Professor Jane Murphy, who is a Registered Nutritionist and Dietitian at Bournemouth University with a special interest in nutrition and older people. It is also supervised by Professor Peter Thomas who is a Professor of Health Care Statistics and Epidemiology and a Co-Director of the Bournemouth University Clinical Research Unit (BUCRU) and Doctor Shanti Shanker who is a Chartered Psychologist. The study is funded by Bournemouth University and supported by Dorset Healthcare University Foundation Trust.

Who has reviewed this study?

All NHS research is looked at by an independent panel of experts and lay members (a Research Ethics Committee). This study has been reviewed and approved by the NHS Health Research Authority and Harrow NHS Research Ethics Committee, whose primary role is to protect and promote the interests of patients and the public in health research. The study has also been reviewed and approved by Bournemouth University's Science, Technology and Health Research Ethics Panel.

Appendix 4: Consent Form

Study Number: 240254

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **The effect of vegetable oil on cognitive functions in MCI patients**

Name of Chief Investigator: Professor Jane Murphy

Please initial box:

1. I confirm that I have read and understood the information sheet dated 30/09/2019 for the above study. ☐

2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

4. I agree to give a buccal swab sample for research in this project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my care or legal rights being affected. ☐

5. I give permission for APO E4 genetic test to be carried out on the sample I give, as part of this project. I have received written information about this test and I understand what the result could mean to me and/or members of my family. ☐

6. I want to be informed of the results of the APO E4 genetic test. I understand I can change my mind about this later. ☐

7. I agree to my General Practitioner being informed of my APO E4 test result ☐

1. I do **NOT** want to be informed of the results of the APO E4 genetic test. I understand I can change my mind about this later. ☐

2. I do **NOT** agree to my General Practitioner being informed of my APO E4 test result. ☐

3. I understand that relevant sections of my medical history, notes and scans (brain imaging) may be looked at by individuals from Bournemouth University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I am aware that some of the study sessions may be audio-recorded in order to facilitate data collection. I also understand that quotes from the audio-recordings will be used anonymously and will not include my name or other personal information. ☐

5. I agree to my General Practitioner being informed of my participation in the study. ☐

6. I agree to provide the research team with my contact details such as address, email and telephone number. I understand that these details will be kept by the researcher for the duration of the study, after which they will be destroyed. ☐

7. I understand that the information held and maintained by Dorset Health Care University NHS Foundation Trust may be used to help contact me or provide information about my health status ☐

8. I understand that in case I lose my ability to consent, advice for continuation of participation will be sought from a family member or a friend. ☐

GP Details:

Name:

Contact Number:

Practice:

Personal Details:

Contact number:

Email:

Address:

Name of Participant Date Signature

Name of person receiving consent Date Signature

Participant Agreement Form

Title of Project: The effect of vegetable oil on cognitive functions in Older Adults

Name, position and contact details of researcher: Raysa El Zein, Postgraduate Researcher, relzein@bournemouth.ac.uk

Name and contact details of supervisor: Professor Jane Murphy, jmurphy@bournemouth.ac.uk

Section A: Agreement to participate in the study

You should only agree to participate in the study if you agree with all of the statements in this table and accept that participating will involve the listed activities.

I have read and understood the Participant Information Sheet (Version 2, dated: 18-12-2019) and have been given access to the BU Research Participant Privacy Notice which sets out how we collect and use personal information (https://www1.bournemouth.ac.uk/about/governance/access-information/data-protection-privacy).
I have had an opportunity to ask questions.
I understand that my participation is voluntary. I can stop participating in research activities at any time without giving a reason and I am free to decline to answer any particular question(s).
I understand that taking part in the research will include the following activity/activities as part of the research:
• undergoing genetic testing by giving a buccal (saliva) swab sample
• undergoing ketone finger prick testing
• being audio recorded during the project
• my words will be quoted in publications, reports, web pages and other research outputs without using my real name.
I understand that, if I withdraw from the study, I will also be able to withdraw my data from further use in the study **except** where my data has been anonymised (as I cannot be identified) or it will be harmful to the project to have my data removed.
I understand that my data may be included in an anonymised form within a dataset to be archived at BU's Online Research Data Repository.

Section B: The following parts of the study are optional

You can decide about each of these activities separately. Even if you do not agree to any of these activities you can still take part in the study. If you do not wish to give permission for an activity, do not initial the box next to it.

		Initial boxes to agree
	I agree that BU researchers may contact my GP as described in the Participant Information Sheet	
	I agree to my GP being informed of my APO E4 test result.	

GP Details:

Name:

Contact Number:

Practice:

Personal Details:

Contact number:

Email:

Address:

I confirm my agreement to take part in the project on the basis set out above.

Name of participant (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of researcher (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature

Appendix 5: Health History Questionnaire

History Questionnaire:

PIN (Participant Identification Number):

DOB:

Gender: Please tick ONE box:

Male ☐ Female ☐ Other ☐

What is your relationship status? Pleas tick ONE box:

Single ☐ Divorced/ Civil partnership dissolved ☐

Married/civil partnership ☐ Widowed ☐

With partner ☐

What best describes your current living situation? Please tick ONE box:

Living alone ☐ Living with family/ friends ☐

What is your highest level of education? Please tick ONE box:

None ☐ Higher education college/ university ☐

Primary School ☐ Further Education/ professional Qualification ☐

Secondary School ☐ Others ☐

Please specify ……

Which of the following best describes your work situation? Please tick ONE box:

Working full time ☐ Retired ☐

Working part time ☐ In full time education ☐

Working as a volunteer ☐ Looking after the home ☐

Unemployed ☐ Other ☐

Please specify ……

Medical History:

Which of the following best describes your physical activity? Please tick ONE box:

Sedentary (No exercise) ☐

Mild exercise (i.e., climb stairs, walk 3 blocks, golf) ☐

Occasional vigorous exercise (i.e., work or recreation, less than 4 times/week for 30 minutes) ☐

Regular vigorous exercise (i.e., work or recreation 4 times/ week or more for 30 minutes) ☐

Please list any medical problems:

Are you currently taking any medication (tablets, drugs)?

Yes ☐ No ☐

If yes, please list:

Do you have any allergies?

Yes ☐ No ☐

If yes, please list :

To the best of my knowledge, the above information is correct:

Participant signature Date

Appendix 6: Adherence Questionnaire

Bournemouth University

ADRC
Ageing & Dementia
Research Centre
Bournemouth University

Adherence Feedback Questionnaire:

PIN (Participant Identification Number) SB06

Date: 8/2/2020

Can you please fill in this questionnaire to provide your feedback on the intervention so far:

Are you taking the oil as required?

☐ No

If no, please explain why?

Have withdrawn from the study

Have you had any issues taking the oil?

Coconut oil is affecting my digestive system.

Were you able to incorporate the oil into your normal diet? Yes until I gave up

Further comments:

I regret having to withdraw and would have continued had I not had an adverse reaction to the coconut oil.

