Effects of a Mediterranean-style dietary pattern on mental wellbeing and cognition

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Abstract

Mood and anxiety disorders, cognitive decline and incident dementia are significant and growing public health concerns. Long-term adherence to a Mediterranean-style dietary pattern (MDP) has been associated with enhanced mood and cognition in observational studies. Yet, the shorter-term effects of a MDP on brain health are poorly understood. To address this, we conducted a systematic review of the available literature from randomised controlled trials (RCT), to provide preliminary evidence on the potential of a MDP to improve attention, alertness and contentment in 10 days, to define research gaps and inform the focus of this research project. Accordingly, we designed a crossover RCT, named MediMood, to assess the postprandial and 5-day effects of a MDP on mood (primary outcome), cognition, cerebral blood flow, sleep (which is an important mediator of mental health) and blood biomarkers in adults with existing mental health complaints (n=25). After 5 days, a MDP reduced total mood disturbance, tension, depression, fatigue, confusion, increased alertness and vigour, improved motor function variability, reduced inflammation and increased serum cortisol levels relative to a Western diet, with enhanced insulin sensitivity observed postprandially following a MDP lunch. Using longitudinal data from C-19 Wellbeing Tracker study, we examined up to 5-day, bidirectional lagged relationships between fruit, vegetable, sugar intake and overall diet quality and happiness, low mood, stress and sleep quality in a cohort (n=674). Consistent associations were observed between diet quality and sleep quality lasting for 5 days. This PhD research offers a novel contribution to the literature on the efficacy of a MDP to improve mental health in the short-term, in particular in those with existing mental health disorders. Future studies are required to confirm and refine the initial evidence we provide.

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AD	Alzheimer's Disease
AE	Adverse Event
AHEI	Alternative Healthy Eating Index
ASL	Arterial Spin Labelling
AUC	Area Under Curve
BBB	Blood Brain Barrier
BDNF	Brain Derived Neurotrophic Factor
BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CBF	Cerebral Blood Flow
CBT	Cognitive Behavioural Therapies
CI	Confidence Interval
CNS	Central Nervous System
COMPASS	The Computerised Mental Performance Assessment System
CRF	Clinical Research Facility
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DAL	Dietary Acid Load
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DHA	Docosahexaenoic Acid
DI	Dietary Intake
DII	Dietary Inflammatory Index
DSM	Diagnostic And Statistical of Mental Disorders
ED	Endothelial Dysfunction
EDTA	Ethylenediamine Tetraacetic Acid
EMA	Ecological Momentary Assessment
EPA	Eicosapentaenoic Acid
EPIC	European Prospective Investigation into Cancer
EVOO	Extra Virgin Olive Oil

FAIR 2	Frankfurt Attention Inventory 2
FFQ	Food Frequency Questionnaire
FIML	Full Information Maximum Likelihood
FLAIR	Fluid-Attenuated Inversion Recovery
FMD	Flow Mediated Dilation
fMRI	Functional MRI
FVI	Fruit And Vegetable Intake
GABA	Gamma-Aminobutyric Acid
GAD	Generalised Anxiety Disorder
GI	Glycaemic Index
HALE	The Healthy Ageing: A Longitudinal Study in Europe
HDLM	Hippocampal-Dependent Learning and Memory
HEI	Healthy Eating Index
HFHS	High Fat High Sugar
HPA	Hypothalamic-Pituitary-Adrenal
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
KSD	Karolinska Sleep Diary
KSS	Karolinska Sleepiness Scale
MCI	Mild Cognitive Impairment
MDMQ	Multidimensional Mood State Questionnaire
MDP	Mediterranean-Style Dietary Pattern
MDS	Mediterranean Diet Score
MEDAS	Mediterranean Diet Adherence Screener
MedEx-UK	Mediterranean Diet, Exercise and Dementia Risk in UK Adults
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
MUFA	Monounsaturated Fatty Acid
NDNS	National Diet and Nutrition Survey
NHS	National Health Service
NICE	National Institute of Care and Excellence
NTB	Neuropsychological Test Battery
PA	Physical Activity

PHQ-9	Patient Health Questionnaire-9
POMS	Profile Of Mood States
PPI	Patient Public Involvement
PREDIMED	Prevencion Con Dieta Mediterranea
PSQI	Pittsburgh Sleep Quality Index
PUFA	Polyunsaturated Fatty Acid
QoL	Quality of Life
RCT	Randomised Controlled Trial
SART	Sustained Attention to Response Task
SBP	Systolic Blood Pressure
SCI	Subjective Cognitive Impairment
SCS	Seven Countries Study
SD	Standard Deviation
SEM	Structural Equation Modelling
SFA	Saturated Fatty Acid
SMD	Standardised Mean Difference
T2D	Type 2 Diabetes
TMD	Total Mood Disturbance
TOF	Time Of Flight Angiography
UEA	University Of East Anglia
UWWBIC	The UEA Wellcome-Wolfson Brain Imaging Centre
VAS	Visual Analogue Scale
WD	Western Diet
WHO	World Health Organization
WMH	White Matter Hyperintensities

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Dedication

In loving memory of my dearest grandpa, Yusuf Ziya Eşgünoğlu, whose passing from Alzheimer's disease in November 2018 at the age of 84 motivated me to do this PhD. His endless unconditional love continues to ignite my soul. To his warmth, kindness and compassion, I owe any goodness that resides within me.

Statement of publications arising from this thesis

Full publications:

Chapter 2: Esgunoglu L, Jennings A, Connole ES, Murphy KJ, Minihane AM. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental well-being: a systematic review of clinical trials. British Journal of Nutrition. 2022 Oct;128(7):1247-56.

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Chapter 5: Esgunoglu, L., Khondoker M., TBC, Naughton F., Jennings, A., & Minihane, A. M. Bidirectional relationships between dietary intake, mental health and sleep: C-19 health behaviour and wellbeing daily tracker study

Conference proceedings:

Chapter 2: Esgunoglu L, Jennings A, Connole ES, Murphy KJ, Minihane AM. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials. Proceedings of the Nutrition Society. 2021 Jan;80(OCE3):E151.

Chapter 3: Esgunoglu L, Liaquat M, Gillings R, Lazar A, Brooks J, Penny W, Hornberger M, Jennings A, Minihane AM. Effects of a short-term Mediterranean diet on mental health, cognition and cerebral blood flow in UK adults: MediMood study protocol. Alzheimer's & Dementia. 2023 Dec;19:e074649.

Statement of presentations arising from this thesis

Oral presentations:

i. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials, FMH Postgraduate Research Student Conference, June 2021, Norwich, UK
ii. Plant-based diets, cognition and mental health: Introducing MediMood, UWWBIC, June 2022, Norwich, UK
iii. The impact of Mediterranean diet versus a Western diet on mood, anxiety and cognitive performance: randomised controlled trial protocol, 3-minute presentation FMH, June 2023, Norwich, UK
iv. MediMood study: protocol, recruitment and sample characteristics, NuBrain Final Meeting, Jan 2024, Newcastle, UK

Poster presentations:

i. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials, The Nutrition Society, The Irish Section Conference, June 2021, online
ii. Acute impacts of a /mediterranean diet and a Western diet on mental wellbeing, cognitive performance and cerebral blood flow in UK adults with mild to moderate mental health symptoms: MediMood study protocol, Alzheimer's Research UK, March 2023, Scotland
iii. The impact of an unsaturated fat-rich Mediterranean diet versus a saturated fat-rich Western diet on mood, anxiety and cognitive performance: the MediMood randomised controlled trial protocol, International Society for the Study of Fatty Acids and Lipids, July 2023, France
iv. Effects of a short-term Mediterranean diet on mental health, cognition and cerebral blood flow in UK adults: MediMood study protocol., Alzheimer's Association International Conference, July 2023, The Netherlands

Chapter 1. General introduction

Nutritional intake plays a central role in the maintenance of health state (1) as defined by the World Health Organization (WHO) as "a complete state of physical, mental and social wellbeing" (2). Whilst the effects of diet on physical wellbeing and the risk of chronic conditions such as type 2 diabetes (T2D) (3) and cardiovascular diseases (CVD) (4) have been extensively researched, the evidence is less clear on the nature of the relationship between nutrition and mental wellbeing which spans psychology and neurology. Thus, a new concept has emerged, called by several names such as psychonutrition (5), neuronutrition (6), nutritional psychiatry (7), nutritional neuroscience (8) and nutritional cognitive neuroscience (9), which is the focus of the present thesis.

1.1. Mental wellbeing and cognition

1.1.1. The concepts of mental health disturbances with a focus on low mood, anxiety, stress, cognition and sleep

Mental wellbeing is an inseparable component of an overall health state as described by the WHO (2). The globally standard manual to define and to classify mental health disorders for research and clinical care purposes is the 'International Classification of Diseases (ICD)', created by the WHO (10) with most up-to-date version being ICD-11 released in 2022 (11). Alongside following ICD-11, NHS England has its clinical guidelines created by the National Institute of Health and Excellence (NICE) based upon ICD, which will be referred to in this thesis (12, 13). Amongst a wide range of mental and cognitive disorders defined by ICD-11, mood, anxiety, neurocognitive and sleep disorders are of key interests to this PhD.

ICD-11 Section 06 presents the 'mood disorders', 'anxiety or fear-related disorders', 'disorders specifically associated with stress' and 'neurocognitive disorders' under the 'mental, behavioural and neurodevelopmental disorders', while the 'sleep-wake disorders' are listed as Section 07 (Table 1.1) (14). Comparably, the NICE covers anxiety,

dementia and depression under 'mental health, behavioural and neurodevelopmental conditions' whilst dementia is also presented under 'neurological conditions' (15). NICE currently does not have an umbrella guideline on sleep disorders, with the most relevant to this thesis covered by NICE being insomnia (16).

Table 1.1. Classification of mental health disorders according to the different guides

ICD-11	NICE
Mental, behavioural and neurodevelopmental disorders	**Mental health, behavioural and neurodevelopmental conditions**
Mood disorders	Depression
Anxiety or fear-related disorders	Generalised anxiety and panic disorder
Disorders specifically associated with stress	Post-traumatic stress disorder
Neurocognitive disorders	Dementias
Sleep-wake disorders	**Neurological conditions**
	Dementias
	Insomnia

ICD: International Classification of Diseases by World Health Organization; NICE: National Institute of Excellence and Care by National Health System England. Bold font represents the parenting titles within the relevant manuals. Only the subtitles that are relevant to this PhD are presented.

Mood disorders

According to the ICD-11, mood disorders include a group of depressive and bipolar disorders which are described depending on the type of mood episodes and their specific patterns, as illustrated in the Figure 1.1. The depressive episode is one of the four main types of mood episodes, which then form depressive disorders and bipolar disorders.

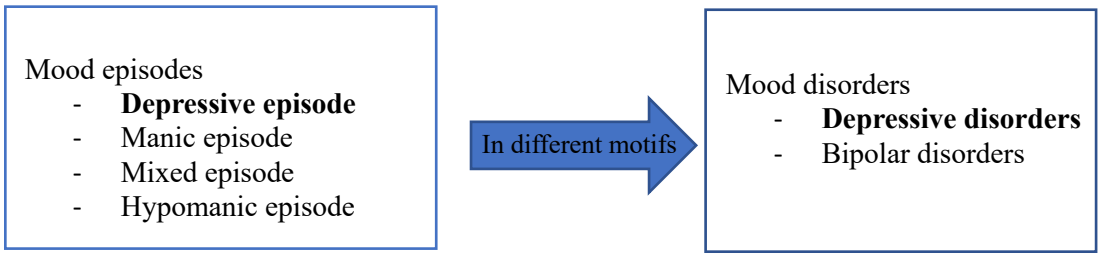


Figure 1.1. ICD-11's description of mood disorders (14)

ICD-11: International Classification of Diseases. Bold font represents the interests for this PhD.

ICD-11 clusters the features of depressive episodes into "affective, cognitive-behavioural and neurovegetative groups" (14). A depressive episode must have minimum five of those features with at least one being from affective disorder (17), and the symptoms must be lasting for a minimum of two weeks (Figure 1.2) (18).

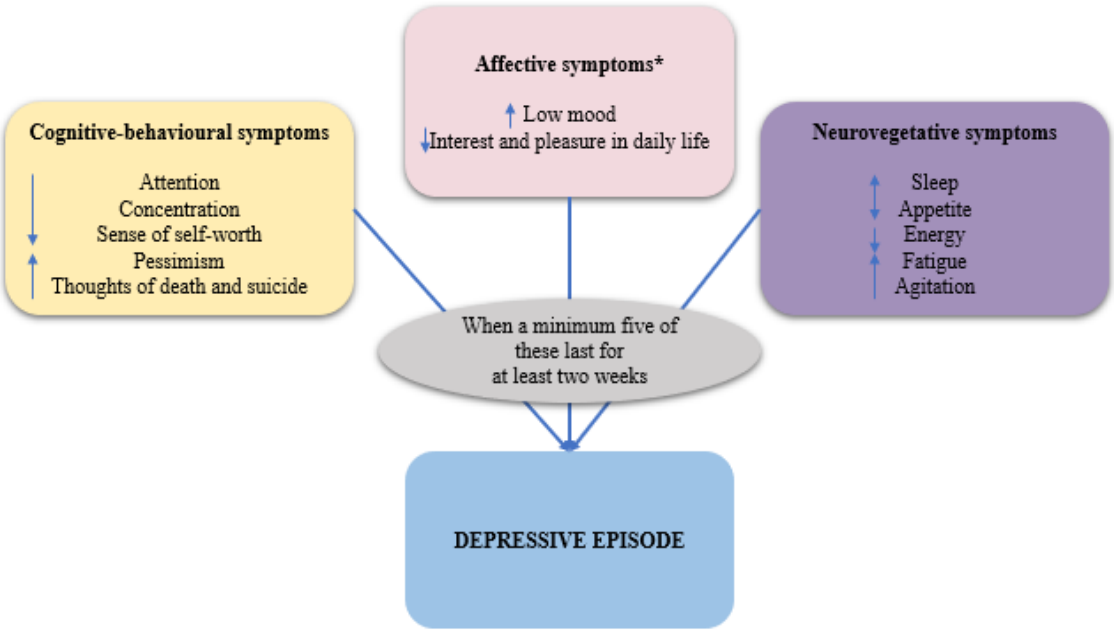


Figure 1.2. Symptoms required for a depression diagnosis

According to International Classification of Disease (ICD-11) and The National Institute of Health and Excellence (NICE) guidelines, to diagnose depression, at least one of five symptoms from the three groups should be presenting with at least one being from the affective group*, and symptoms should last for a minimum of two weeks. Sleep and appetite can display either a decrease or an increase.

Depression is classified into categories as mild, moderate and severe depending on the severity and the frequency of symptoms (17). In mild depression, no symptom is intense and no significant disturbance is seen in essential areas of life such as self-care and family, with difficulties being limited to social and occupational life (17), whilst moderate level depression is presented with a higher number of symptoms with a substantial struggle in several areas of daily life (14). This PhD focuses on mild and moderate level of depression/low mood.

Anxiety

Anxiety, as a general term, is characterised by excessive worry that is hard to control (14). The generalised anxiety disorder (GAD), which is the most common type of anxiety disorder and will be discussed in this thesis, marks the excessive worry as its central feature, that is shown to be associated with shorter cardiac intervals compared to non-anxious individuals as its autonomic characteristic (19). Additional somatic symptoms of GAD can be fatigue, tiredness, being anxious/tense, feeling on edge, and difficulty in concentration and sleep (20), which, in turn causes increased distress and loss of functioning in daily life (21). At least half of the individuals diagnosed with either anxiety or depression present the other disorder too, displaying a common comorbidity pattern (22).

Stress

Stress is examined under a different title in ICD-11. 'Disorders specifically associated with stress' including such as post-traumatic stress disorder and adjustment disorder caused by a stressful or a traumatic event and characterised by similar symptoms to depression and anxiety (14). For instance, the COVID-19 pandemic was defined as a stressor for adjustment disorders in Poland (23). "Acute stress disorder' is caused by factors influencing health status and defined as a temporary presentation of "emotional, somatic, cognitive or behavioural symptoms as a result of exposure to an event or situation" (14). Depression, anxiety, anger and worry are observed in acute stress reaction (24). Of note, stress is a response to real challenging situations and fear is activated by real threats whereas anxiety is usually triggered by the situations that do not pose immediate danger, nevertheless, chronic exposure to stress is likely to cause anxiety and/or depressive disorders (25).

Cognition

The term cognition or neurocognition covers specific cognitive functions and associated brain regions, neural pathways and networks (26). ICD-11 lists "attention/concentration, memory, language, visual spatial/perceptual skills, processing speed and executive functioning (e.g. problem solving, judgement)" as the main cognitive

functions (14). Six main cognitive functions listed by the Diagnostic and Statistical of Mental Disorders (DSM-5) are "complex attention, executive functioning, learning and memory, perceptual-motor function, language, and social cognition", of which subdomains are presented in Table 1.2 (27). The cognitive domains that are of interest to this PhD are attention, motor function, executive function, memory, impulse control and visuospatial function.

Table 1.2. Cognitive key domains and subdomains according to the DSM-5

Complex attention	**Executive functioning**	**Learning and memory**	**Perceptual-motor function**	**Language**	**Social cognition**
Sustained attention	Planning	Free recall	Visual perception	Object naming	Recognition of memories
Divided attention	Decision making	Cued recall	Visuocons-tructional reasoning	Word finding	Theory of mind
Selective attention	Working memory	Recognition memory	Perceptual-motor coordination	Fluency	Insight
Processing speed	Responding to feedback	Semantic long-term memory		Grammar and syntax	
	Inhibition				
	Flexibility	Implicit learning		Receptive language	

DSM-5: Diagnostic and Statistical of Mental Disorders (27).

Cognitive disorders are characterised by a decline in cognitive abilities compared to the individual's previous level (14), which may begin as early as the third or fourth decades of life (28). Cognitive decline is also often presented in mental disorders (14, 29). ICD-11 divides neurocognitive disorders into three groups, namely, mild neurocognitive disorder, amnestic disorders (dementias) and delirium, with common symptoms such as disturbed attention, global cognition and sleep (14).

Clinical stages are defined based on the severity of cognitive loss (Figure 1.3). Subjective cognitive impairment (SCI) is the first step en-route to incident dementia,

where individuals complain about their memory (30, 31). However, it is unlikely to be diagnosed through objective clinical tests (30, 31). The next phase is the 'mild cognitive impairment (MCI) (32), presenting with early signs of 'dementia' (33). The term 'dementia' refers to the severest form of cognitive decline that dramatically restricts a person's daily living and independence (34). Dementia is an overarching term, which is loosely defined as a loss of cognition which is greater than would be expected for biological age and impact on the ability to live independently (35). It has a multi-faceted aetiology and the term dementia is a collective for over 100 individual progressive neurodegenerative disorders (35). Additionally, pseudo-dementia is a concept occurring in depression and/or anxiety where pathophysiological features of dementias do not exist, yet patients with mental health disorders still experience cognitive symptoms similar to Alzheimer's Disease (AD) (36). This PhD will not focus on a specific neurocognitive disorder but cognitive performance in general.

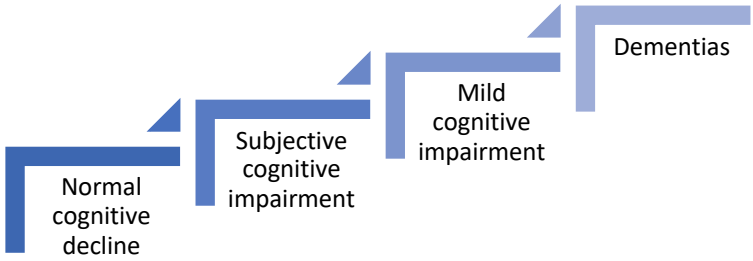


Figure 1.3. The steps of cognitive decline severity

Sleep

Sleeping is core to maintain health and wellbeing (37). It is an inert unresponsive state as a result of lower cerebral activity (38), but it is metabolically dynamic and actively regulated process (39). Sleep is proposed to have multiple functions such as tissue restoration (38) and hormonal regulation of, for example, adrenaline, noradrenaline and dopamine (38, 40, 41). It was later argued that these bodily functions cannot be the only explanation to sleep as they are not able to explain the unconsciousness state, the basic feature of sleep (42). Thus, the primary focus of sleep medicine has been moved to the central nervous system (CNS) and the brain (43).

Sleep plays a critical role in emotional regulation. For example, people with low sleep quality experience negative emotions more (44). Yet, the most important sleep function is proposed to be cognition (43) as it engages in several cognitive functions, particularly attention (45), learning (46) and memory (47, 48). Comparably, low sleep quality is associated with reduced cognitive performance in attention and executive functioning tasks regardless of depression and anxiety presence (49). Cerebral metabolism (50), network organisation (51), plasticity (43, 52) and synaptic homeostasis (46) are theorised to be other functions of sleep related to mental and cognitive health. Sleep difficulties are one of the diagnostic symptoms of mood and anxiety disorders (14). ICD-11 defines several sleep-wake disorders (14). Not a specific sleep-wake disorder, but the overall sleep quality is interest of this PhD.

Incidences of mental and cognitive disorders

Disorders in mental, cognitive and sleep health are related to each other and accounts for a significant rate of disease burden (53). In 2019 almost a billion people suffered from mental health disorders worldwide, of which depressive and anxiety disorders were the most common, affecting people from childhood to later life (53). Mental disorders were in the top three main causes of non-fatal health loss in terms of the years lived with disability in 2017 (54). Furthermore, depression is projected to become the first cause of disease by 2030 (55). Mental disorders may also be fatal by leading to suicide which accounts for more than 700,000 global deaths annually (56). According to UK 2022 statistics, over 15% of the population suffer from moderate to severe depression, with the prevalence being nearly 20% in women, 30% in young adults (16-29 years) and 40% in young females (57) .

The range of SCI prevalence has been reported to be 25-56% among people over 65 years (30), while MCI rates were estimated to vary between 5-30% (58). Ten to twenty percent of people with MCI advance to dementia every year (33). The global number of individuals living with dementia is expected to reach 150 million by 2050 (59), with 1.7 fold higher prevalence in women despite the age standardisation (60). According to a 2023 study, the most common dementia type was AD accounting for 54% of the dementia cases (61). Regarding mortality rates, in 2021, dementias were the number seven cause of death in the world, and number four in high income countries (62).

A 2024 NICE report stated that one third of Western adults suffer from insomnia, the most prevalent form of sleep-wake disorders leading to significant challenges in daily functioning (16, 63). Bidirectional relationships were highlighted between sleep difficulties and mental health disorders (16). Two third of people with mood disorders report sleep problems (64), while approximately 35-50% of people with sleep disturbances experience mood disorders (65). Similarly, approximately half of the individuals with anxiety suffer from insomnia (66).

1.1.2. The brain regions associated with mental and cognitive health and sleep regulation

Various brain regions are more important than others in regulating key brain functions of interest in the current thesis. These regions will be particularly targeted in our MRI analysis as part of Chapters 3 and 4.

The temporal lobe is a part of the cerebral cortex alongside the occipital, parietal and frontal lobes (67) (Figure 1.4) (68). In terms of its clinical significance; pathological lesions in the temporal lobe are linked to cognitive impairments including age-related cognitive loss and AD (67). Deep inside the temporal lobe, the hippocampus is mainly involved in memory and decision making (69, 70). Structural changes, e.g. loss of neurons in the hippocampus, are one of the early markers in AD and vascular dementia (69). The role of the hippocampus in memory has been a long research interest. In 1957, Scoville and Milner conducted surgeries on temporal lobes of 10 patients and damaged their hippocampus, and observed significant memory loss and a linear correlation between the level of the hippocampal damage and the severity of the memory loss (71).