Appendix 7: Food Diary

The effect of vegetable oil on cognitive functions in Mild Cognitive Impairment patients

PIN:

Food Diary:

How to complete this diary:

- **Please write down everything consumed (FOOD and DRINK) and time** throughout the day. Include between meal snacks (e.g., fruit, biscuits, sweets) and all fluids taken (e.g., water, tea, coffee, etc).
- **Please be as descriptive as possible**. For example, describe the type of milk (full fat, semi-skimmed or skimmed) and spread (butter, sunflower margarine or low fat spread etc.) or the type of bread (wholemeal, white, granary or high fibre white, etc.) used. State the brand of manufactured goods where known, for example McVities digestives, Heinz tomato soup. Provide any food labels where appropriate.
- **Remember to include approximate amounts of food**. For example, ½ slice of bread (please write whether thin or thick sliced), 1 tablespoon cereal, 3 scoops of mashed potato, etc. Write down whether you spread butter, margarine or preserves, thickly or thinly.
- **State whether the weight recorded is for the raw or cooked weight of a food.**
- **If possible, please give recipes for home baked foods (you may use additional sheets) and how many portions the recipe provides.**
- **Please state the individual foods that make up mixed dishes,** for example salad = lettuce, cucumber, and tomato.
- **Write down "nothing" when nothing is taken at a meal.**

How to fill in your diary:

- **Do not alter what you usually eat just because you are filling in the diary.**
- **Remember to write down <u>everything</u> you eat and drink, even water. Include all nibbles and snacks and any food eaten outside of the home.**
- **If you are not weighing food, give quantities in household measures e.g., 2 tablespoons peas, 2 slices wholemeal bread.**
- **Put the brand names of manufactured foods (provide labels of foods).**
- **Put the method of cooking e.g., grilled, fried etc.**
- **If any dishes are home-made e.g. Meat bolognaises, you may wish to make a note of the recipe.**

Please answer the following questions:

1. What type of bread do you eat?

Is your bread sliced:

Thick? Thin? Medium? Sliced at home?

2. What type of fat do you put on bread? e.g., butter, low fat olive spread

---

3. What type of milk do you use? e.g., full fat milk, soya(brand)

---

4. Do you put sugar in tea or coffee? Yes / No

If yes, in Tea how many teaspoons? ----------

If yes, in Coffee how many teaspoons? ----------

5. Do you put sugar on cereals? Yes / No

If yes how many teaspoons? ----------

6. What drinks do you have daily or weekly?

Please specify amounts, e.g., cups/mugs/large, or small glasses/pints

7. Do you take any dietary supplements, e.g., vitamins? Yes / No

If yes, please specify ----------

8. What type of oil do you use in cooking? ----------

DAY 1 DATE:

	Time	Location	Food/drink description	Cooking method	Amount	Leftovers	Comments
Before breakfast							
Breakfast							
During the morning							
Lunchtime							
During the afternoon							
Evening meal							
During the evening							
Through the night							

DAY 2 DATE:

	Time	Location	Food/drink description	Cooking method	Amount	Leftovers	Comments
Before breakfast							
Breakfast							
During the morning							
Lunchtime							
During the afternoon							
Evening meal							
During the evening							
Through the night							

DAY 3 DATE:

	Time	Location	Food/drink description	Cooking method	Amount	Leftovers	Comments
Before breakfast							
Breakfast							
During the morning							
Lunchtime							
During the afternoon							
Evening meal							
During the evening							
Through the night							

DAY 4 DATE:

	Time	Location	Food/drink description	Cooking method	Amount	Leftovers	Comments
Before breakfast							
Breakfast							
During the morning							
Lunchtime							
During the afternoon							
Evening meal							
During the evening							
Through the night							

Appendix 8: Lone working Policy

Appendix 03: Standard Operating Procedure: Lone Worker

The effect of a dietary intervention on cognitive functions in people with Mild Cognitive Impairment (MCI)

The Health and Safety at Work Act (HSW Act 1974), extended by the Management of Health and Safety Regulation (MHSW) require identifying hazards at work, assess the risk and provide necessary guidelines to avoid or control the risks which involve a lone worker.

The following points support the clarification of the procedures in place to address the potential risks involved whilst conducting research during the period of this study at Bournemouth University (BU).

Working alone within Bournemouth University (Out of Office Hours)

- Risks include allegations made against lone researchers, risk of physical or verbal abuse, and handling any emergencies if necessary.
- When possible, research assessments should be conducted during the daytime and when other BU staff members are in the building. A member of the research team should be available on site to provide support, if necessary.
- In the occasion that the assessments are to be conducted when other team members are not present or during after hours, necessary steps to be taken include:
    - Informing the research team that the assessments are being undertaken by a lone assessor
    - Telephone contact (i.e. mobile) should be available throughout the assessment period
    - The lone worker is trained in basic first-aid.
    - Ensure the researcher wear their ID and carry the mobile phone with them into the assessment

In event the assessment happens out of University hours, security staff should be informed that the building is being used for research purpose. Testing will happen only at Studland House (Lansdowne Campus) and/or Poole House (Talbot Campus). The out-of work logbook will be signed clearly with the name of the researcher, visitor, the room number and time of entry

- mentioned. The security should be informed when leaving the building (extension: SH: 01202317581 PH: 01202965001).
- All researchers should be aware of the emergency procedures.

Working away from Bournemouth University i.e. at participants houses

Although, attempt will be made to ensure all the research activity will be conducted at BU there may be, occasions, or need for the assessment to be conducted away from BU for example, in the participants' home environment.

Risks may include allegations made against the research assessors, risk of harm to investigators when conducting visits, and unknown risks/hazard to both participants and researchers of the chosen research visit location. In such cases the following procedures should be adhered to (a risk assessment will be done within BU for this lone worker policy):

- Whenever possible, rather than visiting the participant at home, chose a public location that is convenient to both the participant and the researcher.
- The researcher should familiarize themselves with the chosen location, taking into account any risks that may occur for both the participant and the researcher at the site (for example, if using a hospital, what the risks would be).
- The researcher should seek permission and consent from the relevant authority to conduct a research visit on the site (for example, if using a hospital, obtain consent for use of their facilities).
- Leave details of the nature of the assessment, the times, dates, estimated length of the assessment, place of visit with a research team member. If there are any changes or cancellations, notify a team member as soon as possible.
- Ensure the researchers carry their mobile phones at all times.
- The researcher should leave their contact details with a team member, and check-in via phone at regular intervals to confirm the visits are going as planned. If calls, are not made at a pre-arranged time to a designated research team member, further suitable action should be taken.
- Researchers should always wear their I.D badges during assessments, including visits away from BU as well as carry both mobile phones and personal alarms.
- Carry enough money to be able to get a taxi should the need be.

- Maintain constant vigilance of surroundings
- Park the car in a well-lighted area
- Wear sensible attire (minimal jewellery)
- Maintain the demeanour of an invited guest when conducting interviews in participants' house.

Appendix 9: Interview Guide

The effect of vegetable oil on cognitive functions in Mild Cognitive Impairment patients

Topic Guide for Semi- Structured Interviews:

Welcome, introduction of the researcher and to the study

First, I would like to discuss your experiences with using vegetable oil in this study

- Did you have any issues taking the oil?
- What were some barriers, if any, that you encountered by including the oil in your diet?
- Were there any approaches that worked better than others?

Now can I ask about some of the measurements that were used?

- Please share your thoughts on the measures we've used. Did you experience any problems? Do you feel some measures were more important than others?
- What were your thoughts on the randomization that took place? Would you have preferred to be in another group?

Now can I ask some questions about participating in the study?

- What did you hope to gain by participating in this study? What do you feel are the most important aspects of this study?

- What has worked well for you? What do you feel could be improved?
- What effect, if any, do you feel the study has had on you?
- Have you noticed any changes in your memory?
- What do you think you would like to happen next?

Is there anything else you would like to discuss or comment on?

Thank you for your time and participation today.

Appendix 10: NHS Ethics

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Jane Murphy
R104, Royal London House, Faculty of Health & Social Sciences
Bournemouth University, Christchurch Road
Bournemouth, Dorset
BH1 3LT

Email: hra.approval@nhs.net

29 January 2019

Dear Professor Murphy

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A study evaluating the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in adults with Mild Cognitive Impairment.**
IRAS project ID:	**240254**
Protocol number:	**1718/IRASREZ/1**
REC reference:	**18/LO/1624**
Sponsor	**Bournemouth University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?

You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?

You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Mrs Julie Northam
Tel: 01202 961208
Email: jnortham@bournemouth.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **240254**. Please quote this on all correspondence.