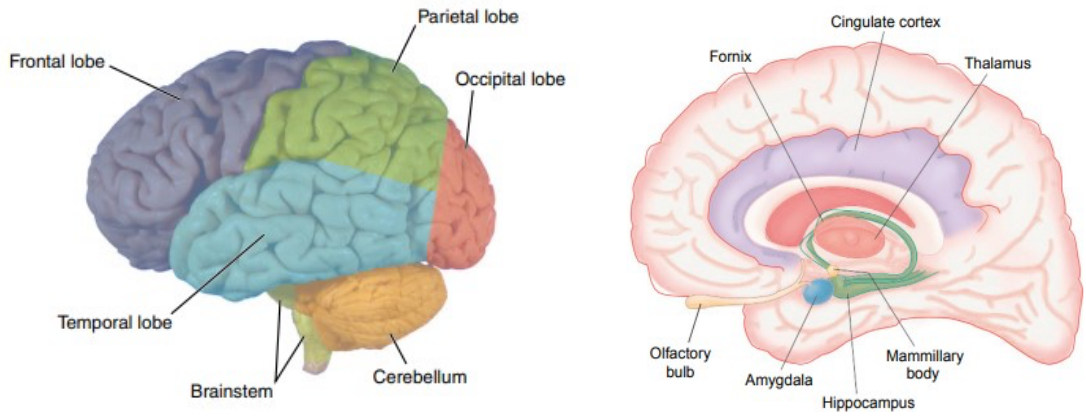


Figure 1.4. Brain regions hosting the structures of interest

The images were taken from Moini *et al.*'s book "Epidemiology of brain and spinal tumours" (68).

Another important structure within the temporal lobe is the amygdala, also known as the emotional brain, the centre of fear, stress, psychosocial functions, motivational activities and the reward-related mechanisms such as the limbic system (72-74), which manages impulses driven by pleasure, for instance, eating and sleeping (74). From a clinical point of view, lesions in the amygdala have been related to depression and anxiety (72, 75, 76). Furthermore, pathologic proteins and asymmetries in the amygdala were observed alongside the hippocampus in AD patients (77), suggesting its possible involvement in cognitive diseases (75). Alongside the temporal lobe, morpho-pathological changes in the frontal lobe underpin severe neurological diseases such as frontotemporal dementia and stroke (78).

Regarding the brain region(s) regulating sleep, the thalamus plays a pivotal role (79, 80). Moreover, significant changes in the grey matter volume in the left-hippocampus were recorded in people with sleep apnea, a sleep-wake disorder, compared to healthy individuals, suggesting disordered sleep can even trigger morphological changes in the brain (81). The amygdala is also involved in sleep functions (82). For example, the amygdala becomes more reactive to the negative stimuli after sleep deprivation compared to non-sleep deprived participants (82).

The amygdala, the hippocampus and the thalamus are referred to as the subcortical regions while the temporal, frontal, parietal and occipital lobes are the cortical regions (83) as will be referred to in Chapter 4.

1.1.3. Underlying biological mechanisms of mental and cognitive disorders

Several potential underlying neuropathophysiologies have been studied since the early 1900s such as formation of tau tangles and plaques (84) and brain atrophy (85). This section provides insights into the physiological and molecular mechanisms underpinning the modulation of mental wellbeing and cognition, which may be modulated by dietary change in a short-term and are of focus in the current thesis.

Vascular health

Depression was hypothesised to be a vascular disease in 1997 by Alexopoulos *et al.*, (86). Later, both depression and anxiety were thought to be closely associated with the cardiovascular system (87, 88). Likewise, dementia was discussed to be a vascular disease too, as it begins with the systemic vascular degeneration and endothelial dysfunction, followed by a reduced cerebral blood flow (CBF) and disordered glucose delivery to the brain and thus resulting in the progressive neurodegeneration and AD (89). Vascular crisis/attacks such as myocardial infarction (90) and stroke (91) being a significant risk factor for future dementia risk supports this hypothesis. Therefore, targeting cardiovascular pathologies is an interest to brain health research (92).

Atherosclerosis and endothelial dysfunction (ED) modulate the associations of vascular health to depression (93) and to dementias (94). Furthermore, lower flow-mediated dilation (FMD), an indicator of endothelial function, were found in individuals with depression compared to healthy controls (95). Endothelial function can also be modulated by meal compositions (96), presenting itself as an opportunity to rapidly improve CBF. Besides, hyperlipidaemia is a major risk factor for atherosclerosis and ED (97). Consequently, lipid lowering drugs and dietary therapy is recommended to reverse atherosclerosis and ED to repair the impaired vascular function (98), manifesting plasma lipids as a therapeutical target in brain disorders, and hence of relevance to this PhD.

Hypoperfusion

The research built up upon the 'vascular depression' hypothesis led to 'hypoperfusion and inflammatory hypothesis' in depression (99). CBF, also known as brain perfusion, is a core determinant of brain homeostasis, and responsible for glucose and oxygen transportation to the brain (100, 101). If a pause occurs in CBF even if for seconds, it causes permanent damage to neurons, therefore, its healthy and efficient functioning is essential to maintain brain health (101). Reduced brain perfusion particularly in the limbic lobe, where the amygdala is located, has been reported in people with mood and anxiety disorders compared to those free of them (102). Furthermore, decreased CBF was linked with poorer cognition in individuals with anxiety (103), and predicted the progression of MCI to dementia (104). CBF is also a characteristic feature of AD (105). Moreover, people without anxiety were asked to think of worrying events and showed decreased CBF after four minutes in the hippocampus and amygdala (106), suggesting perfusion can be manipulated rapidly through external stimuli. CBF also responds to meal content (107). Therefore, CBF will be investigated as part of this PhD project.

Neuroinflammation

Neuroinflammation is the metabolic response of the CNS to various factors such as ageing and environmental factors, and contributes to neurodegenerative disorders including depression and AD (108). The neuroinflammation studies primarily involve molecular mechanisms such as microglial work, therefore it has been suggested to focus on controlling systemic inflammation in humans which would in turn improve the neuroinflammation through blood brain barrier (BBB) and the gut-brain axis (109). In particular, C-reactive protein (CRP), a marker of systemic inflammation, is thought to hold a potential role to act as a pseudo-biomarker of neuroinflammation in psychiatric (110) and neurodegenerative diseases (111). High levels of peripheral CRP were associated with depression (112), and elevated risk for cognitive decline to progress to dementia (113). Therefore, controlling peripheral inflammation by means of, for example, dietary intake is a strong therapeutic target in neurodegenerative diseases (108, 114).

Brain hypometabolism

The brain plays a central role in the regulation of energy metabolism as both a consumer and an administrator, and its utmost priority is to provide itself with energy (115). Despite representing only 2% of total body weight, it utilizes about 20-25% of the total energy in the body (115). Glucose is the main fuel of the brain, providing 90-95% of energy in healthy individuals, and in case glucose becomes unavailable or insufficient, then ketones are used as the only major substrate for the brain (116, 117).

Brain glucose hypometabolism is a common underlying pathological mechanism and an early biomarker for both mental and neurodegenerative disorders (118). Accordingly, impaired glucose uptake into the brain and particularly insulin resistance are linked with both depressive disorders and AD (119). For instance, people with T2D carry two to three times higher risk of depression (120). Furthermore, reduced glucose metabolism was observed in AD patients compared to the healthy subjects in multiple brain areas including temporal lobe at baseline, with a significant decline in global cerebral glucose metabolism evident in AD patients after a year (121). In parallel with these, the "type 3 diabetes" hypothesis is postulated, which suggests an impaired insulin activity in the brain similar to T2D (122). Taken together, approaches improving glucose and insulin metabolism can help prevent and slow progress of depressive and neurodegenerative disorders, presenting the brain insulin resistance as potential treatment target (119, 123). Therefore, glucose, insulin and insulin sensitivity are of interest to this PhD.

Neuroendocrine factors

The involvement of neuroendocrine system in depression, anxiety and neurologic disorders through hypothalamic-pituitary-adrenal (HPA) axis (124) and gut-brain axis (125) has been well documented. Neuroendocrine changes in the HPA occur as a stress response, which results in alterations in cognitive (i.e. alertness and attention) and vegetative functions (i.e. eating and sleeping) (126). More precisely, the involvement of neuroendocrine factors in mood and cognitive regulation appears to be through stress, as the brain responds stress which in turn causes mental and cognitive disturbances (127). Furthermore, sleep is involved in hormonal regulation in mental and cognitive

disturbances due to its role in regulating nocturnal activity of the HPA axis (128). Cortisol, governed by the HPA axis, is the primary stress hormone linked to hippocampus and amygdala activities (129). Alongside involvement in mental, behavioural and cognitive processes, cortisol levels are responsive to both acute and chronic stressors (130). Dietary intake affects cortisol levels, for instance, a poor quality diet was shown to associate with high cortisol levels in people with T2D (131). Cortisol can be measured in the circulation as a biomarker of tissue levels (132), as will be conducted in this PhD.

Neuroplasticity and brain derived neurotrophic factor

Neural plasticity is the ability of the brain to dynamically respond internal (structural and functional changes) and external factors such as diet, exercise and sleep (133). Brain derived neurotrophic factor (BDNF) is a signalling protein serving as an important marker of the brain plasticity (134). It is heavily involved in the lifecycles of neuronal cells and cognitive functions such as learning and memory (135). The highest concentrations of BDNF are normally found in hippocampus and cortex (136). Likewise CRP, peripheral levels of BDNF are thought to be an indicator of brain BDNF levels (137). One meta-analysis comparing serum BDNF levels of three groups found lower BDNF in antidepressant-free depressed people compared to healthy controls and to antidepressant-treated depressed patients (138), indicating the difference in BDNF levels between treated/healthy and untreated/unhealthy conditions. Similarly, diminished levels of serum BDNF levels were evident in people with AD compared to healthy individuals (139), making it a target for treatment approaches such as antidepressants (140).

1.1.4. Current treatment methods of mental and cognitive disorders

The principal treatment methods for depression and anxiety are medications and psychotherapies, yet their success rate is only 50% (141). Besides, they are not accessible for most people living with mental health disorders (142).

At present, there is no cure to completely reverse cognitive decline (34). Remarkably, the drugs “lecanemab (143) and donanemab (144)” have been developed within the last two years and shown to reduce cognitive decline with a modest effect in

early AD after 18 months; yet, both drugs caused mixed significant side effects including 'amyloid related imaging abnormalities'. Besides, they are found to be 'significantly less tolerable compared to placebo' (145), leaving their clinical efficacy and practical implications in need of further research. In August 2024, NICE released an article informing the public that although the use of lecanemab has been approved, it is not going to be available on NHS due to its inadequate efficacy to judge its high-cost (146).

Pertaining to sleeping difficulties, NHS management strategies involve managing comorbidities, improving sleep hygiene, Cognitive Behavioural Therapies (CBT) and pharmacotherapy which is the least favourable and recommended only if CBT has been tried but not worked (16). Sleep disorders must be taken into account to plan a treatment for mental and cognitive disorders (63).

As mental, cognitive and sleep disorders are often comorbid and contribute to each other and efficient therapeutic agents are lacking, it is crucial to develop prevention and early management strategies for overall brain health (Figure 1.5).

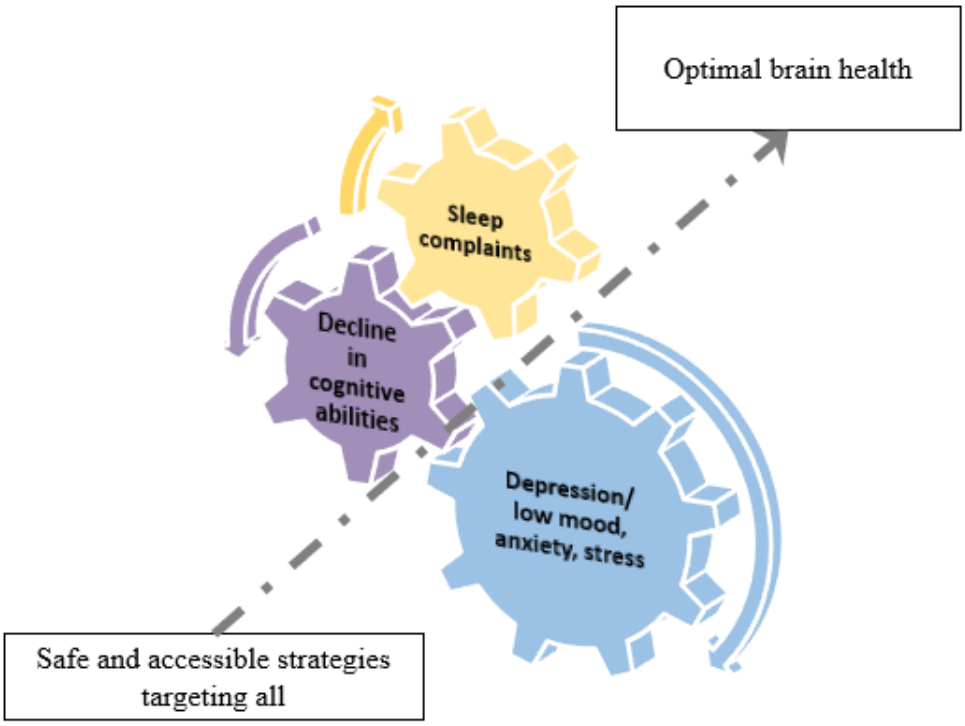


Figure 1.5. The relationships between mental, cognitive and sleep health

Although the aetiology of mental and cognitive and disorders is still not fully understood, some factors are well recognised to influence risk (147-149). The current thesis focusses on dietary approaches, specifically on a Mediterranean-style dietary pattern (MDP), as a safe, widely available, cost effective, and potentially effective approach to improved mental health. It is particularly concerned with short-term modulational of brain health, which is of relevance to all, but in particular to those with either acute or chronic cognitive, or mental health conditions where short term modulation can significantly impact on day-to-day well-being, quality of life (QoL), performance, and ability to live independently. However as will be detailed below most of the research to date have focussed on longer term chronic effects.

1.2. Mediterranean-style dietary pattern

1.2.1. Definition and scoring of a Mediterranean-style dietary pattern

A MDP is an eating style that is traditionally followed in the Mediterranean countries where olive is grown, such as Greece, Italy, Spain, Türkiye and Lebanon (150). It consists of a high consumption of whole or minimally-processed foods such as fruits, vegetables, nuts, legumes, beans, whole-grain cereals, and breads; olive oil as the major fat source; low to moderate consumption of dairy products mainly yoghurt and cheese; fish and poultry; zero to four eggs per week; a low amount of red meat; and wine with meals in a low to moderate amount (151). Yet, there is no single standardised definition and formulation of a MDP either in research or in daily habitual consumption in Mediterranean countries (152). A MDP is also a sustainable eating pattern relative to a Western-style diet (WD) (153). Furthermore, it symbolises a culture with the palatability of the Mediterranean cuisine, cooking and eating as a core social and lifestyle component (154). For this reason, it is listed as Intangible Cultural Heritage of Humanity by UNESCO (155).

As a result of variances in the definition and formulation of a MDP, no gold standard exists to measure the adherence to a MDP (156). The first and most commonly used is the Mediterranean Diet Score (MDS), a MDP pyramid designed by Trichopoulou

in 1995, a 8-point scale consisting of the following components; vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, alcohol and monounsaturated:saturated fat ratio (151). In this system, '0' is assigned to represent 'never or rarely consumed' or if the intake is below the median, with a score of '1' assigned if an individual's intake is above the cohort median value for protective components (fruits, vegetables, legumes, nuts and cereals) or below the median for non-protective components (151, 157). Subsequently, different versions of the MDS have been constructed for different studies (157), and there are now over 50 scoring systems used globally to assess MDP adherence, which are adaptions of the original MDS (158). As pointed out by Murphy and Minihane, the use of different scoring systems, although it "may result in a scoring system better adopted to the local context, makes the integration of results from different observational studies and randomised controlled trials (RCT), and the establishment of size effects, public health messaging and clinical application difficult" (158).

A 14-point questionnaire named 'The Mediterranean Diet Adherence Screener (MEDAS)' was first developed for 'the Prevencion con Dieta Mediterranea (PREDIMED)' study in 2012 (159). MEDAS was reported to be a valid instrument for a quick assessment of a MDP adherence, hence its application in clinical practice was recommended due to its correlations with several blood biomarkers including glucose and lipids (160). It has been commonly used in research since and validated by several countries including the UK (161). For example, the 'MedEx-UK Mediterranean diet, exercise and dementia risk in UK adults' study conducted by our team also utilised MEDAS (162). Therefore, it is used for this PhD in order to measure the MDP compliance. MEDAS consists of the following components;

The original questions with their original explanations regarding the definition of categories and the portion sizes alongside the threshold to obtain 1 point for each item are presented below:

"Q1. Do you use olive oil as your principal source of fat for cooking? (yes or no) (should be yes)

Q2. How much olive oil do you consume each day? (4 tablespoons is equivalent to 50 ml or 50 g. Include all olive oil used for frying, roasting, salad dressings, and that eaten outside the home.) (should be at least 50 ml or 50 g)

Q3. How many servings of vegetables do you consume each day? One serving is 200 g. Count salad garnishes and side servings as 1/2 serving. (Include all vegetables EXCEPT potatoes, sweetcorn, and peas (the latter count as a legume). Vegetable weights are those prepared and ready to eat. (should be at least two portions)

Q4. How many servings of fruit (including 100% fruit juice) do you consume each day? One serving is 80 g, or 30 g of dried fruit, or 150 ml of 100% fruit juice. (Include fresh, cooked, frozen, canned (in fruit juice only) and dried fruit, and up to one serving of 100% fruit juice or smoothie per day.) (should be at least three portions)

Q5. How many servings of red meat do you consume each day? One serving is 100-150 g. Include pork, lamb, beef, veal, venison, duck, and processed red meat products like hamburgers, sausages, and bacon. (Include all items containing red meat such as sausage rolls, meat pies, and pastries.) (should be less than one portion)

Q6. How many servings of butter, margarine, or cream do you consume each day? One serving is 12 g (This includes butter or margarine used to make cakes or pastries.) (should be less than one portion)

Q7. How many glasses of sugar-sweetened soft drinks do you consume each day? One glass is 100 ml. Include fizzy drinks, diluted squash, and cordial. (Do not include diet or zero-calorie drinks.) (should be less than one portion)

Q8. How many glasses of wine do you consume each week? One glass is 125 ml. Include red, white, rosé, or sparkling. (should be at least seven portions)

Q9. How many servings of pulses do you consume each week? One serving is 150 g cooked weight. Include peas, beans (including baked beans), lentils, chickpeas, and soybeans. (Include dried, tinned, and frozen varieties. Do not include green or French beans, or mangetout or sugar-snap peas (these count as vegetables) (should be at least three portions)

Q10. How many servings of fish or shellfish do you consume each week? One serving of fish or shellfish (without the shell) is 125 g (Fish or shellfish can be fresh, frozen, or canned.) (should be at least three portions)

Q11. How many times do you consume commercial sweets (such as cakes, pastries, and biscuits) each week? (Include all commercial cakes, pastries, biscuits, puddings, custard, and ice-cream. Do not include homemade varieties.) (should be less than three times)

Q12. How many servings of nuts do you consume each week? One serving is 30 g (Include all nuts, nut butters, peanuts, and seeds. Do not include salted varieties.) (should be at least three portions)

Q13. Do you preferentially consume white meat instead of red meat each week? (White meat includes chicken, turkey, rabbit, and game like goose, pigeon, pheasant, partridge, and guinea fowl. Red meat includes pork, lamb, beef, veal, venison, duck, and processed red meat products like hamburgers, sausages, and bacon. If you are vegetarian or vegan, please answer 'Yes'.) (should be yes)

Q14. How many times each week do you consume meals prepared with sofrito (sauce made with tomato-based sauce, containing at least one of (onions/garlic/leeks) that have been sautéed in olive oil? (Include commercial tomato-based pasta sauces, passata, canned or fresh tomatoes that have had onions/garlic/leeks sautéed in olive oil added.)" (should be at least two times)" (162).

MEDAS is a self-administered tool. As per the original MEDAS, a discrete (binary) system will be used to calculate the total score. If the condition stated in the points above is satisfied, item is scored as 1 otherwise 0, then summed (159, 163). Thus, the minimum possible score reflecting non-MDP eating style is zero whilst the maximum possible score is 14. One limitation of binary scoring for the MEDAS can be discussed as that it does not account for variations in consumption, as neither the amount nor the frequency of food items is considered. For instance, eating fish three times a week or everyday both score one point, even though the amount of bioactives provided by everyday consumption could make a difference (163).

The full MEDAS questionnaire is also presented in Appendix 1.

1.2.2. Overall health benefits of a Mediterranean-style dietary pattern

In 1950s, the longevity and the low incidence of CVD of people living in Italy drew Ancel Key's attention, leading to the first study assessing the health benefits of a MDP, named as the Seven Countries Study (SCS) which included "Finland, Greece, Italy, Japan, the Netherlands, the US and Yugoslavia" (164). The 25-year follow up demonstrated the variations in saturated fatty acid (SFA) intakes between Italy, Greece and Japan (varying between 10-31% of total energy) versus and the remaining countries (40-89% of total energy) (165). The associations were evident for SFA intake to CVD incidence and to CVD mortality (165). Subsequently, lower risks of CVD-mortality associated with MDP adherence were echoed by several other large longitudinal cohort studies, such as The Healthy Ageing: A Longitudinal Study in Europe (HALE) (166), European Prospective Investigation into Cancer (EPIC)-Norfolk (167) and EPIC-Greek (168).

To date, the PREDIMED is the most comprehensive RCT in the field, with the primary objective being to establish the effectiveness of the MDP interventions on cardiovascular events (169). The study sample included 7447 participants who were between 55-80 years old, at high risk but free of CVD at baseline and lived in Spain (169). The experimental design consisted of three parallel arms; i) a MDP group with additional EVOO (1 L/week), ii) a MDP group with additional mixed nuts (30 g/day as "15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts") and iii) a low-fat control group, none of which were energy restricted (170). The baseline MEDAS scores (mean ± SD) were 8.9 ± 1.8 for the MDP + EVOO group (n=533), 8.9 ± 1.9 for the MDP + nuts group (n=533) and 8.4 ± 1.8 for the control group (n=485) (171). After 5-year follow-up, lower risk of CVD events were seen in the MDP + EVOO and in the MDP + nuts groups compared to controls (172), alongside improvements in plasma glucose levels, blood pressure (BP), blood lipids, inflammation, carotid atherosclerosis after a year (170), and BDNF after three years (173). Moreover, a MDP improves insulin resistance (174) and endothelial function (175). Endothelial function can also be modulated postprandially by MDP meals (176), presenting itself as an opportunity to rapidly improve CBF for two reasons; the endothelium is a dynamic key regulator of vascular homeostasis (177) and CBF is also responsive to acute food/drink intake (178), the mechanisms mentioned in Section 1.1.3.

Overall, a large body of evidence has been accumulated on the effectiveness of a MDP on cardiovascular health. On the other hand, the role of the systemic vascularity in mediating the brain health has been increasingly recognised (Section 1.1.3), which led to research on the relationships between a MDP and mental and cognitive wellbeing.

1.2.3. Impacts of a Mediterranean-style dietary pattern on mental health

Regarding epidemiological evidence, a cross-sectional study (n=3172, aged 18-55 years) reported that the highest adherence to a MDP was associated with a reduced risk of depression, anxiety and psychological distress in comparison to those with lowest adherence, adjusted for multiple covariates (179). The first systematic review examining the relationship between MDP and depression included 26 articles (n=6 interventional, n=20 observational) and stated that all of the RCTs and 17 of the observational studies (no difference obtained from Japanese diets comparisons, characterised by high fish intake) supported the hypothesis that a MDP has a high potential to be a safe therapeutic approach in people with depression as shown to be linked to a lower risk of future depression, ameliorating depressive symptoms compared to low MDP adherence and a WD (180).

The first RCT reporting effects of MDP interventions on depression was the PREDIMED sub-study (2013), in which 224 individuals out of 3923 were diagnosed with depression during the 5.4 years follow-up (Table 1.3) (181). Although a trend was evident for the MDP + nuts group, no overall effect of the interventions on depression incidence was found (181). However, subgroup analysis revealed a 40% reduction in depression incidence in participants with T2D who were in the MDP + nuts group (181).