Yours sincerely

Juliana Araujo
Assessor
Email: hra.approval@nhs.net

Copy to: *Sponsor Representative: Mrs Julie Northam, Bournemouth University*
Lead NHS R&D Office Representative: Dr.Ciaran Newell , Dorset Healthcare University NHS Foundation Trust

Appendix 11: Bournemouth University Ethics

Bournemouth University

Research Ethics Checklist

About Your Checklist	
Ethics ID	29406
Date Created	27/11/2019 13:07:36
Status	Approved
Date Approved	20/12/2019 10:22:27
Date Submitted	19/12/2019 13:28:45
Risk	High

Researcher Details	
Name	Raysa El Zein
Faculty	Faculty of Health & Social Sciences
Status	Postgraduate Research (MRes, MPhil, PhD, DProf, EngD, EdD)
Course	Postgraduate Research - HSS
Have you received funding to support this research project?	Yes
Is this internal funding?	Yes
Please provide the Internal Funding Body	Faculty of Health and Social Sciences; Professor Jane Murphy (research fund), Ageing and Dementia Research Centre

Project Details	
Title	A study evaluating the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in older adults
Start Date of Project	18/09/2017
End Date of Project	18/10/2020
Proposed Start Date of Data Collection	12/01/2020
Original Supervisor	Jane Murphy
Approver	Research Ethics Panel

Summary - no more than 600 words (including detail on background methodology, sample, outcomes, etc.)

Empirical evidence to date has demonstrated associations between nutrition and cognitive impairments in older adults. Neuro-degeneration associated with ageing could be attributed to neuronal glucose hypo-metabolism. Therefore, providing an alternative source of energy (ketones) to the neurons could reduce neuro-degeneration and cognitive decline in older adults.The current study will investigate the use of coconut oil as an alternative energy source; rich in medium chain fatty acids (MCFA); that are converted into ketone bodies in the human body.

Previous studies have used Medium Chain Triglycerides (MCTs) as a source of ketone bodies to improve cognitive functions in older

adults with MCI or Alzheimer's disease. However the current study relies on the consumption of the whole food component (coconut oil) that is rich in MCFA, in older adults.

The aim of the study is to evaluate the feasibility of undertaking an intervention looking into the effect of vegetable oils intake on cognition and quality of life in older adults.

Objectives:

Primary Objectives:

1. To estimate the adherence rate of older adults to dietary coconut oil intake.

2. To test the procedures of the intervention (accuracy of self-reported adherence, delivery of the intervention, recording and monitoring of adverse events, estimate recruitment and retention rates, and refine the selection of outcome measures in preparation for a Randomised Controlled Trial that would test the effectiveness of the intervention).

3. To estimate the standard deviations (SD) of quality of life and the cognitive measures to inform the sample size calculations of a future Randomised Controlled Trial.

4. To collect data on the correlation between pre and post outcome measures to inform sample size calculations for a larger trial.

5. To determine the acceptability of randomisation and of the intervention in participants and obtain feedback about the study procedure from service users.

Secondary Objectives:

1. To provide preliminary estimates of the clinical effect of dietary coconut oil on cognitive functions in older adults compared to the control group.

Outcome measures to be considered:

a. Difference in the cognitive executive measures in older adults taking coconut oil. A composite measure can be calculated based on individual scores from the following tests: 1) Trail Making; 2) Verbal Fluency; 3) Category Fluency; 4) Digit Symbol; 5) Digit Span)

b. Differences in overall cognitive measures in older adults (Measured using the Addenbrookes Cognitive Examination (ACE- III or mACE)).

c. Differences in memory measures in older adults. (A composite measure can be calculated based on individual scores from the following tests: 1) verbal memory (Word list from the WMS-III); 2) Scores from the Super-market task and/or Sea-Hero Quest.)

2. To provide preliminary estimates of the potential effect of dietary coconut oil on quality of life in older adults (by using Alzheimer's disease cooperative study- mild cognitive impairment- activities of daily life (ADCS-MCI-ADL) test).

3. To investigate the dietary energy and macronutrient (carbohydrate, fat and protein) intake of older adults.

Methodology: This will be a feasibility study that will follow a randomized clinical trial design. It will allow the unbiased evaluation of the adherence rate and effect of the dietary intervention on cognitive functions of older adults. Mixed methods using quantitative and qualitative methodologies will be used in the study. Data collection methods will consist of questionnaires, focus groups/interviews, food records, cognitive tests (ACE III, trail making test, verbal fluency test, category fluency tests), quality of life questionnaire (ADCS-MCI-ADL), and finger prick blood tests (beta hydroxyl butyrate).

Outputs/impact: Results from this study could help determine whether such an intervention is applicable in older adults. It will provide new knowledge relating to the feasibility of the implementation of such an intervention, to guide and inform the design of a randomised controlled trial (RCT) that is adequately powered and evidence-based. The RCT could provide a dietary intervention that might have the potential to improve cognitive functions and maintain quality of life for longer in older adults, by reducing cognitive decline.

Filter Question: Does your study involve Human Participants?

Participants
Describe the number of participants and specify any inclusion/exclusion criteria to be used

Sixty participants will be recruitedInclusion criteria:Adults aged 65 years and aboveExclusion Criteria:•Adults with dementia diagnosis•Adults who have Type I or Type II diabetes due to the risks of diabetic ketoacidosis •Adults with neurological disorders •Adults who are unable to communicate in English or those with major physical disabilities (blind, deaf) or unable to use their dominant hand.•Adults with coconut allergy•Adults with a history of hypercholesterolemia	
Do your participants include minors (under 16)?	No
Are your participants considered adults who are competent to give consent but considered vulnerable?	No
Is a Disclosure and Barring Service (DBS) check required for the research activity?	No

Recruitment

Please provide details on intended recruitment methods, include copies of any advertisements.	
•Newsletter of the Ageing and Dementia Research Centre •Participants Pool available within the Ageing and Dementia Research Centre. •Flyers will also be placed in libraries and museums.•Join Dementia Research platform- it can be used to search for healthy individuals with no dementia diagnosis•Dorset Dementia Partnership•Twitter•Advertisements will be placed in local newspapers (Bournemouth Echo, New Milton)	
Do you need a Gatekeeper to access your participants?	Yes
Please provide details, including their roles and any relationship between Gatekeepers and participant(s) (e.g. nursing home manager and residents)	
Join Dementia Research- databse of people willing to participate in research	

Data Collection Activity

Will the research involve questionnaire/online survey? If yes, don't forget to attach a copy of the questionnaire/survey or sample of questions.	Yes
How do you intend to distribute the questionnaire?	
face to face	
Will the research involve interviews? If Yes, don't forget to attach a copy of the interview questions or sample of questions	
Will the research involve a focus group? If yes, don't forget to attach a copy of the focus group questions or sample of questions.	Yes
Please provide details e.g. where will the focus group take place. Will you be leading the focus group or someone else?	
Will the research involve the collection of audio materials?	Yes
Will your research involve the collection of photographic materials?	No
Will your research involve the collection of video materials/film?	No
Will any audio recordings (or non-anonymised transcript), photographs, video recordings or film be used in any outputs or otherwise made publicly available?	No
Will the study involve discussions of sensitive topics (e.g. sexual activity, drug use, criminal activity)?	No
Will any drugs, placebos or other substances (e.g. food substances, vitamins) be administered to the participants?	Yes
Please provide details and measures taken to minimise risks and explain why your research project does not require an ethical review by a NHS Research Ethics Committee	

The study does not require NHS Ethics approval as there are no health risks associated with the consumption of the oils.Please see attached form (Risks)	
Will the study involve invasive, intrusive or potential harmful procedures of any kind?	Yes
Please provide details and measures taken to minimise risks and explain why your research project does not require an ethical review by a NHS Research Ethics Committee	
Please see attached form (Risks)	
Could your research induce psychological stress or anxiety, cause harm or have negative consequences for the participants or researchers (beyond the risks encountered in normal life)?	Yes
Please provide details and measures taken to minimise risks	
Please see attached form (Risks)	
Will your research involve prolonged or repetitive testing?	Yes
Please provide details and measures taken to minimise risks	
Please see attached form (Risks)	

Consent

Describe the process that you will be using to obtain valid consent for participation in the research activities. If consent is not to be obtained explain why.	
Informed written consent will be obtained from participants. Participants will be fully informed about the study and will be given time to read the information sheets and ask any questions or raise any concerns before they are asked to sign the participant agreement form to participate in the study	
Do your participants include adults who lack/may lack capacity to give consent (at any point in the study)?	No
Will it be necessary for participants to take part in your study without their knowledge and consent?	No

Participant Withdrawal

At what point and how will it be possible for participants to exercise their rights to withdraw from the study?
Participants can withdraw from the study at any point until their data is anonymized (after 7 months of starting the intervention).
If a participant withdraws from the study, what will be done with their data?
If a participant withdraws from the study, their data up until the point of withdrawal will be used unless they request for the data to be destroyed.