The SMILES RCT (2017) examined 12-week efficacy of a MDP in adults with major depression (n=67, 18+ years) compared to a social group as a control (182). Participants in the MDP arm (n=33) were provided with nutritional education sessions and their MDP adherences were assessed via the Mod*i*MedDiet tool (recommends consuming "whole grains, fruits, vegetables, low-fat and unsweetened dairy foods, raw and unsalted nuts, chicken, eggs, olive oil and wine" and avoiding "sweets, refined cereals, fried food, fast food, processed meat and sugary drinks all other alcohol

products"), whilst the control group (n=34) gathered at the same frequency for socialising purposes (182). They reported increases in global Mod*i*MedDiet score and total PUFA intake, and decreases in depression and anxiety symptoms (182).

Similarly, The HELFIMED RCT (2019) explored the effect of a MDP enriched with fish oil in improving mental health status in adults with depression (n=152, 18-65 years old) over 6-months with measurements taken at baseline, 3-month and 6-month (183). Nutritional education sessions, cooking workshops and food for MDP components were given to the intervention group (n=75) and their MDP adherence were assessed via MEDAS, whilst the control group (n=77) included befriending (183). The increased MEDAS score, fruit, vegetable, vegetable diversity, wholegrain, legumes and nuts consumption and decreased meat/chicken scores were obtained at the intervention arm between baseline and 3-month compared to control arm (183). MDP caused improvements in depression and quality of life (QoL) at 3-month with no significant change between 3-6 months (183).

Another RCT comparing a MDP to a befriending group was the AMMEND study conducted in men with moderate to severe depression (n=72, aged 18 to 25) for 12-week (184). Higher MEDAS scores and improvements in depressive symptoms and QoL were seen after MDP intervention compared to the control, with the authors suggesting "inflammation, mitochondrial dysfunction, the gastrointestinal tract microbiome, tryptophan, the HPA, neurogenesis/plasticity and BDNF", as a potential underpinning mechanisms aligning with this PhD (184). The aforementioned key RCTs are summarised in Table 1.3.

Table 1.3. A summary of key RCTs examining effects of a MDP on mental health

Study	Country	Year published	Population	Intervention	Comparator	Duration	Primary Outcome	Outcome measures	Results Effect size (95% CI)	Additional notes
PREDIMED	Spain	2013	N=3923; at CVD risk; 55-80 years	MDP + EVOO MDP + Nuts	Low-fat diet	Min. 3 years	Depression risk	Diagnosis of depression	0.85 (0.62, 1.15) 0.73 (0.52, 1.03)	The subgroup analysis* of people with T2D in MDP + nuts: 0.59 (0.36, 0.98)
SMILES	Australia	2017	N=67; with moderate to severe depression; 18+ years	MDP + nutritional counselling	Befriending	12-week	Depressive symptoms	MADRS	-1.16 (-1.73, -0.59)	
HELFIMED	Australia	2019	N=152; with MDD; 18-65 years	MDP + fish oil + nutritional education + cooking workshops + food hampers	Befriending	3- and 6-month	Depression and anxiety symptoms	DASS-21; AQoL-8D	-4.52 (-8.53, -0.52) 0.06 (0.00, 0.11)	
AMMEND	Australia	2022	Male with moderate to severe depression; 18-25 years	MDP + nutritional counselling + booklet + food hampers	Befriending	12-week	Depressive symptoms	BDI-II	14.4 (11.4, 17.4)	

RCT: Randomised controlled trial; MDP: Mediterranean-style dietary pattern; CI: confidence interval; EVOO: extra virgin olive oil; CVD: cardiovascular disease; MDD: major depressive disorders; MADRS: Montgomery–Åsberg Depression Rating Scale; DASS: Depression Anxiety Stress Scale; AQoL: Assessment of Quality of Life; BDI: Beck Depression Inventory scale. Subgroup analyses were done for T2D, hypertension, hyperlipidaemia and obesity.

1.2.4. Impacts of a Mediterranean-style dietary pattern on cognition

Pertaining to epidemiological evidence, the EPIC-Norfolk cohort included healthy adults (n=8009, aged 40 to 79 years) followed up for approximately 15 years was used to test associations between a MDP adherence (established by MEDAS and Pyramid scores) and multiple cognitive domains; global cognition, verbal episodic memory, nonverbal episodic memory, attention, simple processing speed, complex processing speed and memory (185). Higher MDP adherence (5-10/14) was linked to a better performance compared to lower adherence (0-2/14) in global cognition, verbal episodic memory, simple processing speed, complex processing speed, prospective memory and attention (185). Moreover, a 1-point increase in the Pyramid score (15-point scale) was equivalent to 1.7 years less cognitive ageing (185).

A meta-analysis of five longitudinal cohort studies assessing the risks of developing MCI and AD in cognitively healthy individuals and the chance of progression from MCI to AD (186). The highest MDP scores were linked to a lowered risk of developing MCI (186). As for the risk of future AD, every 1-point increase in MDP score on a 9-point scale lowers the risk by 8% in cognitively healthy adults (186). Besides, the highest and middle MDP score tertiles significantly reduced the risk of the transition from the MCI to AD with compared to the lowest tertile (186). A 2022 meta-analysis examining the associations between a MDP and cognition (global cognition, episodic memory and working memory, and diagnosis of MCI, AD and dementias) in cognitively healthy adults included 28 studies (n=2 RCTs, of which the durations are 6 months and 6 years) (187). A reduced MCI risk was detected with no association between a MDP and cognitive performance from the cohort studies, whilst MDP RCTs were linked with improved working memory, episodic memory and global cognition (187).

Cognition was one of the secondary outcomes of the PREDIMED study (Table 1.4) in a sub-cohort of 522 individuals, and it demonstrated that both MDP arms improved cognitive function independent of any potential confounding factors such as age, genetic, education, physical inactivity, vascular risk factors and energy intake (188). The Mini-Mental State Examination (0-30 points) and Clock Drawing Test (0-7 points) were used, both measure several cognitive functions including but not limited to attention, executive

function and working memory (188). Participants in the MDP + EVOO group achieved higher scores (mean points: 28.00 and 5.45) than the those in the MDP + nuts group (mean points: 27.96 and 5.27) and both groups obtained better scores than people in the low-fat control group (mean points: 27.40 and 4.95) after a 6.5-year follow-up (188). Besides, the control group displayed higher incidences of MCI (n=23 in the control, n=19 in MDP + nuts and n=18 in MDP + EVOO groups), and dementia (n=17 in the control, n=12 in MDP + EVOO and n=6 in MDP + nuts groups) (188).

The MedLey study assessed a 6-months MDP intervention on cognitive functions in 137 people (aged 65+ years) compared to a habitual Australian diet, a form of a WD, and found no differences between groups for executive functioning, processing speed, memory, visual-spatial ability and global cognition (189).

The NU-AGE study was the first RCT evaluating the impact of a personalised MDP on QoL, ageing-related changes and overall health in healthy individuals (n=1279, aged 65-80 years) compared to the control group asked to try adhering to the national nutritional recommendations based on the leaflet given (190). The study was conducted in non-Mediterranean European countries; France, Italy, the Netherlands, Poland and the UK (190). The primary outcome was inflammatory status determined by CRP and cognition was a secondary outcome (190). After 1-year intervention, cognitive improvements in both groups in all cognitive domains were seen with no significant differences between groups (191). However, those displaying a greater adherence to MDP demonstrated significantly better improvements in global cognition and episodic memory compared to lower adherers (191).

The MedEx-UK trial led by our group examined the feasibility of a MDP in UK recruited individuals at-risk of dementia (n=105, aged 57-76 years) and consisted of three arms; a MDP arm (provided with food), a MDP + physical activity (PA) arm and a control group (192). After 24-week intervention, alongside improved MDP adherence and improved CVD outcomes, better performance in overall cognition and memory were seen with a positive correlation with increases in MEDAS scores (192). The key RCTs concerning effects of a MDP on cognition were summarised in Table 1.4.

Table 1.4. A summary of key RCTs examining effects of a MDP on cognition

Study	Country	Year published	Population	Inter-vention	Compara-tor	Duration	Primary Outcome	Outcome measures	Effect size HR, RR, OR or Mean differences (95% CI)	Comment
PREDIMED	Spain	2013	N=522; at CVD risk; 55-80 years	MD + EVOO MD + Nuts	Low-fat diet	6.5 years	Global cognitive performance	MMSE (0-30) CDT (0-7)	MMSE; MD+EVOO: 27.73 (27.77, 28.19), MD+Nuts: 27.68 (27.20, 28.16), Control: 27.11 (26.61-27.61). CDT; MD+EVOO: 5.31 (4.98, 5.64), MD+Nuts: 5.13 (4.78-5.47), Control; 4.80 (4.44, 5.16).	Results are multivariable-adjusted mean scores of MMSE and CDT tests for all groups.
MedLey	Australia	2016	N=137; 65+ years; cognitively healthy	MDP	Habitual WD	6-month	Age-related cognitive performance		7.99 (-4.0, 19.9)	Multivariate adjusted. Global cognition score was derived from executive function, memory and processing speed tasks.

NU-AGE	UK	2018	N=1279 Healthy 65-79 years	Personalised MDP diet	Healthy diet	1 year	Global cognition Episodic memory	β 0.20 (0.004, 0.39) β 0.15 (0.02, 0.28)	Adherence to the intervention diet was measured by specifically constructed NU-AGE index. Results are based on higher vs lower adherence.
Med-Ex UK	UK	2023	N=104; 57-76 years; at CVD risk but cognitively healthy	MDP + food hampers + group sessions MDP + PA + group sessions	Healthy diet	24-week	Memory Overall cognition	0.31 (0.10, 0.51) 0.22 (0.05, 0.35)	

RCT: Randomised controlled trial; MD: Mediterranean diet; EVOO: Extra virgin olive oil; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; EPIC: European Prospective Investigation into Cancer; MEDAS: Mediterranean Diet Adherence Screener WHICAP: Washington Heights-Inwood Columbia Aging Project; PA: Physical activity; AD: Alzheimer’s Disease.

1.2.5. *Short-term effects of dietary intake on mental wellbeing and cognitive performance*

Although many of the underlying mechanisms may be acutely modified by dietary intake, very little is known about the short-term/postprandial impact of a MDP on overall brain health. Two Australian studies examined 10-day effects of a MDP on mood and cognition before and reported several improvements in mood and cognitive domains (193, 194). One other short-term study assessing a four-day WD on cognition reported significantly impaired "hippocampal-dependent learning and memory" compared to a healthier diet, which was correlated with changes in blood glucose (195). These short-term studies are discussed in detail in the next chapter (Chapter 2).

1.3. The outline of the thesis

Summary

Mental, cognitive and sleep disturbances are emerging health crises. They influence each other, share multiple cardio- and cerebrovascular underscoring mechanisms, and are often the prodromal phases of more severe diseases such as major psychiatric disorders and dementias. As they contribute to each other, to target improving one of them holds a high potential to be protective against all (Figure 1.5). Currently population mental health services need widely available rapid, practical, and affordable solutions. A MDP has been well recognised to hold a promising potential to improve overall cardiovascular health and appears to be linked to improved mental and cognitive health. Although strategies to acutely improve mental and cognitive wellbeing status on a day-to-day basis can play a critical role in augmenting the QoL for all and in particular for those who are already suffering from the mood and anxiety disorders or from some cognitive decline, knowledge in this area is very limited, which therefore is a priority research area and will represent the focus of my PhD.

The main hypothesis

We hypothesise that a MDP can improve mood and cognition by acutely/sub-chronically (up to ten days) enhancing rapidly responsive physiological and molecular mechanisms (Figure 1.6).

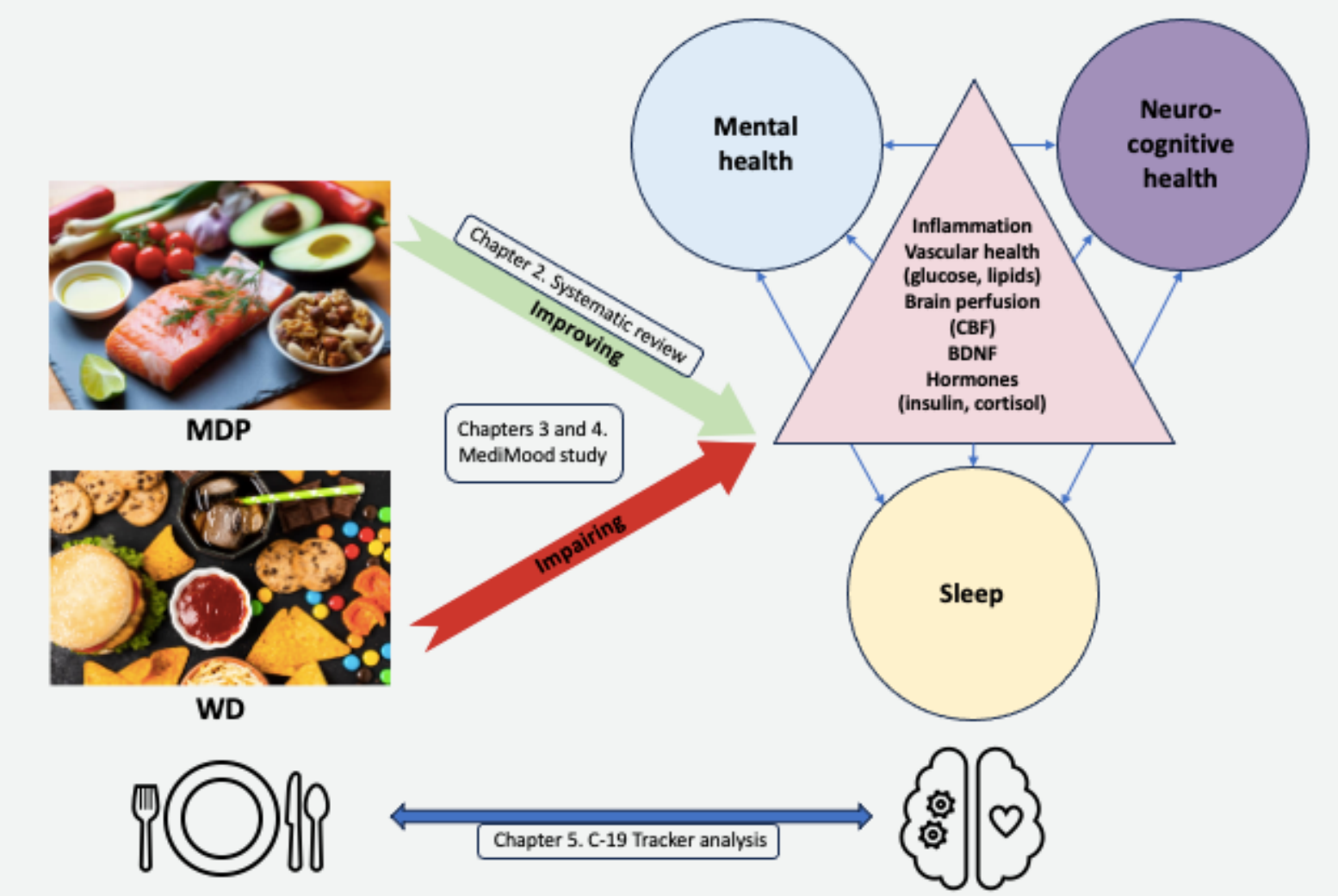


Figure 1.6. The central hypothesis of this PhD project regarding the potential relationships between dietary intake and brain health

CBF: Cerebral blood flow; BDNF: Brain derived neurotrophic factor; MDP: Mediterranean-style dietary pattern; WD: Western diet. Mental health (depression, anxiety and stress), neurocognitive health (higher cognitive skills) and sleep are regulated by the brain, share same underpinning mechanisms, all of which can be manipulated by dietary intake.

Chapter 2 is the systematic review examining the effects of a MDP on mental health and cognition. Chapter 3 and 4 present the RCT component of this PhD project and which compare the impact of a MDP and WD on mental health, cognition and sleep. Of note, sleep data were not analysed for this thesis. Chapter 5 is the longitudinal data analysis examining the bidirectional associations between fruit, vegetable and sweet intake (MEDAS items Q3, Q4 and Q11 alongside a subjective overall diet quality question), and mental health and sleep quality. All hypotheses were built, and findings were discussed based on the postulated mechanisms stated in the triangle shape.

The objectives and hypotheses of each experimental chapter were as follows; Chapter 2 examined the available evidence on the effects of a MDP on mental health and cognition and hypothesised that a MDP can improve cognitive and mental health. Chapter 3 and 4 aimed to assess the impacts of a MDP on mental, cognitive and sleep heath by comparing it to a WD, and hypothesised that a MDP can improve overall brain health compared to a WD. Chapter 5 is the longitudinal analysis assessing the bidirectional associations between fruit, vegetable and sweet intake (MEDAS items Q3, Q4 and Q11 alongside a subjective overall diet quality question), and mental health (happiness, low mood, stress and sleep quality). We hypothesised that fruit and vegetable intake and higher diet quality were in a positively correlated with a better mental health profile (higher happiness and sleep quality and lower low mood and stress) and vice versa.

All hypotheses were built, and findings were discussed based on the postulated mechanisms stated in the triangle shape.

Research gaps, aims and objectives

The accumulated evidence on the beneficial effects of a MDP on mental wellbeing and cognitive health is mainly derived from observational studies which do not provide mechanistic understandings or explain causal relationships. Besides, long-term studies form the vast majority of the available evidence, leaving the questions on the efficacy of diets or individual food items in the short-term unanswered. Based on these research gaps, the overarching aim of this PhD research is to investigate short-term effects of a MDP on brain health components including mood, anxiety, cognition and sleep alongside associated physiological biomarkers such as CBF and circulating blood parameters.

The subsidiary objectives, research questions and hypotheses of each experimental chapter are as follows;

i. Chapter 2:
    a. Objective: To evaluate the existing evidence to understand the effects of short-term MDP adherence on cognition and mood, to rationalise and inform the focus of the RCT component of this thesis.
    b. Research question: Is there consistent evidence available to inidicate a positive impact of a MDP on cognition and mood?
    c. Hypothesis: A MDP can improve cognition and mood in the short-term.

ii. Chapters 3 and 4:
    a. Objective: To design and execute of a short-term/postprandial RCT investigating the impact of a MDP on mental health as a primary endpoint in those with mental health complaints, compared with a WD.
    b. Research question: Can a MDP alleviate symptoms of mental health disturbances and improve cognition, sleep and relevant underpinning biological mechanisms in comparison to a WD?
    c. Hypothesis: A MDP can improve mood, anxiety, cognition and sleep by optimising relevant biological pathways with compared to a WD.

iii. Chapter 5:

a. Objective: To explore the acute bidirectional associations between dietary intake, namely, fruits and vegetable intake as MDP components, alongside sugar intake and overall dietary quality and mental health elements (happiness, low mood, stress and sleep quality) using a longitudinal data analysis.
b. Research question: Can dietary intake and mental health modulate each other?
c. Hypothesis: Dietary intake and mental health affect each other bidirectionally.

Chapter 2. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials

(Published manuscript)

This chapter was published at British Journal of Nutrition (196) (Appendix 2) and presented at Nutrition Society Irish Section conference (197) (Appendix 3).

The focus of this PhD was cognition/Alzheimer's Disease (AD) prior to having to change due to the pandemic, therefore the primary focus of this section is cognition.

2.1. Introduction

With global ageing population demographics, the prevalence of cognitive disorders has surged (59). The number of individuals living with dementia, which is a major cause of loss of independence and disability in older age, was over 55 million worldwide in 2019, and predicted to triple itself by 2050 (59). In the UK, dementia was the number two cause of death in 2020, responsible for 11.5% of all-cause mortality, following COVID-19 related deaths; nonetheless, dementias were still the first cause of death among females (over 15%) (198). Besides, dementia has an enormous economic burden, with the global cost expected to reach $2 trillion by 2030 (199).

The prevalence of mild cognitive impairment (MCI), the transition phase prior to incident dementia, has been estimated to occur in 15-20% of the population aged over 60 years, with 8% to 15% progressing to dementia per year (200). Subjective cognitive impairments (SCI), which is loosely defined as a state in which individuals present with 'self-reported' cognitive decline relative to their previous cognitive status (which is not diagnosed by objective standard tests) occurs in 50-80% of individuals aged 70 years or older (201). SCI is linked to depression, anxiety and future AD risk (201, 202). In addition to cognitive decline, mental disorders, including depression and anxiety disorders are prevalent, occurring in nearly 15% of the global population (142), and are one of the top

three causes of non-fatal health loss in terms of years lived with disability (54). Depression is also a risk factor for future dementia (203).

Currently, AD and other dementias are irreversible with no effective treatments available to reverse the condition (34). Therefore, behaviours (such as altered eating behaviour and nutrition status) which can prevent or delay progression of these conditions have the potential to dramatically reduce both individual risk and the population burden of the disease (34). A Mediterranean-style dietary pattern (MDP) is emerging as having potential positive effects on mental health status. The diet is characterised by high consumption of extra virgin olive oil (EVOO) and plant-based foods such as fruits, vegetables, nuts, legumes, whole-grain cereals; low to moderate consumption of dairy products mainly yoghurt and cheese; fish consumed two to four times a week; low amounts of red meat; and moderate consumption of wine mainly with meals (151). EVOO, in addition to being the major component of a MDP, has been shown to independently confer neuropsychiatric and cardiovascular benefits (204), attributed to its high monounsaturated fatty acid (MUFA) and phenolic content (205).

The cardiometabolic health benefits of a MDP, first reported in the Seven Countries Study (SCS) in 1950's (165), and are now well established (206-208). An improved cardiometabolic phenotype is thought to in part underlie the emerging cognitive benefits of this dietary pattern. However, the majority of this evidence has been acquired from observational studies, such as the EPIC-Norfolk (185), with a dearth of RCTs which report on the causal benefits of a MDP on long-term cognitive and overall mental health. The PREDIMED was the first RCT testing the long-term effectiveness of a MDP in primary prevention which had incidence of cardiovascular diseases as the primary endpoint (169). In a sub-group secondary analysis, the MDP interventions enriched with either EVOO or nuts were shown to improve cognitive function (188) and depressive symptoms (209). Available systematic reviews and meta-analysis focus on the long-term mental health benefits of a MDP, with adherence associated with an overall risk ratio of 0.79 (95% CI, 0.70, 0.90) of developing cognitive disorders (210). Although no association was observed in the cohort analysis, data from 9 cross-sectional studies indicates a negative relationship between adherence to a MDP and risk of depression (OR=0.72; 95% CI, 0.60, 0.87) (211).

In addition to the long-term trajectory, for the ever-increasing number of individuals with pre-existing cognitive or mental health deficits and even in healthy individuals, there is a great need and interest in identifying nutrition strategies which improve cognition, mood and anxiety in the short-term, in order to improve capabilities, independence and overall quality of life. Therefore, the objectives of the current systematic review are, (i) to conduct an evidence synthesis from RCT data to scrutinise whether a MDP has the potential to alter cognition, mood and mental wellbeing in the short-term, and (ii) identify research need and inform the design of future acute RCTs in the area.

2.2. Methods

This systematic review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (212). The full protocol of our systematic review was registered on PROSPERO with the registration number CRD42021221085 (213), and presented in Appendix 4.

2.2.1. Search strategy, eligibility criteria and study selection

"Short-term" is defined as "up to 10 days" following discussions among the authors, where effects on cognition are likely to be mediated by rapidly responsive physiological processes such as brain blood flow, inflammation and oxidative status. Ovid Embase, Ovid Medline and Web of Science Core Collection were searched (214, 215) using "Mediterranean diet", "olive oil", "cognition", "dementia", "mood", "mood disorders", "anxiety", "anxiety disorders", "depression", "depressive disorders" and "wellbeing". Free search terms and medical subject heading terms were combined where the databases allowed, namely EMBASE and MEDLINE. The first search (for the publication) covered the period spanning from the inception dates of the databases, more precisely 1947 for Embase, 1964 for Medline, and 1950 for Web of Science Core Collection (216), to 08 December 2020. The same systematic search was re-executed in order to update the findings for the present chapter with the cut-off date 29 October 2023. Final search strategies were constructed with the assistance of the academic librarian of the Faculty of Medicine and Health Sciences, University of East Anglia. The full electronic search strings used in the three databases are presented in the Table 2.1 below.

Table 2.1. Electronic search strings used

Embase via Ovid (for MDP search)

1. (Mediterranean* adj5 (diet* or eat* or food*)).ti,ab.
2. exp Mediterranean diet/
3. 1 or 2
4. (dementia* or cogniti* or memory or mood* or anxiet* or wellbeing or well-being or depress*).ti,ab.
5. exp cognitive defect/
6. exp cognition/
7. exp cognitive aging/
8. exp memory/
9. exp mood disorder/
10. exp mood/
11. exp anxiety/
12. exp anxiety disorder/
13. exp wellbeing/
14. exp psychological wellbeing assessment/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. crossover procedure/
18. double blind procedure/
19. randomized controlled trial/
20. single blind procedure/
21. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. [m*p*=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
22. 17 or 18 or 19 or 20 or 21
23. 16 and 22
24. exp human/
25. 23 and 24
26. limit 25 to dd=20201208-20231029 (the added cut-off dates for the second search)

Embase Via Ovid (for olive oil search)

1. olive oil.ti,ab.
2. exp olive oil/
3. 1 or 2
4. (dementia* or cogniti* or memory or mood* or anxiet* or wellbeing or well-being or depress*).ti,ab.
5. exp cognitive defect/
6. exp cognition/
7. exp cognitive aging/
8. exp memory/
9. exp mood disorder/
10. exp mood/
11. exp anxiety/
12. exp anxiety disorder/
13. exp wellbeing/
14. exp psychological wellbeing assessment/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. crossover procedure/
18. double blind procedure/
19. randomized controlled trial/
20. single blind procedure/
21. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. [m*p*=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
22. 17 or 18 or 19 or 20 or 21
23. 16 and 22
24. exp human/
25. 23 and 24
26. limit 25 to dd=20201208-20231029 (the added cut-off dates for the second search)

Medline via Ovid (for MDP search)

1. (Mediterranean* adj5 (diet* or eat* or food*)).ti,ab.
2. exp Mediterranean diet/
3. 1 or 2
4. (dementia* or cogniti* or memory or mood* or anxiet* or wellbeing or well-being or depress*).ti,ab.
5. exp cognition/
6. exp cognitive dysfunction/
7. exp cognition disorders/
8. exp memory/
9. exp mood disorder/
10. exp mood/
11. exp anxiety/
12. exp anxiety disorder/
13. exp Mental Health/
14. exp Stress, Psychological/
15. exp depression/
16. exp "Quality of Life"
17. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 3 and 17
19. cross-over studies/
20. single-blind method
21. double-blind method
22. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
23. 19 or 20 or 21 or 22
24. 18 and 23
25. exp human/
26. 24 and 25
27. limit 26 to rd=20201208-20231029

Medline via Ovid (for OO search)

1. olive oil.ti,ab.
2. exp olive oil/
3. 1 or 2
4. (dementia* or cogniti* or memory or mood* or anxiet* or wellbeing or well-being or depress*).ti,ab.
5. exp cognition/
6. exp cognitive dysfunction/
7. exp cognition disorders/
8. exp memory/
9. exp mood disorder/
10. exp mood/
11. exp anxiety/
12. exp anxiety disorder/
13. exp Mental Health/
14. exp Stress, Psychological/
15. exp depression/
16. exp "Quality of Life"
17. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 3 and 17
19. cross-over studies/
20. single-blind method
21. double-blind method
22. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
23. 19 or 20 or 21 or 22
24. 18 and 23
25. exp human/
26. 24 and 25
27. limit 26 to rd=20201208-20231029

Web of Science Core Collection (for MDP search)

1. TI= (Mediterranean NEAR/5 (diet* OR eat* food*)
2. AB= (Mediterranean NEAR/5 (diet* OR eat* food*)
3. AK= (Mediterranean NEAR/5 (diet* OR eat* food*)
4. K*P*= (Mediterranean NEAR/5 (diet* OR eat* food*)
5. 4 OR 3 OR 2 OR 1
6. TI= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
7. AB= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
8. AK= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
9. K*P*= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
10. 9 OR 8 OR 7 OR 6
11. 10 AND 5

Web of Science Core Collection (for OO search)

1. TI= olive oil
2. AB= olive oil
3. AK= olive oil
4. K*P*= olive oil
5. 4 OR 3 OR 2 OR 1
6. TI= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
7. AB= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
8. AK= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
9. K*P*= (dementia* OR cogniti* OR memory OR mood OR mood disorder* OR anxiet* OR anxiety disorder* OR wellbeing OR well-being OR depress*)
10. 9 OR 8 OR 7 OR 6
11. 10 AND 5

Studies were accepted eligible if they:

- had an RCT design,
- intervened with either a MDP or olive oil,
- had an intervention period of up to and including 10 days,
- assessed either cognition, mood, anxiety or depression as a primary or secondary endpoint,
- included adults over 18 years,
- published in the English language.

Observational epidemiological studies were excluded. No sex filter was applied. The reference lists of included studies were manually read in order to obtain further potential publications. Two authors (LE and ESC) independently completed screening the titles and abstracts against the predefined eligibility criteria. Any discrepancies were resolved by discussions until an agreement was reached. For the second search, the results were screened by LE only as the intention was not publication but to update the present chapter. EndNote X9 is used as the reference management tool.

2.2.2. Data extraction and quality assessment

A table which recorded the authors, publication year, country that studies were conducted in, type of RCT, participant characteristics, study duration, intervention, main outcomes, assessment methods used, results (mental health status) and additional results/comments, was generated to extract the data from the included studies.

A quality assessment was done using RoB2, a revised tool for risk of bias by Cochrane (217), which has five domains; bias arising from the randomisation process (D1), bias due to deviations from intended interventions (D2), bias due to missing outcome data (D3), bias in measurement of the outcome (D4), bias in selection of the reported result (D5) and plus overall bias (D6). The results of bias investigation are presented by means of a traffic light plot under low risk, some concerns or high risk.

2.2.3. Data synthesis

A narrative approach was used to synthesise the data. No quantitative analysis was performed due to the small number of studies.

2.3. Results

2.3.1. Study identification

Initially, 3002 studies were obtained from the three electronic databases. After deduplication, 2261 studies remained, with 1721 from the MDP search and 540 from the olive oil search. Of these, 2253 were excluded following the title and abstract screening for reasons such as longer study durations, irrelevant outcomes, supplement interventions, epidemiological studies, animal studies, any type of reviews, meta-analysis and protocols. Full texts were screened for the remaining eight studies. Finally, four studies, three full articles (193, 194, 218) and one conference proceeding (219), met the eligibility criteria, and were included. These four papers yielded a reference list of 85, which were scanned manually by LE and ESC, with no additional publications emerging for inclusion.

The second search that was performed utilising the same methodology to update the results generated 1430 studies. Following the elimination of 181 duplicates, a total of 1249 studies remained to be screened. Subsequent to the title and abstract screening, none of the studies met the predetermined inclusion criteria for the identical reasons stated above, such as observational cohort studies, animal studies, nondietary interventions, longer study durations, populations falling outside the scope of interest (infants, children and adolescents), irrelevant outcomes, reviews, protocols, consensus reports.

Both study identification processes are merged, and the updated version is presented in the PRISMA diagram (Figure 2.1).

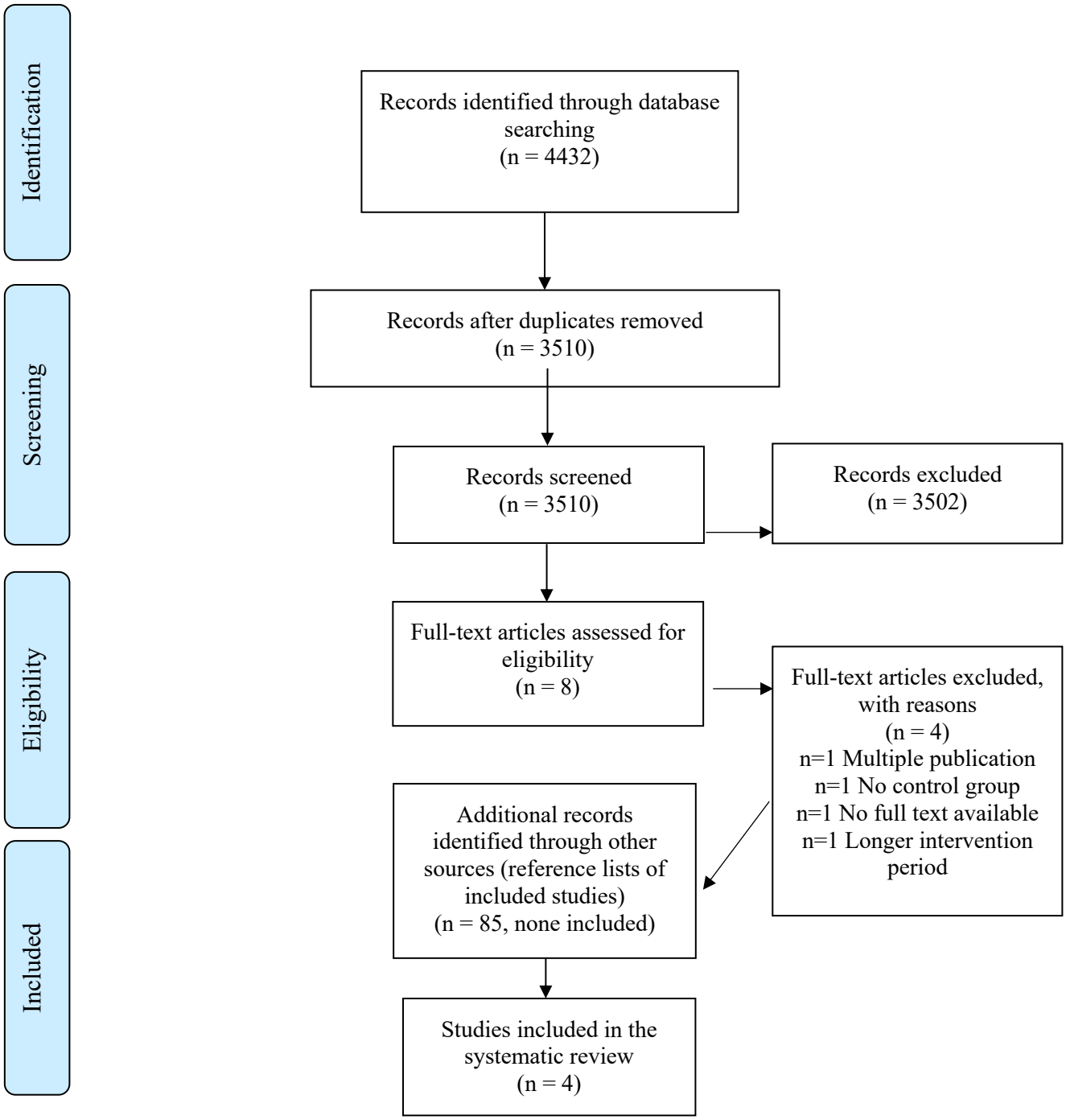


Figure 2.1. PRISMA flow diagram

2.3.2. Study characteristics

All included studies were RCTs, two with a cross-over (193, 219) and two with a parallel design (193, 219) (Table 2.2). All intervened with a MDP and were carried out in non-Mediterranean countries, two Northern European (218, 219) and two Australian (193, 194). The sample sizes ranged from 24 (194) to 53 (219). Three of the studies included young females only, with (mean ± standard deviation) ages, of 21.1±3.3 (193), 22.3±3.7 (219) and 25.6±5.2 (194) years (mean ± standard deviation). The remaining study (218) included both males and females with metabolic syndrome traits with a participant mean age of 70±5 years. None of the four RCTs reported any previous cognitive or mental health issues in the participants. Three had a study duration of 10 days, with one (218) examining the physiological response 4.5 hours after the test meal. One study (218) implemented a MDP alone or with a physical activity intervention (30 minutes moderate walking).

In terms of the MDP intervention, in one cross-over study (218), participants were provided with their test breakfast (4300 kJ) that consisted of ciabatta, smoked salmon, muesli, fruit and vegetables which was described as rich in unsaturated fatty acids, dietary fibre and antioxidative compounds. The remaining three studies did not provide the study foods but rather guided participants in following a MDP. De Vries *et al.* (219) did not provide any detail of the dietary instructions provided to participants. Lee *et al.* (194) requested participants in the MDP group to increase their intake of fruit, vegetables, oily fish, low-fat dairy and nuts with a focus on healthy carbohydrates, fats and proteins, and to exclude meat, butter, margarine, caffeinated/energy drinks, added sugars and salts, alcohol, tobacco and illicit drugs during the study period. Besides, participants were also asked to consume freshly prepared foods and to avoid processed and packaged options where possible. Similarly, McMillan *et al.* (193) asked participants to increase their consumption of fruits, vegetables, oily fish, low-fat dairy and nuts and to combine good sources of carbohydrates (less refined carbohydrates, whole grains, legumes, fruits and vegetables), fats and proteins. Additionally, they were instructed to abstain from red meat, refined sugars refined flour, pre-packaged and processed foods, caffeinated products, soft drinks and condiments.

Regarding dietary assessment methods, food diaries were used over the 10-day study period in order to record the dietary intake in three of the studies (193, 194, 219). The remaining study provided the foods, so no self-reported dietary assessment was required (218).

Table 2.2. Study details and main outcomes

Authors	Year published	Country	Type of RCT	Participant characteristics	Duration	Intervention	Main outcomes	Assessment methods used	Additional outcomes	Results (Mental Health Status)	Additional comments
Diekmann *et al.*	2019	Germany	Cross-over	n=26 8 Female, 18 Male Metabolic syndrome 69.9 ± 4.7 years* BMI= 30.3 ± 2.3 kg/m^2*	4.5 hours 2 weeks wash-out periods	4 interventions (isoenergetic, 4300 kJ/meal): 1.WD + walking 2.WD + resting 3.MDP + walking 4.MDP + resting	Mood Cognition	MDMQ FAIR-2	Appetite Plasma cortisol levels	MDMQ: No effect of diet FAIR-2: Walking group: 1.4-fold increase in attention in MDP compared to WD. Resting group: 1.1-fold increase in attention in MDP compared to WD. *(p*=0.045 from iAUC data, meal x time interaction NS).	No effect of diet on cortisol VAS: No impact of diet on hunger. Satiety was higher after MDP compared to the WD *(p*<0.001).
de Vries *et al.*	2017	Nether-lands	Parallel arms	n=53 Female 22.3 ± 3.6 years*	10 days	MDP or control group	Mood	POMS Bond-Lader		Decreases in vigour/activity *(p*<0.001); tension/anxiety *(p*=0.001); fatigue/inertia *(p*=0.003); anger/hostility *(p*=0.014); confusion/bewilderment *(p*=0.015) and the total mood disturbance score *(p* not stated), and contentment *(p*=0.001); alertness *(p*=0.003) in MDP compared to control group. p values are for the time*treatment	Food diaries were used over 10 days but not reported in the text. No detail given on

										interactions, no effect sizes are presented.	the control group diet.
Lee *et al.*	2015	Australia	Cross-over	n=24 Female Healthy 25.6 ± 5.1 years*	10 days	MDP or NC	Mood Cognition	POMS Bond-Lader COM-PASS	Cardio-vascular function BP, blood flow velocity and arterial stiffness Dietary adhe-rence Anthrop ometric measure s	Confusion reduced in MDP (-1.19) and increased (1.52) in NC. (*F*=6.87, *p*=0.02). Alertness increased in MDP (6.93) and reduced in NC (-8.31) (*F*=14.11, *p*<0.01). Contentment increased in the MDP group (5.35) and reduced in NC (-4.23). (*F*=6.49, *p*<0.02). Immediate word recall: Correct responses increased in MDP (1.14) and reduced in NC (-0.64) (*F*=8.19, *p*=0.01). Incorrect responses decreased in MDP (-0.32) and increased in NC (0.36) (*F*=4.83, *p*=0.04). Delayed word recall: Incorrect responses decreased in MDP (-0.33) and increased in NC (0.71) (F=4.57, *p*=0.046). 3-back task: Correct responses reduced in the MDP (-2.32) and increased in NC (4.14) (*F*=6.64, *p*=0.02).	Food diaries were used over 10 days. Augmentati on pressure (mm Hg) reduced in MDP (-1.05) and increased in NC (0.95) (*F*=6.15, *p*=0.02). 100% dietary adherence to MDP BW: Reduced in MDP group (-1.77 kg) and increase in NC group (0.11) (*F*=10,81, *p*<0.01).

											No change in BMI
Mc Millan *et al.*	2011	Australia	Parallel arms	n= 25 Female Healthy 21.1 ±3.3 years*	10 days	MDP or NC	Mood Cognition	65-item POMS Bond-Lader COM-PASS	Dietary adherence Anthropometric measures	Vigour increased in MDP by 18% (3.67) and reduced in NC by 22% (-5.06) (F=11.25, p=0.003). Alertness increased in MDP by 30% (16.43) and reduced in NC group by 15% (-9.02) (F=22.23, p<0.001). Contentment increased in MDP by 20% (12,89) and reduced in NC by 15% (-10.4) (F=16.634, p<0.001). Numeric working memory: RT increased in MDP by 2% (+15) and decreased in NC group by 14% (-122) (F=5.05, p=0.04). Corsi Blocks task: RT reduced in MDP by 14% (-420) and increased in NC by 27% (837) (F=17.628, p<0.001). Word recognition: RT reduced in MDP by 3% (-29) (p=0.574, NS) and in the NC by 20% (-191) (p=0.001). The difference between groups was significant: (F=5.04, p=0.035).	Food diaries were used over 10 days. 100% dietary adherence to MDP. No effect of diet on BW, BMI and WC.

Asterisk (*) represents mean ± standard deviation. RCT: Randomised controlled trial; BMI: Body Mass Index; kJ/meal: kilojoule/meal; BP: Blood pressure; WD: Western diet; MDP: Mediterranean-style dietary pattern; MDMQ: Multidimensional Mood State Questionnaire for mood; FAIR-2: Frankfurt Attention Inventory-2 for cognition; iAUC: Area under the curve; NS: Not significant; VAS: Visual Analogue Scale for hunger, appetite and satiety; POMS: Profile of Mood States questionnaire for mood (tension/anxiety, anger/hostility, fatigue/inertia, vigour/activity, confusion/bewilderment, depression/rejection and total mood disturbance score); Bond Lader Scale for mood (alertness, contentment and calmness); NC: No change in diet; COMPASS: The Computerised Mental Performance Assessment System for cognitive domains; RT: Reaction time; BW: Body weight; WC: Waist circumference.

While three studies examined both mood and cognition as outcomes (193, 194, 218), one study assessed only mood (219). The assessment methods for mood included the German version of Multidimensional Mood State Questionnaire (MDMQ) for subjective mood (good/bad mood; alertness/fatigue and ease/unease) (218), the Profiles of Mood States (POMS) questionnaires scoring the subscales tension/anxiety, fatigue/inertia, vigour/activity, confusion/bewilderment, anger/hostility, depression/rejection and the total mood disturbance score (193, 194, 219) and the Bond-Lader visual analogue scales for the alertness, calmness and contentment (193, 194, 219). For the assessment of cognition, the German version of the Frankfurt Attention Inventory 2 (FAIR-2, test version A) for attention (218) and the Computerised Mental Performance Assessment System (COMPASS) battery for a variety of cognitive domains were used (193, 194).

2.3.3. Study quality

The study quality assessment showed that all included studies have a low risk of bias in the first three domains (D1), bias arising from the randomisation process; (D2) bias due to deviations from intended interventions; (D3), bias due to missing outcome data), while the other two domains ((D4) bias in measurement of the outcome and (D5) bias in selection of the reported result) were assessed as having some concerns (Figure 2.2).

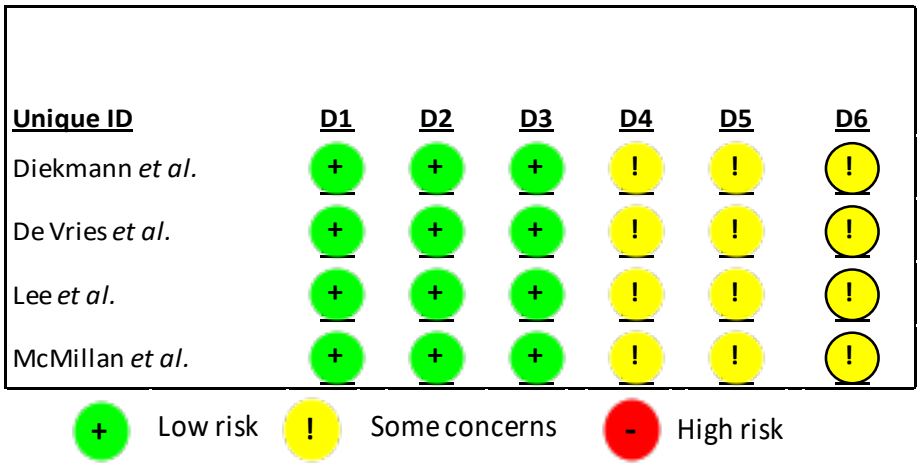


Figure 2.2. Risk of bias assessment results

D1: bias arising from the randomisation process; D2: bias due to deviations from intended interventions; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; D6: overall bias.

2.3.4. Effect of interventions

Primary outcome measures

Cognition:

According to the COMPASS results, increased correct responses (1.14, F=8.19, p=0.01) and decreased incorrect responses (-0.32, F=4.83, p=0.04) were seen in immediate word recall; reduced incorrect responses (-0.33, F=4.57, p=0.046) in delayed word recall were evident in the MDP group relative to the control while correct responses significantly decreased in MDP treatment (-2.32, F=6.64, p=0.02) for the 3-back task (194). Reaction time increased for numeric working memory task in MDP by 2% and decreased by 14% in the control group (F=5.05, p=0.04); reduced for Corsi Blocks task by 14% (-420) in MDP treatment and increased by 27% (+837) in the control group (F=17.628, p<0.001) (193). Whilst reaction times reduced in the word recognition task in both arms, it was not significant in the MDP (3%, -29, p=0.574) treatment and significant in the control group (20%, -191, p=0.001). The difference between the groups was significant (F=5.04, p=0.035) (193).

No overall significant effect of meal type on attention (as assessed by the FAIR-2 method) was recorded. However, in the walking groups a 1.4-fold increase was seen in the MDP group when compared to the WD, while this increase was 1.1-fold higher in the MDP relative to the WD in resting (p=0.045) (218).

Mood:

Using the POMS questionnaire, vigour/activity (p<0.001), tension/anxiety (p=0.001), fatigue/inertia (p=0.003), anger/hostility (p=0.014), confusion/bewilderment (p=0.015) and the total mood disturbance score (p value not stated) were significantly improved in the MDP arm compared to the control group (219). Lower confusion was observed following the MDP treatment (-1.19, F=6.87, p=0.02) with no other changes in the subscales of mood evident (194). Following 10 days of MDP adherence, vigour rose by 18% (3.67, F=11.25, p=0.003) in the MDP condition with no other dimensions of mood significantly affected (193).

Using the Bond-Lader scale, alertness and contentment were improved by MDP in all 3 studies used this scale. The results were as follows; alertness *(p*=0.003) and contentment *(p*=0.001) (219); alertness (6.93, F=14.11, $p<0.01$) and contentment (5.35, F=6.49, $p<0.02$) scores (194); and alertness (16.43 (about 30%), F=22.23, $p<0.001$) and contentment (12.89 (about 20%), F=16.634, $p<0.001$) (193). No significant change was reported for calmness.