Participant Compensation

Will participants receive financial compensation (or course credits) for their participation?	No
Will financial or other inducements (other than reasonable expenses) be offered to participants?	No

Research Data

Will identifiable personal information be collected, i.e. at an individualised level in a form that identifies or could enable identification of the participant?	Yes

Please give details of the types of information to be collected, e.g. personal characteristics, education, work role, opinions or experiences	
Personal information will be collected during the study (address, phone number, email); to ensure the participants safety and to be able to inform the participant's GP (General Practitioner) in case of they consent to it. All data will be psuedonymized and participants will receive a participant identification number (PIN) that will be used on all documents.	
Will the personal data collected include any special category data, or any information about actual or alleged criminal activity or criminal convictions which are not already in the public domain?	Yes
If Yes, please give details of the information you will be collecting	
Data related to health	
Will the information be anonymised/de-identified at any stage during the study?	Yes
Will research outputs include any identifiable personal information i.e. data at an individualised level in a form which identifies or could enable identification of the individual?	No
Please give brief details of how you will address the need for data minimisation or explain why you do not think this relates to the personal information you will be collecting.	
Only necessary data will be stored and will be pseudonymized.	

Storage, Access and Disposal of Research Data	
During the study, what data relating to the participants will be stored and where?	All data collected will be stored on password protected computers and/or on the BU server and will be handled in accordance with the General Data Protection Regulation 2018 and Data Protection Act 2018.Moreover, soft copies of some of the documents such as transcriptions of interviews and data will be stored on a password protected university computer; with the password only known to the researcher. Records of interviews and focus groups will be destroyed once transcribed.
How long will the data relating to participants be stored?	Data relating to participants will be destroyed after publication.
During the study, who will have access to the data relating to participants?	The Chief investigator of the research along with the student who is conducting the research will have access to the participants' personal data during the study.
After the study has finished, what data relating to participants will be stored and where? Please indicate whether data will be retained in identifiable form.	After the end of the study, no personal data will be stored. Data from the study (socio-economic information and medical history) will be anonymized and stored until publication of results. No data will be stored in identifiable form.
After the study has finished, how long will data relating to participants be stored?	After the end of the study, data will be stored until publication of results.
After the study has finished, who will have access to the data relating to participants?	The Cheif investigator and the researcher will have access to the data after the study is finished.
Will any identifiable participant data be transferred outside of the European Economic Area (EEA)?	No
How and when will the data relating to participants be deleted/destroyed?	They will be destroyed in accordance to BU data protection policy.
Once your project completes, will any anonymised research data be stored on BU's Online Research Data Repository "BORDaR"?	Yes

Dissemination Plans	
Will you inform participants of the results?	

Final Review	
Are there any other ethical considerations relating to your project which have not been covered above?	No

Risk Assessment	
Have you undertaken an appropriate Risk Assessment?	Yes

Filter Question: Does your study involve the use of human tissue?

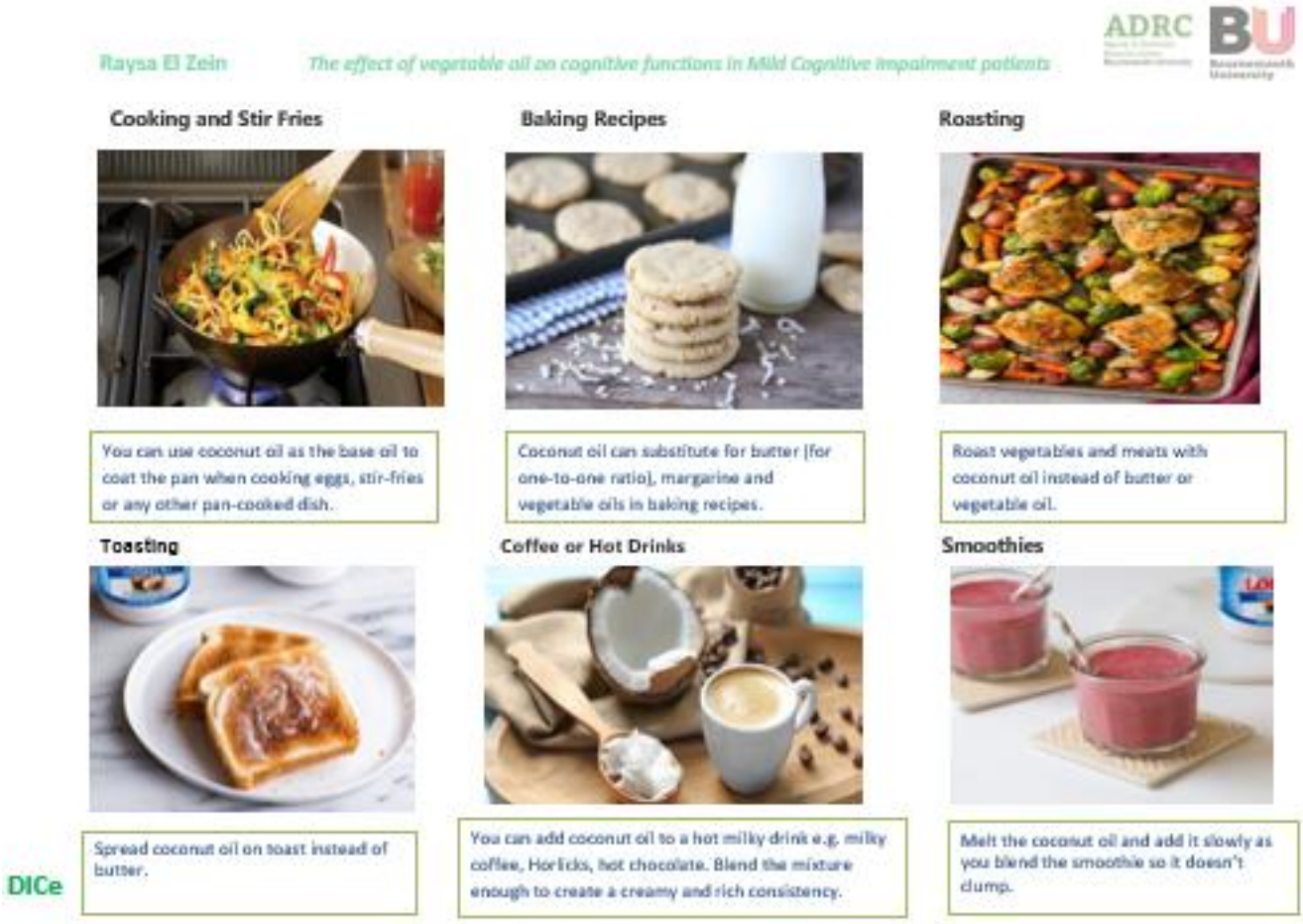
Additional Details	
What is the sample?	•Blood sample •Saliva sample
How will it be obtained?	•Finger prick testing•Buccal swab
Where will the sample be stored and for how long?	Samples will not be stored, blood will be tested directly using a portable ketone metre and the saliva sample will be immediately sent to Viapath for analysis.Viapath is the largest pathology service provider in the UK. The services are provided for the NHS and private sector organisations. The APO E4 test will be conducted in St. Thomas's hospital in London through the collaboration between Viapath and the hospital.
Does your research require NHS REC approval?	No
please explain why your research project does not require ethical review by a NHS REC	
HRA approval is not required because the samples will either be destroyed on the day of testing, or transferred elsewhere.	