Using the MDMQ test, no main effect of meal type interventions was observed for mood (218).

Secondary outcome measures

Two of the studies reported subjective dietary adherence. In the Lee *et al.*'s study (194), an average MDP adherence of 94% was evident which ranged from 80% to 100%. Similarly, in the McMillan *et al.*'s study (193), a mean MDP adherence of 93% for meals (range 80% to 100%) and 95% for snacks (85% to 100%) was reported.

No significant impact of a MDP meal vs WD meal on plasma cortisol levels was evident (218). Only Lee *et al.* assessed the impact of intervention on BP, blood flow velocity and arterial stiffness (194). A significant decrease (-1.05, F=6.15, p=0.02) in augmentation pressure (mmHg) was observed in the MDP condition relative to the control group.

Diekmann *et al.* assessed the desire to eat (218). Overall hunger was not influenced by meal while satiety was higher after MDP as compared to the WD *(p*<0.001).

Body weight and body mass index (BMI) were tracked in two of the studies. Lee *et al.* (194) reported a significant weight loss in the MDP (-1.77 kg, F=10,81, $p<0.01$) group. McMillan *et al.* (193) observed no significant main effect of diet on body weight, BMI or waist circumference between the two groups.

2.4. Discussion

This is the first systematic review to report the short-term effects of a MDP on cognition and overall mental well-being. The findings suggest that a MDP has the potential to affect cognition and mood in as little as 10-days. The findings have also identified important research gaps notably; there are few reported studies and of the studies available most were conducted in young people, aged 18 to 38 years (193, 194, 219) and all conducted in individuals without cognitive or mental health complaints. In addition, there was a tendency to study females with only 18 males in the 128 participants from the four studies. Therefore, the short-term effect of a MDP on mental health status in older adults, and in particular individuals who present with evidence of cognitive or mental health decline, is currently unknown.

Specific cognitive domains improved in all of the studies assessing the cognition although the findings were not consistent (193, 194, 218). Attention was significantly improved after the MDP in one study, with the authors speculating that this difference may be caused by the higher glucose content of the MDP (carbohydrate content of the meals: 133 g in MDP vs 93.7 g in WD) as the brain uses glucose as the primary source of energy (218). Other studies reported improvements in immediate and delayed memory recall tasks, working memory and reaction times (194), and spatial working memory (193). Consistent with these short-term effects, previous studies have reported longer-term (8 weeks) effects of a MDP enriched with dairy foods on processing speed in adults at above average CVD risk in the MedDairy study (220).

Mood dimensions, namely, alertness and contentment, were significantly and consistently improved by MDPs in the short-term in all four studies. Vigour (193, 219) and confusion (194, 219) were also improved following the MDP. Adherence to a MDP has previously been shown to be associated with reduced risk of depression in elderly (221) and in the MedDairy study, a reduction in depression, tension, anger, confusion and total mood disturbance score were recorded following the 8 weeks dietary intervention period (220). Furthermore, polyphenols intake, which are considered an important bioactive in the plant based MDP, have shown to reduce depressive symptoms (222).

Previous short-term studies using other dietary intervention or health endpoints provide insight into the possible mechanistic basis for the effect of a MDP on mental health. Myette-Côté *et al.* (223) examined the effects of a low fat, low glycaemic index diet (GL), to a low carbohydrate diet (LC) or a low carbohydrate plus post-meal walking (LC+Ex), in type 2 diabetes on glucose levels and inflammatory factors in a RCT comprising of three 4-days interventions. While improved glycaemic control was evident in the LC group, plasma monocyte-derived microparticles reduced significantly in the GL group which was similar to a MDP, suggesting that cerebral hypometabolism and inflammation which are features of cognitive disorders may be positively modulated by short-term dietary strategies. Attuquayefio *et al.* (195) reported a decrease in hippocampal-dependent learning and memory (HDLM) following a breakfast high in saturated fat, cholesterol and added sugar and low in protein relative to an isocaloric healthy breakfast for 4 consecutive days, findings which were subsequently confirmed over a one-week intervention period (224). The hippocampus is a core brain area for cognitive functions such as learning and memory (225). Besides, the hippocampus is involved in anxiety-related behaviours (226) and major depression (227). This evidence suggests the hippocampus function can be affected negatively by an unhealthy eating pattern in as short period as four days.

The hippocampus also produces high concentrations of brain derived neurotrophic factor (BDNF) which is important in attention, cognition and total behaviour (228). Decreased levels of BDNF have been linked to cognitive and mood disorders, and it has been identified as a therapeutic target in neurodegenerative and psychiatric impairments (229). In the PREDIMED study, a MDP raised BDNF levels over 3 years whilst a MDP supplemented with nuts was linked to significant improvement in serum BDNF levels in individuals with depression (173). However, the existing literature does not provide any insight into the short-term impacts of a MDP on BDNF levels.

Blood brain barrier (BBB) is a dynamic selective interface between the brain and the bloodstream, in which dysregulations are associated with cognitive (including AD) and psychiatric disorders (230). Although selected dietary components have been shown to affect BBB function such as permeability in animal models (231) and the BBB is susceptible to be impairment by a WD (232), the impact of a MDP in short- or long-term mental health is currently unknown but should be a focus of investigation. Additionally,

a reduction in CBF is associated with cognitive dysfunction (233). Lamport *et al.* (178) investigated the impacts of high flavanones on cognition and CBF in young healthy participants in an acute RCT. A high flavanone citrus juice resulted in a two hour increase in CBF and better performance in one cognitive task (Digit Symbol Substitution) were observed in the experimental group. McManus *et al.* (234) examined the acute effects of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), found in oily fish, on arterial stiffness in men at high risk of CVD. Four hours following to the test meal, vascular function was significantly improved by the DHA-rich oil. Besides, a MDP is known to chronically affect systematic vascular function (175).

The influences of the gut microbiota on cognition and overall mental well-being are well-recognised (235, 236). Therefore, nutritional strategies targeting gut health may represent a meaningful strategy for delaying or even reversing neuropathology (237). David *et al.* (238) demonstrated that the gut microbiota can be changed through both animal-based and plant-based diets in 5-days. Moreover, in a 1-year longitudinal study, the gut microbiota responded to daily changes in diet (239). Hence, accumulating evidence suggests that the gut-brain axis could mediate the even short-term effects of a MDP on cognition and mental wellbeing.

The current review highlighted that all of the participants in the MDP treatments from the two studies tracking dietary adherence (193, 194) reported high dietary adherence with no side effects. Besides, a MDP was linked to higher satiety in one study (218) and significant weight loss despite no caloric restriction in the another study (194). Considering the fact that maintenance of healthy eating behaviours is not an easy task even in the short-term, this available evidence suggests that a MDP is an acceptable implementable approach even in non-Mediterranean countries.

The review has also highlighted a lack of consistency in how the MDP is applied. Despite the small number of included studies, none of them used the same dietary procedure although the two Australian studies gave similar instructions to their participants (193, 194). Abdelhamid *et al.* (240) have previously reported the high inconsistencies in food and nutrient intake through when adopting a MDP. Davis *et al.* (152) also reported discrepancies in how the MDP was defined and the resulting nutrient intakes, with vegetable intakes, for example, ranged from 191-500 g/day in high MDP

adherers. A greater standardisation in the definition of a MDP is needed in order to integrate data from difference sources and translate it in dietary recommendations focussed on improved short- and long-term health.

The main strength of the present paper is that it is the first systematic review to examine the short-term impact of a MDP on mood and cognition. Secondly, the database combination used ensured optimal coverage of the data (214, 215), and has been shown by others to retrieve 95.9% of available references (214). Third, the review covers all available literature up to October 2023. As for limitations, the number of studies found was small, therefore, the conclusions are preliminary rather than robust. However, this limitation provided an opportunity to identify research gaps. The second limitation is the high heterogeneity in the dietary and mental health status assessments used. This methodological variability restricted making comparisons between studies.

In conclusion, the possible short-term beneficial impacts of a MDP on cognitive and mental health have been reviewed systematically for the first time. The results provide some initial evidence that short-term dietary interventions can confer health benefits which directly and/or indirectly improve cognitive and mental health. However, future studies are required to elucidate which cognitive and other mental health domains could be beneficially affected and what are the underlying physiological mechanism mediating the effects. Short-term strategies to improve cognition, mood and anxiety are not only of interest to improve quality of life and capabilities in those with existing mental health deficit but also in healthy individuals. The definition of the MDP in future studies should be carefully considered, with attention given to its population adoption taking into account social, geographical and cultural mediators of eating behaviours.

The second round of searches indicated that there is still a research gap within the field as no eligible study has been published in the last three years. However, it also highlighted ‘the growing interest in the field’, by comparison of the numbers obtained from the search results. The initial search covered the period from the inception dates of the databases to December 2020, and resulted in a total number of 3002 studies, whilst the last three years, between December 2020 and October 2023, generated 1430 studies, nearly half of the previous seventy years. Yet, there remains a dearth of clinical trials.

As per the second objective of the present systematic review which was to "identify research need and inform the design of future acute RCTs in the area", the further lack of acute/sub-chronic studies identified in this systematic review extension re-confirms the need for the MediMood trial presented in the next chapters.

2.5. Author contributions

Anne Marie Minihane and Karen Joy Murphy formulated the research question. Latife Esgunoglu selected the database combination and built the search strings with support from Lee Hooper, RD, PhD, an expert in systematic reviews, and Matthew Smith (Hawkes), the academic librarian of the Faculty of Medical and Health Sciences, University of East Anglia. Latife Esgunoglu and Elizabeth Sanchia Connole screened the records. Latife Esgunoglu and Amy Jennings conducted the risk of bias analysis. Latife Esgunoglu, Amy Jennings and Anne Marie Minihane interpreted the data. Latife Esgunoglu drafted the manuscript with all authors contributing and approving the final version.

Chapter 3. The MediMood study protocol: A randomised controlled trial investigating the acute impact of a plant based Mediterranean-style dietary pattern (MDP) on mood, anxiety and cognition in UK adults with mild to moderate mental health complaints

(Published manuscript)

This chapter has been published as a full article (241) (Appendix 5) and as a conference proceeding (242) (Appendix 6).

3.1. Introduction

Mental health disorders represent a major public health challenge (142). In 2019, depression exceeded 280 million cases globally, and anxiety surpassed 300 million cases, as the two most common forms of mental health disorders (142). Mental health disorders have constituted around 15% of 'years lived with disability' worldwide since 1990 (54), with depression predicted to be the global leading cause of disease by 2030 (55). In England, nearly 20% of adults report depression, anxiety, sleep problems, poor concentration and forgetfulness (243).

The economic impact of mental health disorders are substantial, with an estimated annual global cost of approximately $5 trillion including loss of productivity (244). The NHS has allocated a £2.3 billion budget for the years 2023-2024 for mental health services as part of its Long-Term Plan (245).

The main treatment for mental health disorders are antidepressant medications and psychotherapy; both can cause negative side effects (246), stigma (247), and have poor uptake (243). Despite increased treatment in recent decades, no decrease in the prevalence of mental disorders is evident (248), underlining the need for alternative intervention approaches. The WHO has highlighted the critical need for "affordable, effective and feasible strategies to promote, protect and restore mental health", and

launched several initiatives such as the 'Comprehensive Mental Health Action Plan 2013-2030' (249) and the 'World mental health report: transforming mental health for all' (250) to address these needs.

A Mediterranean-style dietary pattern (MDP) is rich in plant-based foods such as fruit, vegetables, legumes and nuts, provides moderate fish intake and is low in high fat diary, red and processed meat and carbonated beverages, providing a macronutrient balanced diet rich in polyunsaturated fatty acid and unrefined complex carbohydrates, which is in accordance with the healthy eating guidelines of most countries (251). There are several tools available for tracking adherence to a MDP. The MEDAS which has been commonly used in research including our recently completed, one year "MedEx-UK: a Randomized Controlled Trial investigating the feasibility of a multi-domain intervention to increase Mediterranean diet and Physical Activity of older UK adults who are at above average risk of dementia" (162) (ClinicalTrials.gov Identifier: NCT03673722). A few advantages of the MEDAS over others are; it provides a quick assessment of a MDP adherence and is validated for a UK population (161).

Long-term adherence to a MDP has been consistently shown to protect mental health. Longitudinal analysis of the SUN cohort (n=10,094) reported that higher MDP adherence was correlated with a lower depression incidence after 4.4 years (252), supported by a meta-analysis of observational studies showing a reduced risk of depression associated with long-term MDP adherence (OR=0.72; 95% CI: 0.60, 0.87) (211). The PREDIMED study reported a 41% reduction in depression among at-risk individuals who followed a MDP supplemented with nuts for three years (181). The HELFIMED (183), SMILES (182), and AMMEND (184) trials, all of which examined the effects of a MDP on depression in adults with moderate to severe depression over the course of 3 to 6 months, demonstrated significant decrease in depressive symptoms (Table 1.3).

The cognitive benefits of a MDP have been consistently reported. The EPIC-Norfolk study demonstrated that higher MDP adherence is linked with improved global cognition and memory in a UK population (185). Additionally, a meta-analysis reported a linear dose-response relationship between a MDP adherence and the risk of future cognitive disorders (210). The PREDIMED study showed enhanced cognition after MDP

interventions (188) (Table 1.4), while a recent UK Biobank analysis suggested a reduced risk of future dementia associated with MDP consumption (253).

A Western diet (WD) is a term that defines a poor-quality diet consumed in the Western countries including the UK, that is characterised by high consumption of processed food and sugary drinks and snacks, and thus low intake of fibre, vitamins and minerals (254). A long-term WD consumption has been shown to trigger the risk of chronic diseases (255), mental and cognitive disorders and smaller hippocampus (256). One short-term study (four days) looking at the impact of a high-sugar breakfast on hippocampus found impaired learning and memory (195).

Our systematic review investigating the short-term effects (up to ten days) of a MDP on brain health revealed improved mood and cognition, in particular, alertness, contentment and attention domains. There were too few studies to draw firm conclusions, and we identified several limitations and research gaps. Three of the four studies were of ten days duration, with no shorter term or postprandial data available. Besides, in all reviewed studies participants were provided with dietary advice rather than the intervention diet, and adherence to the intervention was not monitored. Furthermore, mental health outcomes were not comprehensively assessed to elucidate which domains are most responsive to a short-term MDP intervention and little attention has been given to possible underlying mechanisms which could be mediating the acute effects of a MDP such as changes in inflammation, glucose regulation, CBF and the gut microbiota (196). Therefore, despite its potential benefits on mental wellbeing and quality of life, the acute effects of a MDP are largely unknown.

3.2. Trial purpose and objectives

The overall aim of MediMood study was to examine the impact of a MDP versus a WD on mood, anxiety and cognition postprandially, at 24-hour (mood and anxiety only) and after five days, and to investigate underpinning physiological mechanisms. The primary hypothesis is that a MDP can elevate mood and reduce anxiety in five days compared to a WD. Our secondary hypothesis is that a MDP can improve cognition, sleep, CBF and relevant biological mechanisms compared to a WD (Figure 1.6).

Five days was chosen as the intervention duration based upon the published literature suggesting meaningful changes in mechanisms which modulate cerebral blood flow, inflammation status and the gut microbiota could be observed in this timeframe (196).

3.2.1. Primary objective

The primary objective of the study was to examine whether adherence to a MDP enhances mood and cognition and reduces low mood and anxiety symptoms postprandially, at 24-hour and after five days with compared to a WD.

3.2.2. Secondary objectives

The secondary objectives were to assess the effects of intervention on (with those included in this thesis in bold:

- **Cognitive performance** including attention postprandially and after five days.
- Cardiometabolic profile, including **BP, insulin, glucose, lipids** and inflammatory markers (e.g. **CRP**) postprandially and after five days.
- Hormones regulating mood, anxiety and stress, including but not limited to adrenaline, **cortisol,** serotonin, dopamine and thyroid hormones postprandially and after five days.
- Biomarkers of mood and cognition regulation, to include but not limited to **BDNF**, tryptophan (precursor of serotonin and melatonin) and choline at postprandially and after five days.
- **CBF** using neuroimaging (brain MRI) postprandially.
- Sleep quality which is a major determinant of mental (257) and cognitive health (45) throughout the five days.
- Changes in gut microbiome profile (which is subject of another PhD thesis)
- **Participants' subjective assessment on adherence to a MDP** upon completion of five days.

3.2.3. Follow-up objective

- To evaluate whether a five-day MDP intervention results in any long-term changes in habitual Mediterranean dietary behaviour of participants at three months.

3.3. Methods

The MediMood study was a single-centre cross-over RCT conducted at the University of East Anglia (UEA), and the NHS Clinical Research Facility (CRF) intervention centre, based at the Quadram Institute (QI), in Norwich, UK.

The study received favourable ethics opinion from NHS Health Research Authority (22/LO/0796) presented in the Appendix 7, and was registered on ClinicalTrials with the identifier number NCT05927376 (Mediterranean-style Dietary Pattern (MDP), Mood and Anxiety - Full Text View - ClinicalTrials.gov) (Appendix 8).

3.3.1. Overview of Trial Design and Study Plan

A five-days cross-over RCT with two arms and a 23-days wash-out period (considering women's menstrual cycle) was conducted in 25 adults. The arms were, (1) MDP and (2) WD. Participants included both males and females (balanced sex distribution will be aimed for), over 18 years, with mild or moderate level mood and anxiety disturbances.

The study steps for potential and recruited participants were as follows:

A participant information sheet (PIS) embedded in an initial invitation email or letter (Appendix 9) was sent to all those who express interest in the study via email at least five days before step A. Consenting (Step B) and below was completed using an online research management portal (MediMood - Home (mantal.co.uk))

A: An online video-conference ZOOM session or a phone call (depending on their preference) was held with potential participants in order to (neither recording nor data collection/storage will be done in this stage)

- Provide potential participants with a detailed information on the study protocol and dietary interventions.
- Provide an opportunity for participants to ask questions regarding the PIS/study protocol and their suitability.

B: For consenting

- Potential participants were provided with a clickable link via email to complete online informed consent (Appendix 10) or were provided with the printed version of the Consent Form (Appendix 11) which was used at the CRF at their first clinical visit to receive traditional consent with wet signature as well.
- Potential participants were given a further 48 hours to take time to consider their decision to participate in the study.

C: Consenting participants were asked to do the followings:

- Complete three online screening questionnaires, in order to determine, 1) current dietary practices to establish their dietary eligibility (MEDAS questionnaire, plus any allergies or other dietary restrictions which would preclude participation) and 2) the assessment of their current anxiety and depressive symptoms (PHQ-9 (Appendix 12) and GAD-7 with an extra question on their antidepressant/antianxiety medication use (Appendix 13). If they passed this stage, a researcher called them to go through MRI Safety Screening Form (Appendix 14) in order to assess the safety of the scan for individuals.

D: Recruited participants were asked to do the followings:

1. After the completion of screening step B above and before their baseline visit, complete the EPIC food frequency questionnaire (FFQ) (Appendix 15) to capture their habitual dietary intake before the study.
2. On the day before the baseline visit, collect a faecal sample according to the instructions and packaging provided and to fast from 8 pm, with no food or drink except water.

3. On the morning of the baseline visit, collet a urine sample in the container provided.
4. Attend an on-site baseline visit at the morning of day-1 for weight, height and BP measurements, and the provision of a fasting (no food or drink from 8 pm the night before apart from water) venous blood, along with the already collected urine and stool sample.
5. Following a small breakfast (water and an oat and honey cereal bar), mood, anxiety, cognition and sleep were assessed.
6. 2.5 hours after the breakfast, have an intervention lunch (either MDP or WD, administered at CRF), and 90 minutes later, have an MRI scan and undergo mood, anxiety and cognitive testing, and provide a venous blood sample.
7. Consume the allocated diet (either MDP or WD) over five days
8. Complete on-line mood and anxiety tests on the morning of day two
9. Complete an initial sleep questionnaire on day-1, keep a sleep diary and wear an Actiwatch over five days
10. On day six, repeat the steps 2-5 above, with an extra question assessing the subjective view on how easy/hard intervention was for the end of treatment arm assessment.

E: 23-days wash-out period.

F: Step D was repeated in a cross-over fashion.

G: All participants were asked to reply to an email including the MEDAS questionnaire three months after the second arm ends.

Figure 3.1 represents the study flow diagram for the entire study.

Table 3.1 demonstrates a timeline of the intervention for participants randomised onto the trial.

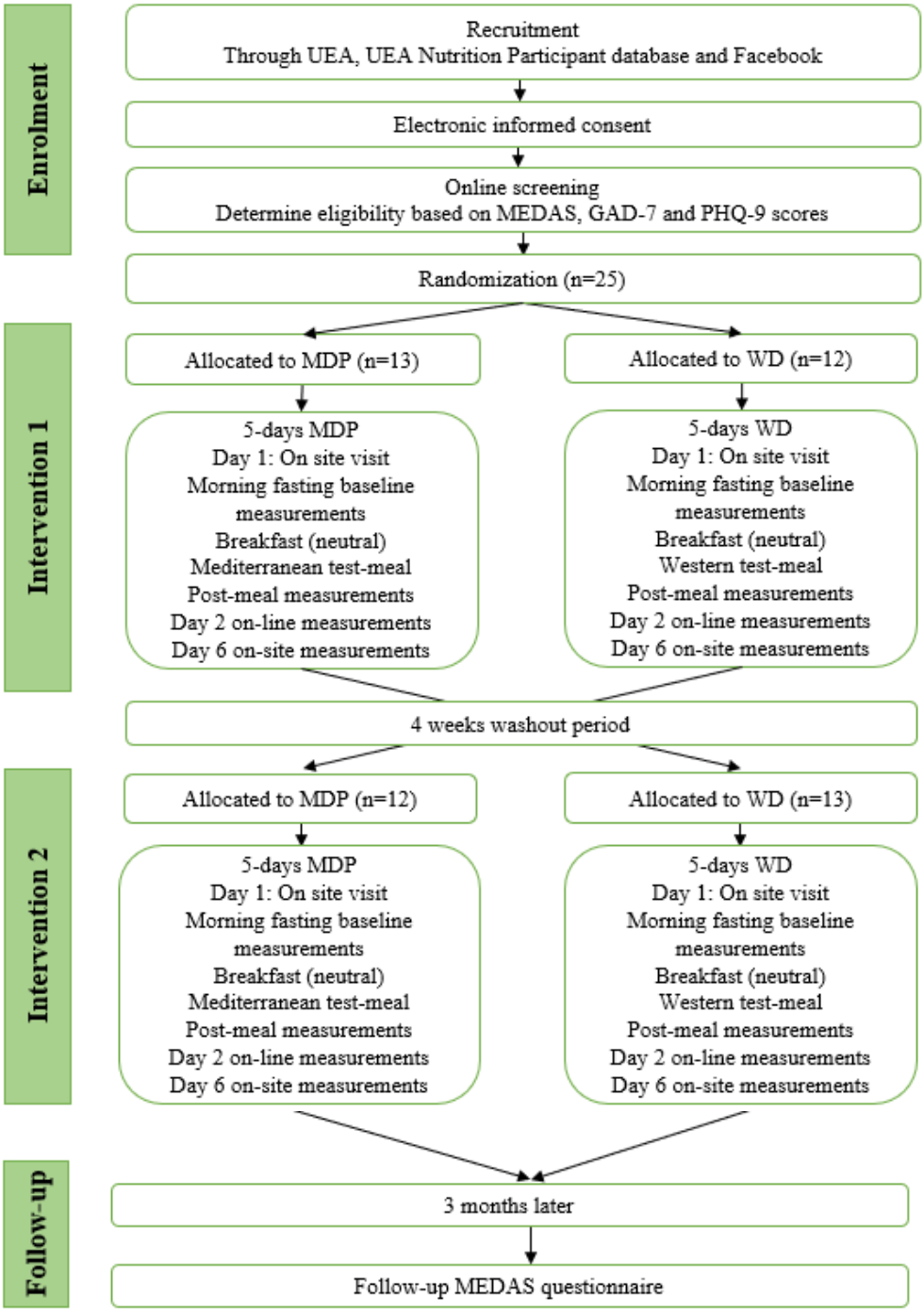


Figure 3.1. Study Flow Diagram

Table 3.1. Study timeline showing intervention and approximate time burden for participants in each study arm

Weeks	Days	Procedures
-2		Recruitment Online consent meeting, 30 mins Online screening (questionnaires), 30 mins EPIC FFQ, 30 mins
-1		
1	Day 0	Collection of faecal and urine samples (at home)
	Day 1	On-site visit (weight, height, blood pressure, blood samples collection x 2, mood and cognitive tests x 2, lunch, MRI scan), 8 hours
	Day 2	On-line tests (at home) (mood questionnaire), 30 mins
	Day 3	
	Day 4	
	Day 5	Collection of faecal and urine samples (at home)
	Day 6	On-site visit (weight, height, blood pressure, blood sample collection, mood and cognitive tests), 2,5 hours
2		Wash-out period
3		
4		
5		
6	Day 0	Collection of faecal and urine samples (at home)
	Day 1	On-site visit (weight, height, blood pressure, blood samples collection, mood and cognitive tests, lunch, MRI), 8 hours
	Day 2	On-line tests (at home) (mood questionnaire), 30 mins
	Day 3	
	Day 4	
	Day 5	Collection of faecal and urine samples (at home)
	Day 6	On-site visit (weight, height, blood pressure, blood sample collection, mood and cognitive tests), 2,5 hours
7		Follow-up waiting period
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		On-line follow-up questionnaire, 15 mins

Wear an actigraph watch
Keep a sleep diary
Follow the diet

Wear an actigraph watch
Keep a sleep diary
Follow the diet

3.3.2. Recruitment and eligibility criteria

Potential participants were recruited from the general population and from the UEA staff and students, using advertising poster/leaflet (Appendix 16), internal emails and social media. Those interested along with potential suitable individuals on the UEA Nutrition participant database, were sent an invitation email or letter (Appendix 17). Eligibility of potential participants was assessed online by the researchers using step B above.

Individuals were included if they

- were over 18 years.
- had mild to moderate level of anxiety and/or depression.
- did not have a habitual high adherence to a MDP.
- were able to have an MRI scan.
- were fluent in written and spoken English.

The full inclusion/exclusion criteria are presented in Table 3.2.

Table 3.2. The full eligibility criteria

Inclusion criteria	Exclusion criteria
Males and females aged 18 or over	Vegan, vegetarian, pescatarian
Mild to moderate level anxiety and/or depression (PHQ-9 and/or GAD-7 scores of 5-14)	Allergic to any of the study components e.g., nuts and fish
Low MDP adherence (MEDAS score ≤ 7/14)	On anti-anxiety and/or antidepressant medication which has changed in the last 3 months or likely to change in the next 3 months.
Able to have an MRI scan	Unwilling or unable to make changes to their diet for 10 days (2 x 5 days)
Computer literate with internet access	Unable to attend the intervention centre
Fluent in written and spoken English	
Gave consent for the study team to contact their GP	

PHQ-9: Patient Health Questionnaire; GAD-7: Generalised Anxiety Disorder; MDP: Mediterranean-style dietary pattern; MEDAS: Mediterranean Diet Adherence Screener tool.

In order to establish the mood and anxiety profiles, two different questionnaires were used. The Patient Health Questionnaire-9 (PHQ-9) is a 9-item questionnaire which assesses depressive symptoms (258) while the Generalized Anxiety Disorder-7 (GAD-7) measures anxiety on a 7-point scale (259). Both are commonly used in research and primary care. Both questionnaires are interpreted based upon the total score, of which classifications are as follows: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe for PHQ-9 and, similarly, the scoring system of GAD-7 is 0-4 no to low risk, 5-9 mild, 10-14 moderate, 15+ severe. Individuals will be included if they score 5-14 from PHQ-9 and/or GAD-7. MDP adherence status was assessed using MEDAS. Participants with a score of ≤ 7/14 were eligible to participate. An MRI Safety Screening Form was used to establish if it was safe for individuals.

In addition, if people reported antibiotic use in the last month, their participation was postponed for a month to ensure that their gut microbiota composition has returned to its habitual status. Furthermore, participants were asked to keep their probiotic supplement use (as it affects the gut microbiota) and physical activity level stable over the course of the study.

Safeguards for maintaining psychological wellbeing of participants

Recruited participants' GPs were contacted to inform them about the study, the participation of their patients, and their baseline scores on the PHQ-9 and GAD-7 which indicated levels of depression and anxiety (Appendix 18). In addition, we contacted GPs of participants who were not suitable for participation due to high levels of anxiety and/or depression (moderately severe or severe on PHQ-9 and/or severe on GAD-7) to inform them about the mental health status of their patients which may require further and urgent attention (Appendix 19).

People scoring below the threshold on both the PHQ-9 and GAD-7 were not eligible to participate. They were informed of this but given there was no identified potential mental health concern there was no communication sent to the GP.

Participants who were screened and did not meet criteria for inclusion into the study due to elevated scores on the PHQ-9 or GAD-7 were informed that their scores

were above threshold for entry into the study. It was made clear that an elevated score on the PHQ-9 and GAD-7 is not a clinical diagnosis of depression or anxiety but does indicate consistencies with this, and this might be something they wish to explore further. Participants were given information about services available to support with this including the NHS wellbeing service should they wish to explore this and seek potential treatment. If those excluded people were affiliated with UEA, they were signposted to the university wellbeing support services. The PIS included information ad signposting for mental health and wellbeing support.

In the unlikely event that the principal investigator or anyone involved with participants contact becomes concerned about the psychological wellbeing of a participant, they consulted the Consultant Clinical Psychologist from the local NHS trust who was part of the research team who could advise and direct on steps to take to ensure safety. This was however not needed. As we recruited participants who had already high adherence to a WD (MEDAS score≤ 7), we did not anticipate that following this diet for five-days would have any significant detrimental impacts on their long-term health.

3.3.3. Design of the intervention

The proposed study was intended to be an efficacy trial which quantified the mental health and cognitive impact of a five-day optimised MDP intervention in comparison to a WD intervention. It was expected to maximise the probability to detect the potential intervention effects by conducting a high-quality cross-over RCT under as ideal as possible conditions (260, 261).

3.3.4. Dietary interventions and food provision

The diets were designed using the MEDAS scoring system which is a 14-point tool capturing the main components of a MDP. For the MDP arm, we aimed for a full score of 14 to be achieved over the five days. However, 12 points or above was also accepted in order to provide some flexibility to the participants. As for the WD arm, a poor diet with 0 point on MEDAS was generated, with a score up to 2 permitted again to suit participants' dietary preferences.

The PREDIMED diet was taken as a reference to optimise the MDP diets (262), and the nutrient profile of the WD was based on extreme nutrient intakes of 2.5% of the UK population using the UK National Diet and Nutrition Survey (NDNS) (https://www.gov.uk/government/collections/national-diet-and-nutrition). The total macronutrients (carbohydrates, fat and protein) distribution, and their breakdowns into free sugars, fibre, saturated and unsaturated fat contents of the diets were designed to ensure they represent MDP and WD, and in particular that free sugars and SFA match a typical WD, and fibre and MUFA match a representative MDP.

Moreover, the MDP arm involved foods requiring some level of preparation and cooking at home, whilst the WD plan consisted mostly of ready-to-eat food. The food processing techniques are known to affect the bioactive components, in particular, phytochemicals that are found in primary MDP components for example olive oil and vegetables and hold anti-inflammatory and antioxidant properties (263). Given the logistical and practical constraints, we adhered to the food availability in stores, which ensured not only the feasibility but also authentically reflected the nature of both dietary patterns.

The full meal plans are presented in the Table 3.3.

Table 3.3. Full meal plans

3.3a. The 5-day meal plan of the Mediterranean diet arm

	Day 1	Day 2	Day 3	Day 4	Day 5	List of allowed snacks
Breakfast	Nature Valley Crunchy Oats & Honey cereal bar, General Mills International Sarl, Switzerland, 42g	Nature Valley Crunchy Oats & Honey cereal bar, General Mills International Sarl, Switzerland, 42g (before testing) Tesco Greek Style Yoghurt*, 110g Tesco Blueberries*, 80g	Tesco Large Free Range Eggs, 2 boiled eggs Hovis Wholemeal Medium Bread, The Hovis Team, Hovis Bakeries Ireland, 1 slice of wholemeal bread, 40g	Tesco Greek Style Yoghurt*, 110g Tesco Blueberries*, 80g Tesco Walnut Halves*, 30g	Tesco Greek Style Yoghurt *, 110g Tesco Blueberries *, 80g Tesco Walnut Halves *, 30g	- Rice cakes, oat cakes, wholemeal bread, toast - Cottage cheese or low-fat cream cheese spread - Low sugar breakfast cereal with milk - A small glass of wine (125ml/day) - Sugar free drinks
Morning snack	NA	Innocent Orange Juice Smooth, Fruit Towers, London, 150ml	Innocent Orange Juice Smooth, Fruit Towers, London, 150ml	Innocent Orange Juice Smooth, Fruit Towers, London, 150ml	Innocent Orange Juice Smooth, Fruit Towers, London, 150ml	
Lunch	Salad with salmon and lentils - Princes Skinless Boneless Wild Red Salmon, Princes Ltd., Liverpool, UK, 170g	Falafel salad - Gosh Mediterranean Falafel, Gosh! Food Ltd., Milton Keynes, 150g - Tesco Houmous*, 30g	Bol Creamy Coconut Turmeric Daal Power Pot, BOL, London, UK, 400g/1 pot Tesco EVOO*, 25ml	Baked potato with tuna and salad - Tesco Tuna Chunks in Spring Water *, drained 105g - Tesco Whole Cucumber *, 90g	Pasta and tomato sauce - Tesco Whole Wheat Penne Pasta *, 75g - Tesco Red Onion, 75g - Tesco Organic Garlic *, 6g	

	- Merchant Gourmet Puy Lentils Ready To Eat, London, 125g - Tomato 140g - Lettuce 100g - Tesco EVOO*, 25ml - Tesco Lemon Juice*, 1 tbsp - Tesco Balsamic Vinegar of Modena*, 1 tbsp Tesco Walnuts*, 30g Innocent Orange Juice Smooth, Fruit Towers, London, 150ml	- Tesco Whole Cucumber*, 60g - Tesco Mixed Leaf Salad*, 40g - Tesco Cherry Tomatoes*, 90g - Tesco EVOO*, 25ml - Tesco Balsamic Vinegar of Modena*, to taste		- Tesco Cherry Tomatoes *, 105g - Tesco EVOO *, 25ml - Tesco Balsamic Vinegar of Modena*, to taste	- Tesco Italian Finely Chopped Tomatoes*, 200g - Tesco Red Pepper*, 80g - Tesco EVOO*, 25ml
Afternoon snack	Banana*	Tesco Houmous*, 30g Tesco Whole Cucumber*, 90g	Tesco Walnut Halves*, 10g Tesco Large Conference Pears Loose Class 1	Tesco Soft Figs *, 30g	Tesco Houmous*, 60g Tesco Whole Cucumber*, 90g Tesco Carrot Batons, 80g
Dinner	Tesco 3 Chilli Bean Soup*, 300g Tesco EVOO*, 25ml Hovis Wholemeal Medium Bread, The Hovis Team, Hovis Bakeries Ireland, 2	Black bean and butternut squash chilli - Tesco Leaf Spinach (frozen)*, 80g - Tesco Butternut Squash Chunks (frozen)*, 125g	Salmon, new potatoes, salad - Tesco 2 Boneless Salmon Fillets*,1 fillet - Tesco Classic Green Pesto*, 24g/1tbsp - Tesco New Potatoes*, boiled 85g	Grilled chicken with Mediterranean vegetables and couscous - Tesco 2 British Chicken Breast Fillets *, 1 fillet	Chicken with chickpeas in tomato sauce - Tesco 2 British Chicken Breast Fillets, 1 fillet - Tesco Red Onion, 75g

	slices of wholemeal bread 80 g	- Tesco Red Onion, 75g - Tesco Cherry Tomatoes*, 200g - Tesco Black Beans*, 120g - Chilli pepper 10g - Tesco Tomato Puree*, 10g - Tesco Organic Garlic*, 3g - Tesco Fresh Cut Coriander*, 15g - Tesco EVOO*, 25ml	- Tesco Mixed Leaf Salad*, 40g - Tesco Cherry Tomatoes*, 90g - Tesco Organic Garlic*, 3g - Tesco EVOO*, 25ml	- Tesco Butternut Squash Chunks (frozen) *, 125g - Tesco Sliced Mixed Frozen Peppers,125g - Tesco Whole Wheat Cous Cous *, 50g - Tesco EVOO *, 25ml	- Red pepper 160g - Tesco Organic Garlic*, 6g - Tesco Italian Finely Chopped Tomatoes *, 200g - Tesco Red Pepper*, 160g - Tesco Chickpeas in Water*, 120g - Tesco Leaf Spinach (frozen)*, 80g - Tesco EVOO*, 25ml
Evening snack	Tesco Winter Fruit Salad (apple, pear, grapes, plum/nectarine) *, 200g	Tesco Walnut Halves*, 10g Tesco Soft Figs*, 30g	Tesco Mixed Nuts*, 25g Tesco Prunes*, 205g	Tesco Mixed Nuts *, 25g Tesco Large Conference Pears Loose Class 1	Tesco Large Pink Lady Apples Loose Class 1 Tesco Large Conference Pears Loose Class 1

Day 1 lunch meal was the test meal for the postprandial assessments, which were administered in the Clinical Research Facility. The standard MEDAS binary scoring system, which is designed for a weekly assessment, was applied directly to our 5-day MDP plan without adjusting the minimum thresholds, as the three portions for example fish in 5-day would also meet the 7-day requirement when extrapolated proportionally (See section 1.2.1 for further details). The MDP meal plan above scores 13 out of 14, with one optional point for wine intake.

*: Products that are produced for Tesco by Tesco Stores Ltd., Welwyn Garden City, UK.

Note: If the ingredients are not listed underneath, it is a ready-to-eat food.

EVOO: Extra virgin olive oil

3.3b. The 5-day meal plan of the Western diet arm

	Day 1	Day 2	Day 3	Day 4	Day 5	List of allowed snacks
Breakfast	Nature Valley Crunchy Oats & Honey cereal bar General Mills International Sarl, Switzerland, 42g,	Nature Valley Crunchy Oats & Honey cereal bar General Mills International Sarl, Switzerland, 42g, Hovis Soft White Medium Bread, 1 slice, 40g, Hovis Ltd, High Wycombe Tesco Strawberry Seedless Jam *, 18 g Tesco British Salted Block Butter *, 12g	Kellogg's Frosties Cereal, Kellogg's, Greater Manchester, UK, 50g Tesco British Semi Skimmed Milk *, 135g	2 fried eggs 2 sausages - Tesco British Salted Block Butter *, 12g Hovis Soft White Medium Bread, 1 slice, 40g, Hovis Ltd, High Wycombe	Kellogg's Frosties Cereal, Kellogg's, Greater Manchester, UK, 50g Tesco British Semi Skimmed Milk *, 135g	- White bread, toast with jam or marmalade (no butter) - High sugar breakfast cereal with milk - Chips - Crisps - No fruit juice - No wine (other alcoholic drinks allowed if they wish to do so)
Morning snack	NA	KitKat 2 Finger Milk Chocolate Biscuit Bars, 20.7g	KitKat 2 Finger Milk Chocolate Biscuit Bars, 20.7g	KitKat 2 Finger Milk Chocolate Biscuit Bars, 20.7g	KitKat 2 Finger Milk Chocolate Biscuit Bars, 20.7g	
Lunch	Ham roll - Tesco Soft White Rolls 6 pack, 1 roll - Tesco British Wafer Thin Oak Smoked Ham *, 120g	Tesco Quiche Lorraine *, 160g/1 quiche Tesco Potato Salad *, 100g	Bacon roll - Tesco Unsmoked Back Bacon *, grilled 150g - Tesco Brioche Buns *, 1 roll 63g	Tesco Cream of Chicken Soup *, 400g Hovis Soft White Medium Bread, 2 slices, 80g, Hovis Ltd, High Wycombe	Tesco Quiche Lorraine *, 160g/1 quiche Walkers Ready Salted Crisps 25g/1 pack, Walkers Snack Foods Ltd.	

	- Heinz Mayonnaise sachets12g - Butter 14g Coca Cola Original Taste 330 ml Mars Chocolate Bars, 2 x 39.4g, Freepost Mars Wrigley Confectionery UK Ltd.		- Tesco British Salted Block Butter *, 12g - Tesco Tomato Ketchup *, 24g		Coca Cola Original Taste 150 ml
Afternoon snack	Twix Caramel & Milk Chocolate Fingers Biscuit Bars, 20g, Freepost Mars Wrigley Confectionery UK Ltd.	Coca Cola Original Taste 150 ml	Mr Kipling Cherry Bakewell Tarts, 46g, Premier Foods ROI, Ireland	Aero Chocolate Mousse 59g/1 pot, Nestle UK Ltd., York, UK	Mr Kipling Cherry Bakewell Tarts, 46g, Premier Foods ROI, Ireland
Dinner	Tesco Cream Of Chicken Soup *, 400g Hovis Soft White Medium Bread, 1 slice, 40g, Hovis Ltd, High Wycombe Tesco British Salted Block Butter *, 6g	Tesco British Pork Sausages *, 2 sausages grilled/oven baked Tesco Homestyle Straight Cut Oven Chips *, 165g Tesco Tomato Ketchup *, 24g	Chicago Town Deep Dish Mega Meaty Pizza, 157g, Chicago Town, Dublin, Ireland Tesco Potato Salad * 100g Coca Cola Original Taste 150 ml	Tesco Spaghetti Carbonara *, 400g Coca Cola Original Taste 150 ml	Burger and chips - Tesco Beef Quarter Pounders *, 114g - Tesco Brioche Buns, 1 roll/63g - Tesco British Salted Block Butter *, 12g - Tesco Homestyle Straight Cut Oven Chips 135g - Tesco Tomato Ketchup *, 24g

Evening snack	Mr Kipling Cherry Bakewell Tarts, 46g, Premier Foods ROI, Ireland	KitKat 2 Finger Milk Chocolate Biscuit Bars, 20.7g	Tesco Chocolate Cheesecake * 90g	Cadbury Caramel Cake Bars 50g, Premier Foods ROI, Ireland	Aero Chocolate Mousse 59g/1 pot, Nestle UK Ltd., York, UK

Day 1 lunch meal was the test meal for postprandial assessments, which were administered in the Clinical Research Facility. The standard MEDAS binary scoring system, which is designed for a weekly assessment, was applied directly to our 5-day MDP plan without adjusting the minimum thresholds, as the three portions for example fish in 5-day would also meet the 7-day requirement when extrapolated proportionally (See section 1.2.1 for further details). The WD meal plan above scores 0 out of 14.

*: Products that are produced for Tesco by Tesco Stores Ltd., Welwyn Garden City, UK.

Note: If the ingredients are not listed underneath, it is a ready-to-eat food.

The diets were designed to be isocaloric, providing a standard approximate 2000 calories per day (±10% flexibility per day, ranging between 1800-2200 kcal) and 10,000 calories in total over five days. Test lunch meals were aimed to be approximately 1000 kcal, which were administered at the CRF. Participants were provided with guidance as to which additional foods and snack can be consumed if required, which would not impact on the overall MEDAS score. Table 3.4 represents the nutrient compositions of the test lunch meals, and Table 3.5 represents the nutrient compositions of the full five-day diets. Regarding beverages, a glass of wine per day was allowed (optional) only in the MDP arm. Consumption of other alcoholic drinks was discouraged during the 5-day intervention periods. Drinks such as water, tea, coffee, diet drinks and low sugar squashes could be consumed ad libitum. Participants were asked to record their beverage intakes on the daily checklists. Dietary compliance was tracked by using a daily checklist, designed for the MediMood study (Appendix 20).

Table 3.4. Nutrient composition of the lunch test meals (day 1) taken from the product labels

		Mediterranean diet	**Western diet**
Energy	Kcal	982	987
Carbohydrates	g	42.2	136.4
	%	16.1	51.8
Free sugars	g	18	83
Fibre	g	12.1	3.6
Proteins	g	60.1	34.8
	%	24.5	14.1
Total fat	g	64.9	37.4
	%	59.4	34.1
SFA	g	9.3	14.6
	%	8.5	13.3

MUFA	g	30.5	15.3
	%	28	14.0
PUFA	g	20.4	4.8
	%	18.7	4.4
Omega-3 PUFA	g	5.3	0.9
	%	4.8	0.8
Omega-6 PUFA	g	14.3	3.0
	%	13.1	2.8

SD: standard deviation; kcal: kilocalories; g: grams; %: contribution to the total daily energy intake as percent; SFA: saturated fatty acids. Free sugars included "added sugars and sugars naturally present in honey, syrups and fruit juices, as defined by Scientific Advisory Committee on Nutrition" (264). The amounts (both g and %) of saturated fat, MUFA and PUFA do not sum to the total fat stated due to unstated non–fatty acid lipid constituents that contribute to the total fat value (265).

Table 3.5. Nutrient composition table of the 5-day test diets

		Mediterranean diet (mean ± SD)	**Western diet (mean ± SD)**
Energy	Kcal/day	1878 ± 46	2027 ± 79
Carbohydrates	g/day	154.2 ± 16.2	230.8 ± 24
	%	32.8 ± 3.0	45.5 ± 4.6
Free sugars	g/day	30.9 ± 14.8	84.8 ± 20.3
Fibre	g/day	34.8 ± 6.4	10.6 ± 2.9
Proteins	g/day	80.8 ± 19.1	64.6 ± 11.4
	%	17.1 ± 4	12.7 ± 2.3
Total fat	g/day	105.0 ± 8.9	94.2 ± 11.2
	%	50.3 ± 4.6	41.8 ± 4.6
SFA	g/day	16.1 ± 2.0	37.1 ± 3.9
	%	7.2 ± 1.0	16.5 ± 1.3

MUFA	g/day	43.5 ± 6.1	5.0 ± 2.6
PUFA	g/day	16.9 ± 7.5	2.6 ± 3.0
Omega-3 PUFA	g/day	2.4 ± 1.5	0.7 ± 0.1
Omega-6 PUFA	g/day	9.3 ± 6.6	0.6 ± 0.7

SD: standard deviation; kcal: kilocalorie; g: grams; %: contribution to the total daily energy intake as percent; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids. Free sugars included added sugars and sugars naturally present in honey, syrups and fruit juices, as defined by Scientific Advisory Committee on Nutrition (264).

All meals were standardised with all foods provided over the five days. Both diets were designed considering UK dietary habits. In order to promote adherence, all foods were supplied by an online supermarket ordering system by the study team to be delivered to individuals' addresses on the day before each 5-day intervention period. Participants were provided with detailed instructions on weights of food to be consumed and preparation.

3.3.5. Delivery of the intervention

Potential participants were given detailed instructions on the five-day diets (for both the MDP and WD arms) and the opportunity to ask their questions to the trained researchers during the consent meeting. The day before the study started, they were sent emails or given a call (depending on participants' preferences) to remind them of the study procedure and the opportunity to ask further questions.