Attached documents
Participant Agreement Form 28-11-2019.docx - attached on 28/11/2019 17:03:44
Ethical Consierations BU.docx - attached on 28/11/2019 17:04:11
APO E4 genotype fact sheet V6-30-09-19 .docx - attached on 28/11/2019 17:07:48
Food diary V1 BU.doc - attached on 29/11/2019 12:59:43
History Questionnaire v1 BU .docx - attached on 29/11/2019 13:00:53
Feedback Questionnaire v1 BU.docx - attached on 29/11/2019 13:01:43
Topic Guide for interviews V2 BU.docx - attached on 29/11/2019 13:04:50
Participant Information Sheet- BU- 27-11-2019.docx - attached on 29/11/2019 13:10:45
Participant Information Sheet- BU-V2 19-12-2019 .docx - attached on 19/12/2019 13:24:00
Participant Agreement Form BU V2.docx - attached on 19/12/2019 13:24:42
APO E4 genotype fact sheet V2 BU .docx - attached on 19/12/2019 13:25:50
History Questionnaire v2 BU 19-12-2019.docx - attached on 19/12/2019 13:26:17

Approved Amendments	
Message	Amendment requested to acknowledge the change in BRAND (Coconut Oil) used in the study from Perfectly Pure coconut oil to Lucy Bee extra Virgin raw coconut oil. Required because of low availability and quality of Perfectly Pure Coconut Oil.
Date Submitted	18/02/2020 16:47
Comment	Change of BRAND approved
Date Approved	18/02/2020 16:55
Approved By	Suzy Wignall

Approved Amendments	
Message	In response to Covid19, some amendments were made to the DICe study; these include:-Conducting interviews and focus groups virtually via phone/zoom- Meeting participants in their gardens and maintaining government-recommended length of physical distance during the meeting. -Wearing appropriate PPE during any meeting and disinfecting all equipment used following the meeting -Delivering oil to participant's door step instead of directly giving it to them-Asking participants to conduct the ketone blood test on themselves under supervision of the researcher to reduce contact-Participants will measure their weight using the provided scale by themselves and report back to the researcher -Blood ketone tests for the three months cut off point were delayed. -Extending recruitment for 4 months-Extending the DICe study for 1 year.
Date Submitted	07/07/2020 13:20
Comment	
Date Approved	07/07/2020 14:38
Approved By	Suzy Wignall

Appendix 12: Oil Incorporation Leaflets (CO & SO)



Cooking and Stir Fries

Use sunflower oil to coat the pan when cooking eggs, stir-fries or any other pan-cooked dish.

Baking Recipes

Sunflower oil can substitute for butter, margarine and vegetable oils in baking recipes.

Roasting

Roast vegetables and meats with sunflower oil instead of butter or other vegetable oil.

Appendix 13: Recipes (CO & SO)

Chicken and coconut curry

Ingredients

For the roasted curry powder (makes more than you will need for this recipe)

- handful uncooked basmati rice
- 115g/4oz coriander seeds
- 30–40g/1–1½oz cinnamon pieces
- 30g/1oz black peppercorns
- 30–55g/1–2oz dried chilli (depending on how spicy you like your curry)
- 30g/1oz cumin seeds
- 85g/3oz fennel seeds

For the curry

- 2 tbsp coconut oil
- handful fresh curry leaves (approx. 10–12 leaves)
- 1 onion, finely sliced
- 2 garlic cloves, roughly chopped
- small piece of ginger (approx. 2.5cm/1in), peeled and roughly chopped
- 8 chicken thighs, boneless and skinless, cut into bite-sized pieces
- 2 tbsp roasted curry powder (from above)
- 200ml/7fl oz coconut milk
- salt, to taste
- freshly chopped coriander, to serve

Directions:

1. For the curry powder, heat a wide heavy-based pan over a medium–high heat. Once hot, add the basmati rice and cook for a few minutes. When starting to brown, add the coriander seeds, cinnamon pieces and black peppercorns and toast for a few minutes while stirring. (You can tell when they are almost roasted as the seeds should start to pop and break when squeezed in the hand.)
2. Add the dried chilli, cumin seeds and fennel seeds and continue to roast in the pan for a further 5 minutes, until fragrant and toasted. Remove from the heat and transfer to a large bowl and allow to cool.
3. Once cool, grind the spices in a spice grinder or pestle and mortar until you have a fine powder.
4. For the curry, heat the oil in a large pan and add the curry leaves, onion, garlic and ginger. Cook for 5–10 minutes until the onions are soft and lightly browned.
5. Add the chicken pieces to the pan and allow to brown, whilst stirring frequently.
6. Stir in the roasted curry powder, stir well to evenly coat all the chicken pieces and continue to cook for a further 5–10 minutes.
7. Add the coconut milk and pour in a cup of water (approximately 250ml/9fl oz). Sprinkle in a teaspoon of salt, bring to the boil, then reduce the heat and cover with a lid. Allow the curry to simmer gently for around 30 minutes, until the chicken is cooked through. Remove the lid and allow the sauce to reduce for a further 5–10 minutes to thicken. Stir occasionally and if you think the curry needs a little more coconut milk, add during cooking.
8. Transfer to a serving dish and sprinkle with freshly chopped coriander to serve. Serve with steamed rice (optional).

Coconut Oil Popcorn

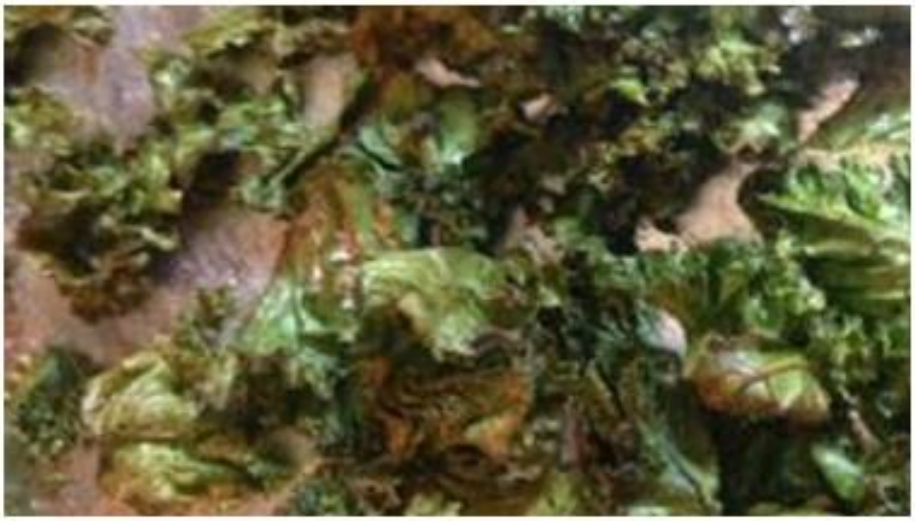
Ingredients:

- 1/2 Cup Organic Popping Corn
- 1 1/2 Tablespoons coconut oil
- Sea salt

Directions:

1. Heat a large, heavy bottom pot over medium heat. Be careful not to go over medium heat, or you may experience a very unpleasant chewy texture where the kernels were heated too fast and did not completely pop.
2. Add the coconut oil and let it completely melt. Once the oil is completely melted put a few kernels into the pan and wait for them to pop. This helps determine when the oil is heated enough to popping.
3. Once the test kernels have popped, place the rest of the popcorn seeds into the pan and cover.
4. After the kernels begin popping, begin to shake every 10 seconds or so until you hear the popping slow down. When the popping slows down to a pop every 2-3 seconds remove the pan from heat and continuously shake for another 10-20 seconds. This helps the popcorn at the bottom from burning.
5. After the 10-20 seconds, or you feel the popping is finished pour into a bowl, salt to taste and enjoy.

Kale Chips



Ingredients

- olive oil cooking spray
- 1 bunch kale, ribs removed and leaves torn into pieces
- 1 tablespoon coconut oil
- 1 pinch garlic salt, or to taste
- salt and ground black pepper to taste

Directions

1. Preheat oven to 450 degrees F (230 degrees C). Spray a baking sheet with cooking spray.
2. Put kale in a bowl and add coconut oil; mix with your hands until evenly coated. Spread coated kale onto the prepared baking sheet. Sprinkle garlic salt, salt, and pepper over kale.
3. Place baking sheet in the oven and turn off oven. Leave kale in the oven until crisp, about 20 minutes.

Roasted Sweet Potato Bites

Ingredients

- 1 cup peeled and cubed sweet potato
- 1/2 teaspoon coconut oil, melted
- 1 1/2 teaspoons chopped fresh rosemary
- 1 1/2 teaspoons chopped fresh thyme
- salt and ground black pepper to taste

Directions:

1. Preheat oven to 375 degrees F (190 degrees C).
2. Place sweet potato cubes in a bowl. Drizzle coconut oil over potatoes and toss, using your hands, until each cube is coated. Spread sweet potato cubes onto a baking sheet; season with rosemary, thyme, salt, and pepper.
3. Bake in the preheated oven until potatoes are softened, about 20 minutes.

Roast Beef with Yorkshire Pudding

Ingredients:

- 3–4-lb. beef top sirloin roast, tied
- salt and freshly ground pepper, to taste
- 1⁄4 cup plus 1 tbsp. Coconut oil
- 2 tbsp. finely chopped fresh thyme
- 2 tbsp. finely chopped fresh rosemary
- 4 cloves garlic, finely chopped
- 1 1⁄4 cups milk
- 1 cup plus 2 tbsp. flour
- 3 large eggs
- 1 lb. red potatoes, diced
- 1 lb. baby carrots
- 1 large shallot, finely chopped
- 1⁄2 cup red wine
- 1 cup beef stock

Directions:

1. Season beef with salt and pepper. In a small bowl, mix together coconut oil, thyme, rosemary, and garlic. Rub beef with herb mixture. Place beef in a small roasting pan, cover loosely with plastic wrap, and refrigerate for at least 8 hours or overnight.

2. Remove beef from refrigerator 2 hours before you are ready to roast; allow it to come to room temperature. Meanwhile, make the yorkshire pudding batter: Whisk together milk, 1 cup flour, 1 tsp. salt, and eggs in a bowl. Cover; let batter sit at room temperature for at least 1 hour.

3. In sauté pan, heat 1 tbsp. coconut oil, add potatoes and carrots until tender.

4. Heat oven to 500°. Remove plastic wrap and roast beef until browned, 18–20 minutes. Reduce temperature to 250°. Roast until a thermometer inserted into center

of beef reads 120° (for medium rare), about 25 minutes. Remove from oven, transfer to a cutting board, and let rest, tented with foil, while you make the yorkshire pudding and gravy. Pour pan drippings into bowl, leaving about 3 tbsp. in pan. Set roasting pan aside.

5. Raise oven temperature to 450°. Spoon 1⁄2 tsp. reserved drippings from bowl into each cup of a nonstick muffin pan. Heat in oven for 15 minutes. Uncover batter; whisk in 1 tbsp. drippings from bowl. Remove pan from oven; pour batter evenly between cups; bake until risen and brown, about 20 minutes. Reduce oven temperature to 350°; bake for 10 minutes to set puddings. Remove pan from oven; set aside.

6. Make the gravy: Heat reserved roasting pan over medium heat. Add shallots; cook until soft, 4–6 minutes. Add wine; cook, scraping up browned bits, until reduced by half, 4–6 minutes. Whisk in remaining flour, followed by stock. Cook, whisking, until thick, about 5 minutes. Slice beef; serve with pudding and gravy. Garnish with chopped parsley, if you like.

Beef casserole

Preparation time

Less than 30 minutes

Cooking time

over 2 hours

Serves

Serves 4

Ingredients

- 700g/1lb 9oz braising steak, trimmed of excess fat and cut into 3-cm/1¼-in chunks
- 2 tbsp sunflower oil
- 2 onions, thinly sliced
- 2 tbsp plain flour
- 2 tsp dried mixed herbs
- 150ml/5fl oz red wine
- 450ml/16fl oz beef stock, made with 1 stock cube
- 2 tbsp tomato purée
- 1 bay leaf
- 3 carrots (about 300g/10½oz), peeled and thickly sliced
- 300g/10½oz closed cup mushrooms, sliced
- sea salt and freshly ground black pepper
- handful fresh flat leaf parsley, roughly chopped, to garnish

For the kale mashed potato

- 575g/1lb 4½oz floury potatoes, preferably Maris Piper or King Edward, peeled and cut into roughly 5-cm/2-in chunks
- 25g/1oz butter
- 4 tbsp semi-skimmed milk
- 100g/3½oz kale, trimmed, hard stalks removed, roughly chopped
- sea salt and freshly ground black pepper

Method:

1. Preheat the oven to 180C/160C Fan/Gas 4. Season the beef well with salt and pepper.

2. Heat half of the oil in a large, non-stick frying pan and fry the beef in two batches for 2–3 minutes, or until browned on all sides. Transfer to a casserole dish using a slotted spoon or spatula once each batch is done.

3. Add the remaining oil and the onions to the pan and fry over a medium–high heat for 4–5 minutes, or until lightly browned. Place the onions into the casserole dish and sprinkle with the flour and dried herbs. Toss well together.

4. Pour the red wine and stock into the casserole dish and add the tomato purée and bay leaf. Stir well and bring to a simmer on the hob. Cover with a lid and bake in the oven for 1½ hours.

5. Carefully remove the casserole from the oven and stir in the carrots and mushrooms. Cover and bake for a further 45 minutes, or until the beef and vegetables are just tender.

6. Meanwhile, to make the kale mashed potato, place the potatoes into a large saucepan and cover with cold water. Bring to the boil and cook for about 15 minutes, or until very tender. Drain well then return to the saucepan. Mash with the butter and milk until smooth. Season with salt and pepper.

7. Place the kale into a saucepan and add 500ml/18fl oz water. Cover with a lid and bring to the boil for 5 minutes, or until tender, removing the lid and stirring the kale three or four times as it cooks. Drain well then stir into the mash.

8. Serve the kale mash alongside the casserole, garnished with the parsley.

Korma-style chicken curry

Preparation time

Less than 30 minutes

Cooking time

10 to 30 minutes

Serves

Serves 4–6

Ingredients

- 5 skinless and boneless chicken breasts, sliced into thin strips
- 3 tbsp sunflower oil
- 2 brown onions, thinly sliced
- 2 garlic cloves, crushed
- ½ fresh red chilli, seeds removed, finely chopped
- 2 tbsp medium curry powder
- 1 tsp ground cumin
- 10 green cardamom pods, crushed to remove the seeds
- 450ml/16fl oz chicken stock
- 125g/4½oz ground almonds
- 2 tbsp mango chutney
- ½ lemon, juice only
- 200g/7oz full-fat natural yoghurt
- salt and freshly ground black pepper
- boiled or steamed rice, to serve
- coriander leaves, to garnish

Method

1. Season the chicken pieces with salt and pepper.

2. Heat a large, deep non-stick frying or sauté pan until piping hot and add 2 tablespoons of the oil. Quickly fry the chicken for 4–6 minutes until sealed and slightly golden. (You may need to cook the chicken pieces in batches if they don't fit in your pan in a single layer.) Remove with a slotted spoon and set aside.