Participants were asked to visit the intervention centre on day one (Figure 3.2), from 08:00 until approximately 15:30. Before their arrival, they were required to collect a urine and faecal sample at home using sample collection kit provided at least two days prior to their day 1 visits. The kit included a stool sample catcher, two plastic tubes with scoop, a biohazard bag, a sealable bag, a urine sample collection pot with a sealable bag, a pair of disposable gloves, an insulated cool bag, two freezer blocks with two sterile outer bags, and instructions. They were asked to collect the faecal sample within 24 hours

prior to their clinical visit, and the urine sample as the first pass on the morning of their visit (day 1). Participants arrived at the intervention centre in a fasted state (fasted from 20:00 the night before). Upon arrival, anthropometric (weight and height) and BP measurements were taken. A nurse collected the baseline blood sample. Participants were then provided with a honey and oat cereal bar. After 15 mins rest, participants underwent the mood, anxiety, cognition and sleep testing via the study website. 90 minutes after completing these tests, participants were served either a MDP or a WD test meal (at 11:30) depending on the arm they are randomised to. Following the meal, participants' BP was measured at 12:45 and started postprandial mood and cognitive testing at 13:00. At 14:00, they underwent the brain MRI scan and provided a postprandial blood sample at 15:15. Afterwards, participants were provided with an afternoon snack before leaving the unit and consume their day 1 dinner at home. On day two morning, participants completed online mood and anxiety testing at home after having a honey and oat cereal bar. On days two to five, participants complete a sleep diary. An actigraphy was worn throughout the intervention period. Upon completion of the five day intervention, participants returned to the intervention centre on the morning of day six (08:00-10:00) to repeated the morning assessments, as carried out on day 1 (Figure 3.3).

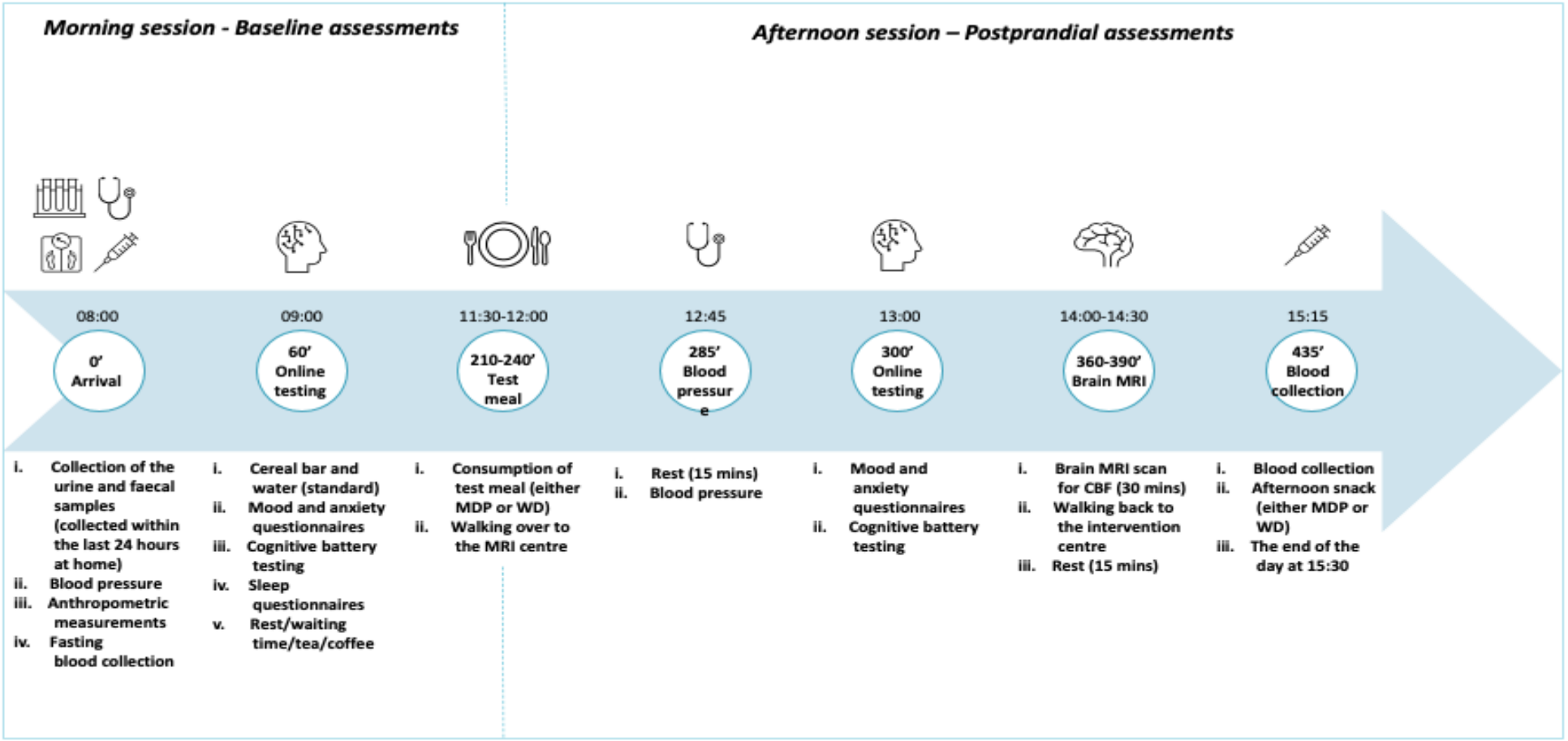


Figure 3.2. Day 1 protocol of CRF visits

On the day 1 visit, participants undergo the full protocol. MDP: Mediterranean-style dietary pattern; WD: Western diet; MRI: Magnetic Resonance Imaging; CBF: Cerebral Blood Flow.

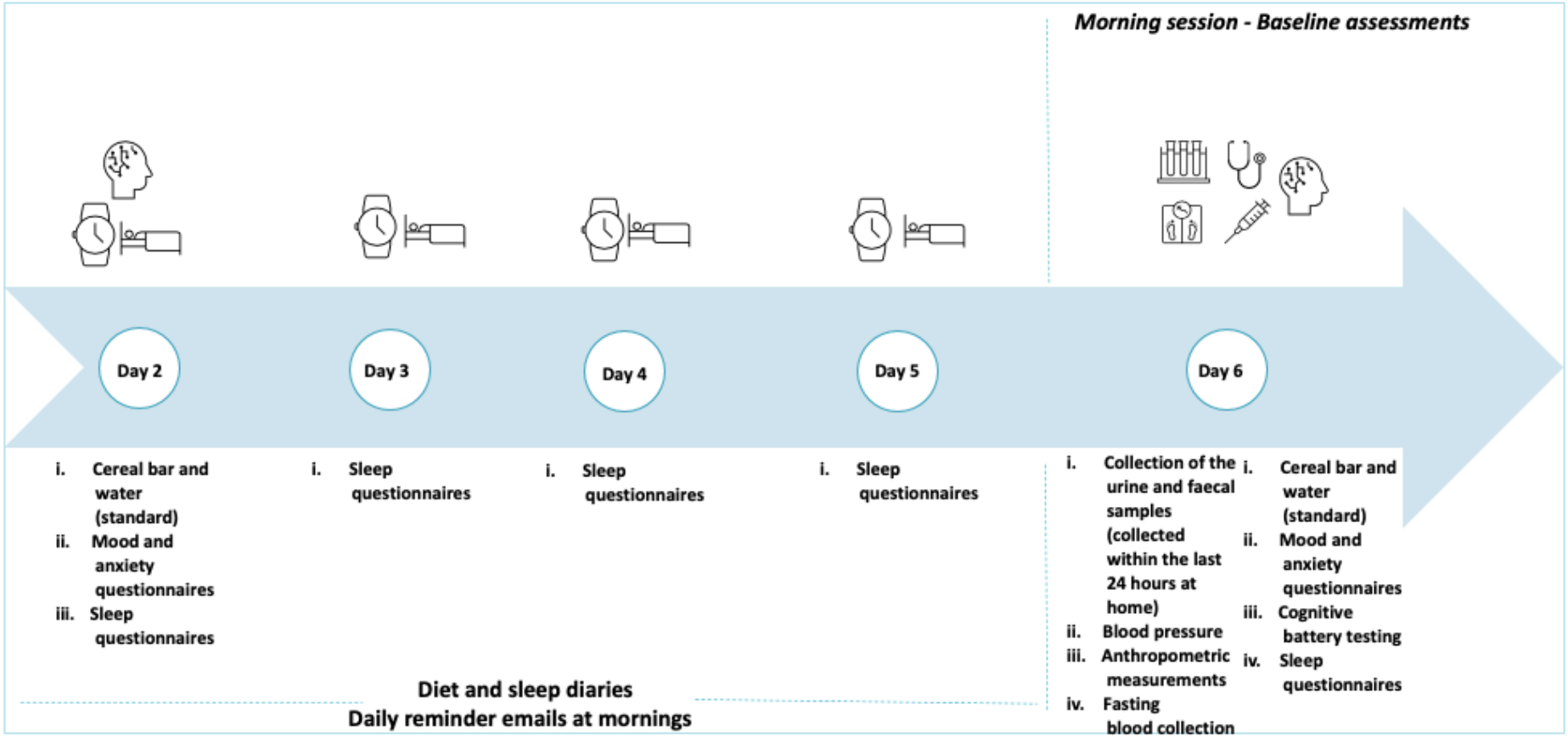


Figure 3.3. The procedure of day 2 to 6

On the day 2 morning, they repeat mood testing from home. Actigraphies are worn, and sleep and diet diaries are filled over the five days. Upon completion of five days interventions, participants attend CRF visit on the morning of day 6 to repeat the baseline assessment of day 1.

Participants were contacted daily (Appendix 21) to encourage dietary adherence. The systematically reviewed evidence shows the consistent positive impact of daily reminders in boosting the adherence in health care studies such as weight loss, physical activity and smoking cessation (266, 267).

The enrolled participants were asked to complete the EPIC FFQ (https://www.epic-norfolk.org.uk/about-epic-norfolk/nutritional-methods/ffq/) before their baseline visit to capture their habitual dietary intake prior to this study.

Upon the completion of each arm as the last step of day six visit, participants were asked how hard/easy they have found following to the intervention using the following question, "Did you find following the five-day meal plan easy or difficult? Please rate on the scale from very easy to very difficult." with 1 being easiest and 10 being the most difficult" in order to gain an understanding on the feasibility of MDP adherence in a non-Mediterranean population. Although we were mainly interested in to find out their opinions on the MDP adherence, we asked the question at the end of both arms to blind participants.

3.3.6. Follow-up

Participants were sent an email (Appendix 22) including the MEDAS questionnaire, three months after completing arm 2.

3.4. Outcome measures

3.4.1. Primary outcome measures

Mood and anxiety

Changes in mood and anxiety levels were monitored using two scales. The primary outcome measure were the Profile of Mood State score (POMS) (Appendix 23) (268) with mood also scored using the Bond-Lader questionnaire (Appendix 24) (269).

The former has 65 items measuring 6 elements of mood, namely, anxiety, anger, confusion, depression, fatigue and vigour, whilst the latter has 16 items (alert, drowsy, calm, excited, strong, feeble, muzzy, clear-headed, well-coordinated, clumsy, lethargic, energetic, contented, discontented, troubled, tranquil, mentally slow, quick witted, tense, relaxed, attentive, dreamy, incompetent, proficient, happy, sad, antagonistic, amicable, interested, bored, withdrawn, gregarious) under four categories (mental sedation or intellectual impairment, physical sedation or bodily impairment, tranquillisation or calming effects, other types of feelings or attitudes) or three mood factors (alertness, contentment and calmness).

The primary mood outcome is contentment from Bond-Lader scale, whilst the anxiety from POMS is the primary anxiety outcome measure.

Both are commonly used in research. Furthermore, three of the four studies included in our systematic review (196) employed both, which will allow a direct comparison of our findings with the limited published literature.

3.4.2. Secondary outcome measures

Cognitive performance

Changes in cognition were tracked by means of a composite score for which neuropsychological test battery was administered by using NeurOn which is an online platform (https://neuropsychology.online). It consisted of the following tests:

1. Reaction Time for motor function,
2. Sustained Attention to Response Task (SART) for attention,
3. Digit Span Backwards for executive function,
4. Trail Making A & B for executive function,
5. Word Encoding for episodic memory,
6. Word Recognition for episodic memory,
7. Go/No-Go for impulse control and executive function,
8. Fragmented Letters for visuospatial function.

Attention was an important secondary outcome as it was prominent in our systematic review findings (196). In order to measure attention, the SART (270) was used, which briefly includes administrating of visual presentation of 225 digits on a computer screen in random order over 4.3 minutes period (1150 msec. between the onsets of digits) and participants are expected to respond with a key press except when they see the digit 3 (270, 271). SART is commonly used in research and is postulated to be sensitive to everyday attention tasks in traumatic brain injured patients as well as normal (control) individuals (270, 271). One advantage of SART over other attention tests is that it keeps the demand at a minimum for other cognitive tasks such as memory, planning and general intellectual effort (270).

Cardiometabolic profile

Blood pressure (BP): Brachial BP was measured with the participant seated and following a five-minute rest period. Measurements were taken using an automatic BP monitor (Omron, 705IT). To ensure the accuracy of the assessment, BP was taken three times and averaged in accordance with published guidelines (272).

Biochemical markers: Several blood biomarkers of mental and cognitive health were assessed including, glucose, selected inflammatory markers, adrenalin, cortisol, serotonin, dopamine, BDNF and tryptophan. The plasma/serum was stored for the quantification of further selected biomarkers of cardiometabolic and brain health and dietary compliance emerging in the published literature.

A blood sample of no more than 30 ml was collected at baseline (day 1 morning, fasted), after the test meal (day 1, post-prandial) and on day six (morning, fasted) in three separate tubes (EDTA, Heparin, Serum). Blood was collected in the CRF by a research nurse or other approved phlebotomist using a standard butterfly system into vacutainer tubes. A part of the blood sample that was already collected was sent to the Norfolk and Norwich University Hospital (NNUH) laboratories for immediate blood glucose, blood lipids and cortisol analysis.

The separated plasma and serum samples, the urine, and the stool samples (collected at home as explained at section 3.3.5) were stored in the university -80°C

freezers for a period of 10 years, after which time any remaining samples will be disposed of in accordance with approved Clinical Waste Disposal SOPs.

Neuroimaging

Previous studies have shown that endothelial function is acutely altered by meal composition (96, 273, 274). One study demonstrated that a single MDP meal which is enriched with walnuts improved postprandial endothelial function (275). Gut blood flow, for example, increases at postprandial stage due to the increased digestive activities, proving that not only systemic blood flow, but also blood flow in specific organs is changed by the content of a meal (276). Similarly, CBF can be stimulated by food (277, 278) and by bioactives such as polyphenols (279) found in MDP is rich in. Furthermore, reduced brain energy glucose metabolism and CBF is evident in major depressive disorder (280) and cognitive decline (281, 282). Overall, vascular reactivity and CBF is affected by food intake, therefore, we plan to take a sequence of MRI images as it is considered the gold standard in measurement of CBF (279). We hypothesise greater CBF after the MDP compared to the WD.

MRI scans (Siemens) were performed in order to assess the impact of intervention on CBF (which is predicted to partly underpin the effect of intervention on mood, anxiety and cognitive outcome) by comparing the post prandial effects of a MDP and WD, and were conducted following the test lunch meal on day one of both intervention periods. The sequences below were used:

i. Time of flight angiography (TOF), used to determine the labelling plane to be used with pseudo-continuous Arterial Spin Labelling (p-CASL). Echo time (TE) / Repetition time (TR) = 3.8/22 msec, field of view (FoV) = 200x200 mm, voxel size 0.7x0.5 mm, 0.6mm slice thickness, 40 slices covering the vertebral arteries at the level of the brainstem. Duration 3 minutes.

ii. Pseudo-Continuous Arterial Spin Labelling (p-CASL) provides a means of quantifying regional CBF (283). ASL has previously been used to monitor changes in CBF in Alzheimer's disease and MCI patients (284). A single p-CASL scan was acquired with multiple post-labelling delays 0.25, 0.5, 0.75, 1, 1.25, and

1.5 (seconds) and labelling duration 1.4 seconds. Whole brain data were acquired with echo planar imaging (EPI), TE/TR = 13 ms/4 sec, image matrix 64x64, FoV 220mm and slice thickness 5mm. For each scan 96 volumes will be acquired to give 6.5 minutes scanning time. Analysis will be performed using FSL's optimised ASL analysis pipeline (BASIL).

iii. Magnetization Prepared Rapid Gradient Echo (MPRAGE) was used to image the whole brain, with 1mm iso-tropic resolution (TE/TR/inversion time = 2.7/2300/900 msec, flip angle 9°) MPRAGE has previously been demonstrated to be superior to show the contrast between grey and white matter and brain lesions (285). The scan time 4.5 minutes.

iv. Fluid-Attenuated Inversion Recovery (FLAIR) was used to visualise the white matter hyperintensities (WMH). FLAIR decreases the signal from cerebrospinal fluid, thus, increases the image quality providing "a high lesion contrast against a muted background of brain and a very low signal intensity from cerebrospinal fluid" (286). Acquisition parameters: TE/TR/TI = 395 ms / 5 sec / 1.8 sec , flip angle = variable, FoV = 256 mm , matrix size 256x256, voxel size = 1x1 mm, slice thickness = 1.1 mm. Scan duration = 5 mins 52 sec.

MPRAGE and FLAIR sequences were implemented to help eliminate potential confounders influencing CBF in the present study such as atrophy and WMH.

v. Resting State functional Magnetic Resonance Imaging (rs-fMRI) was used to explore resting neural activity and connectivity between different brain regions including those that are concerned with self-referential processing and salience networks (287). During the scan subjects wore a pulse oximeter and respiratory belt to record the influence of cardiac and respiratory processes on measured signal. The scan parameters were taken from the UK-Biobank protocol (288), allowing comparison to the larger sample contained in that repository. Resolution = 2.4x2.4x2.4 mm, in-plane matrix 88x88, 64 slices, TE/TR: 39/735ms, multi-band factor 8, flip angle 52°. Duration = 6 minutes (490 timepoints). Analysis utilised physiological noise modelling, white matter/CSF signal regression and spatial independent components analysis (ICA) to define resting state networks.

Seed-based analysis utilised regions of interest e.g. insular cortex, to determine whole brain connectivity.

Sleep quality

Data shows that sleep disturbances, anxiety and depression are linked bidirectionally (257). Sleep deprivation negatively affects aspects of cognition including alertness and attention (45). Another bidirectional relationship has also been postulated between food intake composition and sleep (289). A recent systematic review reveals that despite the limited evidence, a high chronic MDP adherence promotes high sleep quality (290). Therefore, we aimed to understand the effects of both diets on the sleep quality in the short-term. By doing so, we also targeted to eliminate the shadowing effect of low sleep quality on mood and anxiety.

In order to establish the initial sleep profile to detect sleep disturbances the Pittsburgh Sleep Quality Index (PSQI) (Appendix 25) (291) was used on the day 1 visit. Objective and subjective sleep quality were tracked over the course of the two five-day intervention periods by a wrist-worn waterproof and light sensitive accelerometer (MotionWatch 8) and the Karolinska Sleep Diary (KSD) (Appendix 26) (292).

The MotionWatch 8 is the next generation of medical-grade actigraphy watch for the monitoring of sleep, circadian rhythm and physical activity. It is one of the leading actigraphy solutions for convenient long-term behavioural monitoring with high patient compliance (MotionWatch 8 - CamNtech). The MotionWare Software provides a suite of analysis functions for Sleep quality (e.g. sleep efficiency, sleep fragmentation), circadian rhythmicity (e.g. macro- and micro-circadian instability), activity levels, and ambient light data. The KSD will ask participants to estimate the duration, timing and quality of all sleep periods and will complement the actigraphy data to increase the accuracy of the objective sleep quality estimation (i.e. ascertainment of bedtime and wake-up time).

Subjective sleepiness will be measured using the Karolinska Sleepiness Scale (KSS) (Appendix 27) administered on day one baseline and day-6 follow-up visit as well as during the 5-day intervention period alongside the KSD. The KSS is a 9-point scale and asks the user to circle the number that represents the sleepiness level during the immediately preceding 5 min. The KSS has been used in experimental studies of sleep

deprivation, shift work and driving and validated against polysomnographic measurements (293).

All outcome measures are summarised in the Table 3.6 below.

Table 3.6. Summary of the outcome measures

	Measurement	Tool used	Time point	Time per measurement point	Location
Screening	Mood	PHQ-9	Pre-Baseline	9 mins	Home
	Anxiety	GAD-7	Pre-Baseline	6 mins	Home
	Initial dietary habits	MEDAS	Pre-Baseline	10 mins	Home
During interventions	Initial dietary profile	EPIC FFQ	Baseline	30 mins	Home
	Mood and anxiety	Bond-Lader VAS, POMS	Baseline, postprandial, 24-h, Day 6	30 mins	Home (24-h) and intervention centre (baseline, postprandial and day 6)
	Cognitive functions	NeurOn battery	Baseline, postprandial, Day 6	30 mins	Intervention centre
	CBF	MRI	Postprandial	30 mins	UWWBIC
	Blood pressure		Baseline, postprandial, Day 6	5 mins	Intervention centre
	Blood samples		Baseline (≥10h fasting), postprandial, Day 6 (≥ 10h fasting)	15 mins	Intervention centre
	Urine and faecal samples		Baseline, Day 6		Home collection kits are provided

	Weight and height	SECA scale	Baseline, Day 6	5 mins	Intervention centre
	Initial sleep profile	PSQI	Baseline	10 mins	Intervention centre
	Sleep quality	Actigraphy KSD KSS	Over five days	Continuously (for actigraphy) 5 mins (for KSD and KSS)	Home
	Subjective dietary review score	Non-validated single question	Day 6		Intervention centre
Follow-up	Dietary behaviour	MEDAS	3 months	10 mins	Home

PHQ-9: Patient Health Questionnaire; GAD-7: Generalised Anxiety Disorder; MEDAS: Mediterranean Diet Adherence Screener tool; EPIC FFQ: European Prospective Investigation into Cancer and Nutrition study Food Frequency Questionnaire; VAS: Visual Analogue Scale; POMS: Profile of Mood States; CBF: Cerebral Blood Flow; MRI: Magnetic Resonance Imaging; UWWBIC: University of East Anglia Wellcome-Wolfson Brain Imaging Centre; PSQI: Pittsburgh Sleep Quality Index; KSD: Karolinska Sleep Diary; KSS: Karolinska Sleepiness Scale.

3.5. Randomisation, statistical analyses and sample size calculations

Allocation: Participants were randomly assigned to the intervention arms using Random Number Generator function in Microsoft Excel.

Power calculations and analysis of diets: Our sample size calculation was based on data from a previous cross-over trial of the effect MDP adherence in a young healthy adult group (194). Assuming an error rate of 0.05 and 90% power we would require 15 and 20 participants to complete each arm for contentment (9.6 unit expected difference, SD 10.3). To account for dropouts between random allocation to treatment sequence and study completion we will aim to recruit 20% more participants per group; thus, we will recruit 25 individuals. We targeted to detect a difference of at least 6-points in contentment factor and at least a 2-point reduction in anxiety from POMS level between

treatment groups. These targets were set based upon the results of two previous similar studies (194, 294).

Analysis: The main aim of the trial is to test if mood and anxiety can be improved over five days of intervention. The primary outcome analysis will use a linear mixed model taking mean change-scores.

CBF Data Analysis steps:

i. Data Pre-processing: Raw data will be converted into the Brain Imaging Data Structure (BIDS) format for standardised data organisation.

ii. Structural Processing: Individual subject-level processing includes structural image processing and segmentation and normalisation to enhance the quality of anatomical data.

iii. Single-Subject ASL Processing: Specific processing steps tailored for ASL data will be applied at the individual subject level, including motion correction, registration, partial volume correction and quantification of perfusion.

Group-Level Analysis: Group-level processing through template creation producing a group-average image and subsequent atlas-based ROI statistical analyses (66).

Machine learning analysis: Machine learning holds considerable potential for identifying biomarkers and enhancing clinical decision-making in varied contexts and is effective in discerning clinical interventions. Our study will utilise the Random Forest algorithm to enhance the interpretability of the heterogeneous data. This is a supervised machine learning approach recognised for its adeptness to handle missing values, alleviate data noise and mitigate the risk of overfitting making it a robust choice for our analytical framework (67).

3.6. Adverse events and incidental findings

Due to the nature of the intervention, i.e., commercially available food products, no adverse events (AEs) are expected. If participants feel in anyway adversely affected by any foods or the principal investigator feels an AE necessitates cessation, the participant will be advised not to continue, and the appropriate measures will be taken. All AE's will be recorded and handled in accordance with Good Clinical Practice (GCP) guidelines.