3. Add the remaining oil to the pan with the onions, garlic and chilli and fry over a medium–high heat for 10 minutes, or until the onions are golden brown. Add the spices and fry for another minute, stirring well to coat the onions. Stir in the stock, ground almonds and mango chutney, then bring to the boil and allow to bubble for 2–3 minutes.

4. Return the chicken to the pan and stir in. Reduce the heat, cover with a lid and simmer for about 5–7 minutes, or until the chicken is cooked through.

5. Stir in the lemon juice and yoghurt, check the seasoning, adding salt and pepper to taste. Serve with boiled or steamed rice and garnish with coriander leaves.

Easy chicken and pea risotto

Preparation time
Less than 30 minutes

Cooking time
10 to 30 minutes

Serves
Serves 4

Ingredients

- 2 tbsp sunflower oil
- 1 onion, cut in half, coarsely grated
- 2 garlic cloves, grated
- 250g/9oz arborio risotto rice
- 100ml/3½fl oz white wine, dry vermouth or water
- 1 litre/1¾ pints chicken stock cube, made with 1 stock cube
- 250g/9oz cooked leftover chicken, skin removed, cut into small pieces
- 200g/7oz frozen peas
- 75g/2¾oz Grana Padano or other hard Italian-style cheese, finely grated
- 25g/1oz butter
- freshly ground black pepper

Method

DICe Sunflower Oil Recipes

1. Heat the oil in a large, non-stick saucepan over a medium heat. Add the onion and garlic and fry for 2-3 minutes, stirring occasionally, until softened and just beginning to colour.

2. Add the risotto rice to the pan and stir well for 30-40 seconds, until the oil has coated the grains of rice.

3. Pour in half of the wine and allow to bubble for 30-40 seconds, then add all of the stock and bring to the boil, stirring well. Reduce the heat and simmer, uncovered, for 8-10 minutes, stirring frequently, until the rice is almost tender and the risotto is creamy in appearance.

4. Stir in the remaining wine, the chicken and the frozen peas, then continue to cook, stirring constantly, for a further 4-5 minutes, or until the chicken and peas are heated through and the rice is tender with a slight bite.

5. Remove the pan from the heat, then stir in the butter and cheese. Season with black pepper. Cover the pan with a lid and set aside for 5 minutes before serving.

Vegetarian chilli

Preparation time
30 minutes to 1 hour

Cooking time
30 minutes to 1 hour

Serves
Serves 4-6

Ingredients

- 175g/6oz green lentils
- 2 tbsp sunflower oil
- 1 large onion, chopped
- 1-2 cloves garlic, crushed
- 1-2 tsp chilli powder
- 1 tsp cumin seeds
- 1 red and 1 green pepper, stalk and seeds removed, and chopped
- 2 carrots, peeled and chopped
- 2 x 400g/14oz cans chopped tomatoes
- 1 heaped tbsp tomato purée
- 300ml/½ pint vegetable stock
- 100g/4oz frozen peas
- 175g/6oz mushrooms, wiped and quartered
- 1 courgette, chopped
- salt and freshly ground black pepper
- 1 can kidney beans, drained

Method

1. Place the green lentils in a large bowl and pour boiling water over them. Leave to soak for 30 minutes. (Alternatively, buy a tin of pre soaked lentils.) Drain.

2. Heat the oil in a large saucepan and fry the onion and garlic together with the chilli and cumin, about ten minutes or until the onions are soft.

3. Add the peppers, carrots and drained green lentils and cook for five minutes, stirring all the time. Add the tomatoes, purée, stock and peas, bring to the boil and simmer until the lentils are tender (about 30 minutes). Add the mushrooms and courgettes and simmer for five minutes more. Season to taste.

4. Add the cooked kidney beans and simmer for five more minutes.

5. Serve with cooked rice.

Appendix 14: TIDieR & Consort Checklists

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located ** Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	_Title, page 1	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	_Page 31-section 2.6_	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	_Page 122, section 6.5	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	_Page 42, section 4.1_	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	_Appendix 1-Protocol___	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	- Page 122, section 6.5_	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	- Page 42, section 4.1_	_____
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	_ Page 42, section 4.1_	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	__ Page 124, section 6.5	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	_Page 63, Section 4.13_	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	__Page 125, Section 6.6__	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	__ Page 125, Section 6.6_	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

TIDieR checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	31 & 34
	2b	Specific objectives or research questions for pilot trial	31
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	42
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	45
Participants	4a	Eligibility criteria for participants	47
	4b	Settings and locations where the data were collected	51
	4c	How participants were identified and consented	49
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	50
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	51
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	63
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	46
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			50
Sequence generation	8a	Method used to generate the random allocation sequence	50
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	50
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	50
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	50 & protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	50
	11b	If relevant, description of the similarity of interventions	43
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	59
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	66
	13b	For each group, losses and exclusions after randomisation, together with reasons	67
Recruitment	14a	Dates defining the periods of recruitment and follow-up	66 & 67
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	70
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	72
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	90
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	73
	19a	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	129
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	128
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	120
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	137
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	42
Protocol	24	Where the pilot trial protocol can be accessed, if available	42
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	
	26	Ethical approval or approval by research review committee, confirmed with reference number	appendix

Appendix 15: APO E4 Fact Sheet

The effect of vegetable oil on cognitive functions in Older Adults

APO E4 genotype fact sheet

Humans have around 25,000 genes; some are the same among people while others differ from one person to another. Different genes affect the body in different ways.

We are interested in the Apo E4 gene, which is why we will test for the variations of this gene in your blood. This fact sheet will explain what the Apo E4 gene is and its function in the body.

What is Apo E4, and what is its function in the body?

APO E4 is one version of the APO E gene which produces the protein APO E. This is a portion of lipoproteins which are particles that transport fats in the body. Studies have shown that APO E4 plays a role in brain functions.

Does everyone have the same Apo E gene?

The Apo E gene differs from person to person. The three common versions of the gene are E2, E3 and E4, and they result in very small differences in the Apo E protein. These differences lead to changes in the functions and activities of the gene. Every person inherits two Apo E genes, one from each parent. The possible combinations are:

Gene	Presence in UK Population
E2/E2	1 %
E2/E3	11%
E2/E4	2%
E3/E3	61%
E3/E4	23%
E4/E4	2%

How does this affect me as an individual?

Our main interest is in the effect of consuming vegetable oil on memory, which would be affected by the Apo E4 genotype. Research has shown that Apo E4 gene combinations (E2/E4, E3/E4; E4/E4) may increase a person's risk of developing memory loss and Alzheimer's disease at an earlier age. While having the E2/E3 or E2/E2 combination reduces the risk by up to 50%.

The results of your genetic profiling will be made available to you only if you had requested for it at time of consenting. Wishing not to receive the results will not affect your participation in the study, or your care.

If you were to be told that you have the APO E4 gene, we would recommend you to contact the genetic counselling service to discuss what it means. Within specific NHS catchment regions there are Genetics Clinics that provide specialised services for anyone who may be concerned about a particular genetic condition. If you would like to access this service, please contact us and we would be able to send a copy of your result to your GP requesting them to refer you on. Alternatively, you could share your report and request for a referral from your GP.

Currently, there is no available treatment that would completely reduce the risk of developing dementia. However, there is good evidence that food intake changes, sports, quitting smoking, and a healthy weight might reduce the risk of the disease. The evidence might not be fully strong now but it is important that those more at risk take advantage of any available information.

Implications for health insurance:

The genotyping that will be doing is called 'predictive testing', thus you do not have to disclose the results of test to your insurance company.

How will the test be performed?

A saliva sample will be collected from you through a buccal swab, in which cells will be collected by scraping a cotton stick on the inside of your cheek. The sample will be anonymized and sent to the laboratory for analysis. We will receive the result of your test within 14 working days and will inform you of the results if you request to know. After receiving your results, your sample will be destroyed.

Why are researchers interested in this gene?

We are interested in the effect of increase in ketone bodies (which are substances/molecules in the blood produced in the liver during the release of energy from fats /oils in your food or body) due to consuming vegetable oils on memory. However, the presence of APO E4 gene might alter this effect because people

carrying that gene absorb and digest fats/oils differently. **This means that the intervention we are testing might have a different effect on them.**

Contact Details:

Study supervisory Team:

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Thank you for reading this fact sheet, if you still have any questions or concerns please contact us.

Appendix 16: Risk Assessment

General Risk Assessment Form

Before completing this form, please read the associated guidance on 'I: Health & Safety/Public/Risk Assessment/Guidance. This form should be used for all risks except from hazardous substances, manual handling & Display Screen Equipment (specific forms are available for these). If the risk is deemed to be 'trivial' there is no need to formally risk assess or record.

All completed forms must give details of the person completing the assessment and be dated. Risk assesses the activity with its present controls (if any), then re-assess if action is to be taken and after further controls are put in place.

The completed form should be kept locally within the School/Professional Service.

1. Describe the Activity being Risk Assessed:

This risk assessment covers the taking of small (<50 µL), fingertip capillary blood samples, and the subsequent analysis for concentrations of: ketones

When blood sampling, only the PhD student who holds a current first aid certificate and are vaccinated (for Hepatitis B) may undertake this procedure.

2. Location(s)
Participant's houses

3. Persons at potential Risk (e.g. consider specific types of individuals)
i) Subjects from whom blood is taken
ii) Experimenters taking blood
iii) Cleaning staff disposing of waste material
iv) Others liable to cross-contamination (i.e. family members, carers)

4. Potential Hazards (e.g. list hazards without considering any existing controls):
i) Cross-contamination between the subject's and the experimenter's blood during blood sampling leading to a risk of transmitting Hepatitis and/or HIV;
ii) Contamination due to lancet puncture of the experimenter's skin;
iii) infection of the subject through an open capillary puncture due to an unclean environment;
iv) Wounds due to needle accident (i.e., slippage, lancet mechanism not firing upon first attempt);
v) Repeated punctures on the same finger may result in additional discomfort, bleeding and bruising;
vi) Contamination of work space with infected blood/contaminated materials;
vii) The subject or experimenter fainting during fingertip blood collection or analysis;

5. Any Control Measures Already In Place:

Prior to blood taking:-

5.1.1 Personnel and training
Only the PhD student who holds a current first aid certificate will be allowed to take blood. All staff are appropriately trained to inform clients of any high-risk values recorded in a manner which produces the least amount of distress.

All experimenters, technicians and designated core staff who have responsibility for technical matters associated with blood sampling must declare themselves to be knowingly free of any blood-borne disease and have evidence of current immunisation for Hepatitis B. A disposable apron and powder-free nitrile gloves are always worn during testing.

5.1.2 Equipment
Blood sampling is by capillary puncture using an Autoclix or similar spring-loaded lancet. The lancets are sterile and single-use, and are ejectable directly into a sharps container without being touched. The use of commercially available lancets designed to reduce the risk of stick injury are used.

Following cleansing with an antiseptic wipe and puncture, blood is taken by capillary action, with the finger squeezed until sufficient blood is collected into a microvette for analysis.

Blood is analysed with the use of Abbott Optuim neo analyser. The punctured finger is squeezed until there is sufficient blood to cover the tip of test strip. The equipment is sensitive enough to only require 0.3 µL blood sample for measurement. Blood measurement takes 15 seconds and the used test strip is placed directly into the sharps container.

5.1.3 Environment

All equipment will be kept within a specific holdall bag clearly identified as potentially hazardous containing contaminated materials. Only trained individual administering the test will be allowed contact with the blood sampling equipment bag. The above-mentioned precautions and countermeasures will be taken by the student responsible.

All soiled materials are placed immediately within an appropriate clinical waste container.

5.1.4 Participants

Participants complete and sign a health questionnaire and informed consent form prior to participation. This includes full explanations of what is required and what can be expected (informed consent) which includes questions about blood-borne disease. Any person providing the blood sample has the right to withdraw participation at any time without recrimination.

5.2 During Blood Testing:-

5.2.1 Experimenters

Gloves are always worn.
Only those approved to take blood may collect samples.
Any minor scratches or cuts are covered with a dressing.
The greatest risk is an accidental puncture of the skin and cross contamination.

This risk is minimised by formal training, the careful handling of equipment and managing one test at a time. Used lancets and test strips are placed immediately into the sharp's container, and contaminated waste (including alcohol wipes, used plasters and waste tissues) into the appropriate clinical waste container.

The experimenter/technician holds the sole responsibility of emptying the biohazard waste bin in the laboratory on a regular (less than monthly) basis. An external company then is responsible for removing the waste from sharps containers and biohazard waste bins, from the university site.

Experimenters do not resample the same test area.

5.2.2 Participant

The subject will be given written, detailed information on the test, prior to providing informed consent to testing, and blood sampling. Upon testing, the subject is re-briefed upon test and blood collection, in particular, the sensation of giving blood and all potential risks involved. The puncture site is always prepared with an antiseptic wipe. A plaster is always used to cover the puncture immediately.

5.3 After blood taking

5.3.1 Waste

All sharps are placed into a Sharps Bin and all contaminated non-sharps placed in a separate Clinical Waste Bin. Full bins are transported to the local hospital for incineration. BU Talbot campus and Lansdowne have services already in place to remove clinical waste.

6. Standards to be Achieved: (ACOPs, Qualifications, Regulations, Industry Guides, Suppliers instructions etc)
Emergency First Aid Training

7. Estimating the Residual Risk (e.g. remaining risk once existing control measures are taken into account)

Choose a category that best describes the degree of harm which could result from the hazard and then choose a category indicating what the likelihood is that a person(s) could be harmed.

	Slightly Harmful (e.g., minor injuries)	**Harmful** (e.g., serious but short-term injuries)	**Extremely Harmful** (e.g., fatality, long-term injury, or incurable disease)
Highly Unlikely	Trivial Risk ☐	Tolerable Risk ☐	Moderate Risk ☐
Unlikely	Tolerable Risk ☒	Moderate Risk ☐	Substantial Risk ☐
Likely	Moderate Risk ☐	Substantial Risk ☐	Intolerable Risk ☐

8. Note the advice below on suggested actions and timescales:

Risk (from No.7)	**Action/Timescale**
Trivial Risk ☐	No action is required and no records need to be kept.
Tolerable Risk ☒	No additional controls are required, although consideration may be given to an improvement that imposes no additional cost/s. Monitoring is required to ensure that the controls are maintained.
Moderate Risk ☐	Efforts should be made to reduce the risk, but the costs of prevention should be carefully measured and limited. Any new measures should be implemented within a defined period. Where the moderate risk is associated with extremely harmful consequences, further assessment may be necessary to establish more precisely the likelihood of harm as a basis for determining the need for improved control measures.
Substantial Risk ☐	Work should NOT commence until the risk has been reduced. Considerable resources may have to be allocated to reduce the risk. Where the risk involves work in progress, urgent action MUST be taken.
Intolerable Risk ☐	Work should not be started or continued until the risk has been reduced. If it is not possible to reduce the risk even with unlimited resources, work MUST remain prohibited.

9. If 'Moderate' 'Substantial' or 'Intolerable': What New Control Measures are to be Considered to reduce risk?	**10. Referred to:**	**11. Date:**
• All control measures have been considered. Vigilance and continued mindfulness about the risks associated with blood sampling should prevail at all times to ensure that all strategies incorporated to manage risk are maintained to a high standard.		

12. Ensure those affected are informed of the Risks & Controls
(Confirm how you have done this e.g. written instructions):
Only trained individuals will be allowed to collect blood samples. The training is designed to cover the standards required for safe and effective blood handling.

13. Person who did Assessment:	Raysa El Zein	**14. Date:**	21/08/2018	**15. Review Date:**	31/01/2019