Measurements taken from participants enrolled onto the study that are deemed to be outside the normal clinical range were reported as incidental findings to the patient and his or her GP (see appendices 22 and 23 respectively for template letters). Potential incidental finding were noted from the online screening process (if they score above moderate level on the PHQ-9 and/or GAD-7 questionnaires), (if those excluded people are affiliated with UEA, they will be directed to the university wellbeing support services), during analysis of the neuropsychological test battery, during blood analysis (either blood samples or BP measurements) or during the MRI scans where a UEA staff member has reasonable grounds for believing that a scan shows abnormalities they shall discuss with relevant UWWBIC colleagues and where concerns persist refer the scan case to the NNUH Consultant Radiologist to determine whether a formal incidental findings report is required. It was the responsibility of the UWWBIC Head of MRI or their delegate to contact the participant's GP forwarding the radiologist's report, who will then make the necessary referrals. In the event that UEA researchers feel that a more urgent review is required the Head of MRI or their delegate can contact the NNUH Consultant Radiologist via the Radiology secretaries or (workflow Manger) after image transfer. If the NNUH Consultant Radiologist agrees that this needs urgent attention the patient should then be advised to attend the Emergency Department as per public methods of entry or via 999.

3.7. Ethical and legal aspects

3.7.1. Ethical Conduct of the Study

The procedures outlined in this protocol, pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the sponsor and investigator abide by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki.

3.7.2. Finance and Insurance

The funders of this trial were:

- MRC-NIHR NuBrain Consortium Grant
- The Republic of Turkey supporting the PhD studies of Miss Latife Esgunoglu
- The Commonwealth Scholarships supporting the PhD studies of Miss Marrium Liaquat
- Return to Research Grant by Rank Prize, awarded to Miss Latife Esgunoglu

The UEA, UK is the sponsor of the trial and will provide indemnity and insurance.

3.7.3. Confidentiality and Data Storage

To maintain anonymity, participants were allocated a numerical identifier. After consent was obtained, only these numbers identified participants. The principal investigator kept the file containing each participant's name and file number in a locked cabinet separate from the questionnaire data. This information is not accessible unless a justified scientific or ethical reason is provided to the PI and kept confidential and known only to the study co-ordinator and other relevant members of the research team. Any electronic information has restricted access and/or password protection as appropriate. Data will be retained for 15 years from the date of publication of the results from the study. In all publications and findings, participants will be anonymous.

3.8. Conclusion

The MediMood study was designed considering potential physiological mechanisms that rapidly modulate brain health and are driven by dietary intake (Chapter 1). The study aimed to explore the short-term effects of a MDP on mood and cognition in

order to satisfy the research gaps identified by Chapter 2. The present chapter details the background/rationale and methodology, whilst the results will be presented in the following chapter (Chapter 4), alongside a brief introduction and methods sections.

3.9. Author contributions

The initial research question was formulated by Anne Marie Minihane, with the study further conceptualised by Latife Esgunoglu, Amy Jennings and Anne Marie Minihane and gut microbiome arrangements were added by Marrium Liaquat. The ethical approval and trial registration processes were managed by Latife Esgunoglu with guidance from Amy Jennings and Anne Marie Minihane. Blood biomarker analysis and blood sampling protocols were created by Latife Esgunoglu, Marrium Liaquat, Amy Jennings and Anne Marie Minihane. Cognitive testing selection was planned by Michael Hornberger. MRI sequences was designed by Michel Hornberger, John Brooks and William Penny. MRI data analysis was conducted by Sam Maddox and Saber Sami. The sleep assessment was designed by Alpar Lazar. The mental health safety network was set by Adrian Leddy. Sample size was calculated by Amy Jennings. The study website was built by Latife Esgunoglu, Marrium Liaquat and Rachel Gillings under the guidance of Alex Howard (Mantal). The dietary booklets were created by Rachel Gillings. The diets were planned by Latife Esgunoglu, Rachel Gillings and Amy Jennings. All authors drafted and revised the manuscript with Latife Esgunoglu, Amy Jennings and Anne Marie Minihane taking the lead role. All authors approved the final version of the manuscript.

Statement of the assessment of MediMood protocol

A supplementary essay is presented as an opportunity to allow for an evaluation of the MediMood study protocol design and development process reflecting on the experiences that helped me to improve my personal and professional skills throughout (Appendix 28).

Chapter 4. Results from the MediMood study

4.1. Introduction

The global increase in the prevalence of depression and anxiety (142) are of great importance to public health due to their economic burden and associated reduced quality of life (55). Besides, they elevate the risk of chronic diseases such as dementias (295). The continuously increasing incidences of depression and anxiety highlights the need for further prevention and management approaches (248).

Chronic consumption of a Mediterranean-style dietary pattern (MDP) characterised by high intakes of extra virgin olive oil (EVOO), fruits and vegetables, fish, nuts, legumes and wine (251), is associated with reduced depression (181) and improved cognition (188) (Chapter 1). On the other hand, a long-term Western diet (WD) consumption is linked with worsened mental health (256, 296). The empirical evidence on short-term dietary effects on brain health remain scarce (196). A RCT reported impaired hippocampal-dependent learning and memory (HDLM) after consuming a Western breakfast (high in sugar and saturated fat) on four consecutive days compared to a healthier breakfast (195). To evaluate the potential of short-term MDP consumption on mental health, we conducted the first systematic review of RCTs which implemented a MDP versus any control arm in a maximum of 10-day and examining any mood and/or cognition outcome, and identified the lack of research in the area with only four studies available (196) (Chapter 2). Despite the low number of results and their diverse methodologies, contentment, alertness and attention were improved by MDP interventions (196).

Using our systematic review findings, we designed the MediMood study (Chapter 3), with the primary objective being to investigate the efficacy of a MDP on mental health in adults with mild to moderate level low mood and/or anxiety symptoms postprandially, at 24h and after five days with compared to a WD. The secondary objectives were to determine the impact of dietary regime on (i) cognitive performance, blood pressure (BP), and serum c-reactive protein (CRP) as a circulating marker of inflammation, glucose, insulin, lipids, cortisol and brain derived neurotrophic factor (BDNF), ii) postprandial

cerebral blood flow (CBF), (iii) sleep quality, quantity and circadian rhythm and (iv) MDP behaviour after three months.

4.2. Methods

The full methodology was explained in detail in the previous chapter (Chapter 3). MediMood is a single-centre cross-over RCT conducted by Norwich Medical School, UEA. The study was registered on ClinicalTrials.gov (NCT05927376) and obtained favourable ethics opinion from NHS London Queen Square Research Ethics Committee (REC) (22/LO/0796). Informed consent was provided by participants in the presence of certified research personnel. The Quadram Institute Clinical Research Facility (CRF) and UEA Wolfson and Welcome Brain Imaging Centre (UWWBIC) facilities were used as study locations. An online study platform (MediMood - Home (mantal.co.uk) was designed using a research management portal (Mantal - Home) and screening information and data collection for mood, anxiety, cognition, and sleep diaries along with follow-up MEDAS data were conducted online through this website. Cognitive tasks were imported from the NeurOn platform (NeurOn - Neuropsychology Online) into our study website.

4.2.1. Recruitment and screening

Twenty-five participants were recruited from Norfolk, UK using invitation emails, recruitment posters and Facebook adverts. Individuals (both sexes, aged ≥18 years) were deemed to be eligible if they, i) had mild to moderate depression (5-14/29 on Patient Health Questionnaire, PHQ-9) (258) and/or anxiety (5-14/27 on Generalised Anxiety Disorder, GAD-7) (259), ii) were not already following a MDP (<8/14 on MEDAS) (162), and iii) were able to undergo a brain MRI scan. They were ineligible if they had a dietary restriction (e.g., vegetarian, pescatarian), were unable to attend the required clinical visits or were computer illiterate.

4.2.2. Dietary design and study procedure

Participants underwent two five-day interventions, a MDP and a WD, in a random order with a 23-day wash-out period. Diets were planned based on the extreme ends of the MEDAS tool (162) with score 13/14 for the MDP arm with optional wine

consumption and a MEDAS score of zero for the WD arm. Within the week prior to the start of their intervention, participants received booklets containing a grocery shopping checklist, detailed instructions on food storage and preparation, and a food checklist/diary to assess compliance. Participants received a full 5-day grocery basket on the day before their intervention began via supermarket delivery.

Participants were required to visit the CRF for four times in total (2 x day-1 visits for 8 hours and 2 x day-6 visits for 2.5 hours) (Figure 3.1). On arrival (08:00) urine and faecal samples that were collected at home within the last 24 hours were given to the research team for processing. BP, weight and height measurements were taken, along with a 30 ml blood sample. A honey and oat cereal bar alongside water were served at 08:45. Following a 15 mins rest, the first online testing session assessing mood, anxiety, cognition and sleep was started at 9:00. Actigraphy devices (measuring their sleep and activity) were then provided with the instruction to keep them on throughout the intervention periods. The test lunch meals were served at 11:30 with participants requested to aim finishing it in 30 minutes. At 12:45 a postprandial BP measurement was taken. Participants were administered mood and cognitive testing at 13:00 and underwent a 30-minute brain MRI scan at 14:00. Postprandial blood samples were collected at approximately 15:15, followed by an afternoon snack, with the day 1 visit concluding at 15:30. On day 6 visit, the morning part before the lunch meal was repeated.

4.2.3. Primary outcomes

Contentment and anxiety

Bond-Lader is a 16-item visual analogue scale and measures alertness, calmness and contentment (269). Profile of Mood States (POMS) is a 65-item questionnaire with each question having 0-4 scale answers (five points) and assesses anxiety, depression, anger, vigour, fatigue, confusion and an overall Total Mood Disturbance (TMD) composite score (268). Contentment from Bond-Lader was selected as the primary mood indicator as per our systematic review (Chapter 2) with the anxiety domain from POMS being the primary anxiety endpoint.

4.2.4. Secondary outcomes

Further mood and anxiety assessment

The remaining Bond-Lader and POMS domains listed above, namely, alertness, calmness, depression, anger, vigour, fatigue, confusion and an overall TMD, were presented as secondary mood and anxiety outcomes.

Cognitive assessment

The cognitive tasks below were employed to examine different aspects of cognition;

1. Reaction Time for motor function,
2. Sustained Attention to Response Task (SART) for attention,
3. Digit Span Backwards for executive function,
4. Trail Making A & B for executive function,
5. Word Encoding for episodic memory,
6. Word Recognition for episodic memory,
7. Go/No-Go for impulse control and executive function,
8. Fragmented Letters for visuospatial function.

Additionally, a global cognition score was calculated. To do so, we first defined an inclusion criterion; participants who achieved a full score on the Fragmented Letters task were included. One key main variable was selected from each task as follows:

1. Reaction Time: Mean value of reaction speed after false answers were excluded,
2. Digit Span Backwards: Number of correctly recorded digits,
3. Trail Making A: Total interval time,
4. Trail Making B: Not included in the global score because of the substantial amount of missing data due to a technical error occurred in the testing platform,
5. SART: Number of wrong answers,
6. Word Recognition: Source memory of correct answers (%),
7. Go/No-Go: Error rate (%),

8. Fragmented Letters: Total correct answers (%) was used as the eligibility criterion, not included in the global score.

The chosen variables for Reaction Time, Trail Making A, SART and Go/No-Go were reversed so that higher number always reflected an improvement. All scores were converted into percentages (except the ones which were already percentages) with the average of the % in the individual six tasks (excluding Trail Making B and Fragmented Letters) representing the global score.

MRI: Cerebral blood flow (CBF) and brain connectivity assessment

Data were collected using a 3T Siemens Magnetom Prisma Scanner at the UWWBIC. The following MRI sequences were utilised in the following order with aims;

- Time of flight angiography (TOF) to determine the labelling plane for the next sequence
- Pseudo-Continuous Arterial Spin Labelling (p-CASL) quantified regional CBF (283)
- Magnetization Prepared Rapid Gradient Echo (MPRAGE) for routine whole brain imaging (285) and Fluid-Attenuated Inversion Recovery (FLAIR) to visualise the white matter hyperintensities (WMH) (286). MPRAGE and FLAIR sequences help to eliminate potential confounders influencing CBF such as brain atrophy and WMH.
- Resting state functional Magnetic Resonance Imaging (rs-fMRI) was used to explore resting neural activity and connectivity between different brain regions (287).

MPRAGE and FLAIR are structural MRI methods whilst ASL and fMRI are functional sequences. As it is unlikely for the brain to develop a morphologic change in only five days, we reported the ASL results only for the purposes of the present thesis.

Blood pressure and assessment of circulating metabolic markers

Systolic and diastolic blood pressure (SBP and DBP) were measured using an automatic BP monitor (Omron, 705IT). Following blood collection, the whole blood tubes were sent immediately to the NHS laboratories at the Norfolk and Norwich University Hospitals (NNUH) for immediate analyses of plasma glucose, serum lipids and serum cortisol analyses using Abbott Allinity analysers. Serum insulin and high sensitivity CRP were analysed in-house by Norwich Medical School's Bioanalytical Facility using standard immunochemical methods using the assays, respectively, 'Elecsys Insulin' and 'CRPHS, Cardiac C-Reactive Protein (Latex) High Sensitive' procured from Roche Diagnostics Ltd (Burgesshill, UK). Serum BDNF levels were measured using an ELISA assay (ab212166, Human BDNF Simple Step Elisa Kit, Abcam).

Dietary behaviour and evaluation of feasibility of diets

Participants were sent the MEDAS questionnaire three months after completing both arms to compare it to the screening data to investigate any change in their dietary behaviour. Participants were also asked to evaluate the easiness/difficultness level of at the dietary regime end both interventions (on day 6 morning visit) using a feedback question we created "Did you find following the five-day meal plan easy or difficult? Please rate on the scale from very easy to very difficult (1-10)".

4.2.5. Statistical analyses

The statistical analysis was conducted in collaboration with our Medical Statistician (Mizanur Khondoker). The short-term (taking day 1, day 2 and day 6 data, termed study 1) and postprandial (study 2) impact of the MDP vs WDP were analysed separately with linear mixed model employed as the primary statistical model for both studies.

Initially, we discarded one participant's data collected from the day 6 visit on WD arm, as they reported to have a breakfast with an espresso and oatmeal prior to the arrival at the clinical unit. Of note, the same individual dropped out on the last day of their second arm (day 6 visit of MDP arm) and reported they did not comply fully with the intervention. Therefore, we used their day 1 data only from both intervention arms collected at UEA

under our supervision. For the CRP, the results shown as "<1.43 nmol/L" were replaced with zero as it indicates undetectable amount of inflammation (minimal or none).

The normality of the data were checked using histogram and Q-Q plots. Extreme outliers were detected according to mean ± 3 standard deviations (SD) method and removed from the dataset, except the Fragmented Letters task, as per discussions with our cognition expert (Michael Hornberger), due to the small number of the stimulus (n=10) the task had. To create its statistical variable, the proportion of correct answers given were converted into percentages. As this task was relatively easy and participants tended to give full answers (100%), when they gave only one or two incorrect answers resulting in being 90-95% correct, they were mathematically detected as extreme outliers while they were actually not.

To assess the 24-h and 5-day effects of interventions on the outcomes, the baseline level of the individuals had to be taken into account. To do so, two possible ways were considered, either baseline levels could be added to the statistical model as a covariate or change scores (i.e. day 2 – day 1 for 24-h and day 6 – day 1 for 5-day effects) could be calculated to account for the effect of the baseline. Due to small sample size, we eliminated the first option and decided to go for change from baseline. For study 1; treatment, time, and time x treatment interaction effect were computed for mood and anxiety outcomes, as they measured at three timepoints (day 1 morning as baseline, day 2 morning and day 6 morning). For the secondary outcomes in study 1, i.e. cognitive outcomes and blood parameters, the treatment effect was calculated only, the changes from day 1 to day 6 were compared, hence no time effect. For study 2, the data after both test lunch meals were directly compared. Treatment (the diets), sequence (the order of diets) and period (if it was their first or second arm independent of the diet) were assigned as fixed factors, and the participants were allocated as random factors for all analyses. No further covariates were added to the model as the sample size did not provide the statistical power for further complexity. Besides, the cross-over fashion of the study, with every participant serving as their own control, minimises the contribution of participants attributes to the heterogeneity in response. In addition, an exploratory subgroup analysis was conducted to investigate whether participants who were on antidepressant/antianxiety medication responded the interventions differently compared to non-users. The same statistical approach described above was applied, with binary

medication status added as a covariate. This analysis was conducted for only the co-primary outcomes (mood and anxiety) due to our research interests, and the limitation regarding the small sample size as above. The results were presented as preliminary.

MRI data were analysed by the neuroimaging experts in our team (Saber Sami and Sam Maddox). Standardised Brain Imaging Data Structure (BIDS) (297) and Bayesian Inference for Arterial Spin Labelling (BASIL) (298) apps were utilised to pre-process raw ASL data. Before further process, a manual data quality control check was completed, and one session of one participant was removed due to an error in preprocessing. Then the FSL cluster (299) analysis for ASL were applied. MRI data analysis was performed using Phyton and Bash softwares on the UEA High Performance Computing (HPC) cluster and completed with help from the Colour and Imaging Lab within the School of Computing Sciences. As MRI was performed postprandially only, the effects of the MDP and WD lunch were compared in study 2.

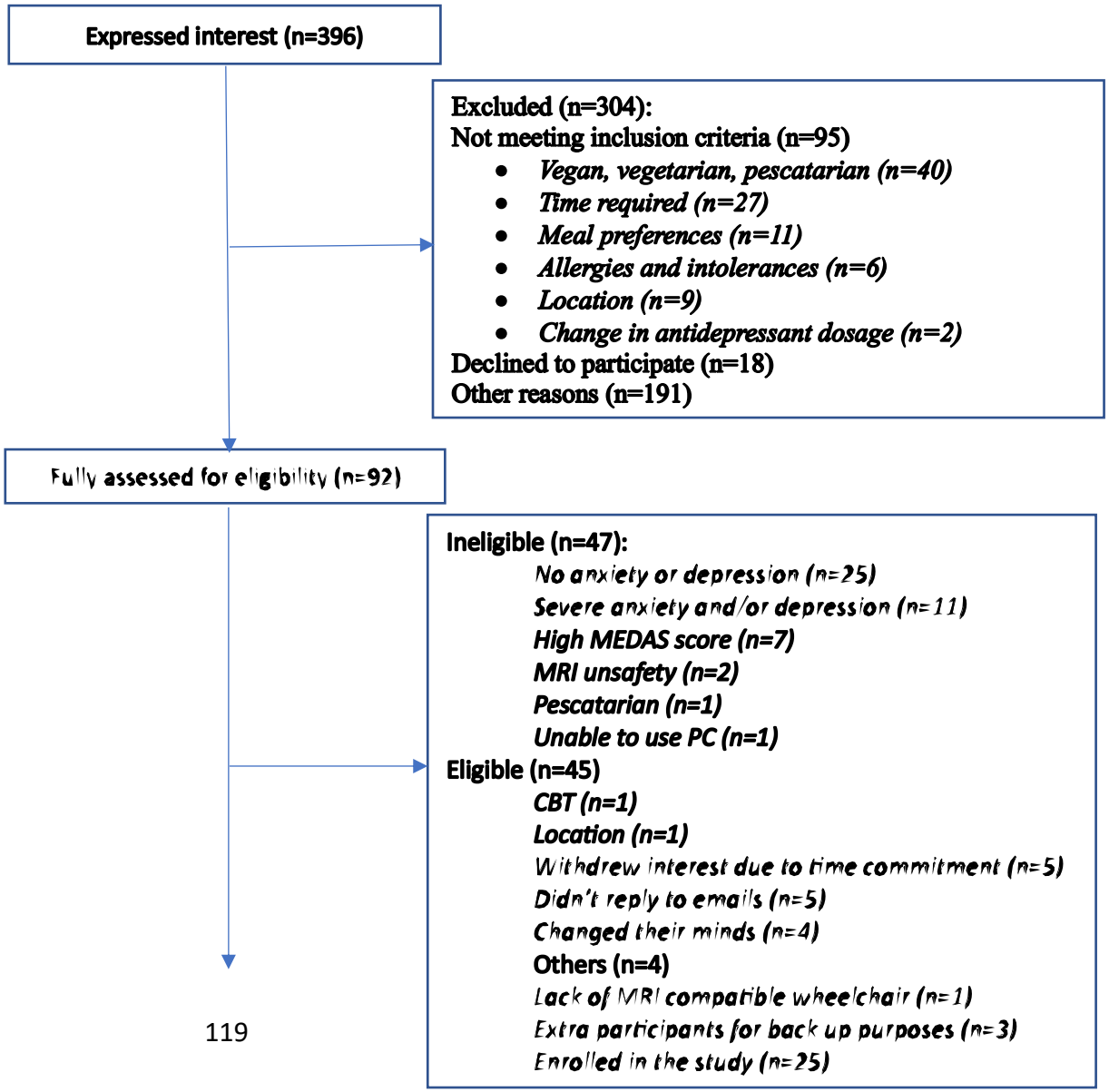
To compare the MEDAS scores at screening and 3-month follow-up MEDAS score, a paired t-test was run. The linear mixed model described above was applied to compare the subjective easiness levels of interventions to take sequence and period effects into account. For all non-MRI data, Stata software (Stata 18) was used to perform the statistical analyses and GraphPad Prism 10 was used to produce the figures.

4.3. Results

4.3.1. Recruitment and sample characteristics

In total, 396 people expressed an interest and were provided with a participant information sheet. For those who replied (n=225), a phone/video call was arranged to allow participants to discuss the study with the research team along with an initial assessment. If eligible/happy to proceed, participants subsequently underwent full online screening where dietary habits, mental health and MRI safety status were assessed (Figure 4.1) (300).

Regarding the demographic characteristics of the enrolled participants (n=25) (Table 4.1), 64% were female (n=16). The age varied from 19 to 86 years with an average of 41.6 ± 20.7 years (mean ± SD). Two thirds had either a higher education degree (n=8) or a postgraduate degree (masters' or PhD, n=8). Pertaining to their employment status, 11 were students, 7 were employed and 7 were non-employed or retired. In terms of their health behaviours and mental health status, the average MEDAS score on the 14-point scale was 5.2 ± 1.3 (mean ± SD). 28% (n=7) presented a low adherence to a MDP by scoring 3 or 4, whilst the others' scores ranged from 5 to 7. Regarding their weight status, the average BMI (mean ± SD) was 25.3 ± 3.2 kg/m^2, with 92% consisted of either normal weight or overweight individuals, with only two individuals (8%) with obesity. Concerning their mental health status, 60% had mild and 20% had moderate depression. 80% displayed mild and 10% displayed moderate level anxiety symptoms. One third of the sample (n=8) had both conditions at either mild or moderate level. 36% (n=9) reported to be on antidepressant/antianxiety medications. Lastly, 76% never smoked and there was no current smoker.


Expressed interest (n=396)
Excluded (n=304):
Not meeting inclusion criteria (n=95)
Vegan, vegetarian, pescatarian (n=40)
Time required (n=27)
Meal preferences (n=11)
Allergies and intolerances (n=6)
Location (n=9)
Change in antidepressant dosage (n=2)
Declined to participate (n=18)
Other reasons (n=191)
Fully assessed for eligibility (n=92)
Ineligible (n=47):
No anxiety or depression (n=25)
Severe anxiety and/or depression (n=11)
High MEDAS score (n=7)
MRI unsafety (n=2)
Pescatarian (n=1)
Unable to use PC (n=1)
Eligible (n=45)
CBT (n=1)
Location (n=1)
Withdrew interest due to time commitment (n=5)
Didn't reply to emails (n=5)
Changed their minds (n=4)
Others (n=4)
Lack of MRI compatible wheelchair (n=1)
Extra participants for back up purposes (n=3)
Enrolled in the study (n=25)

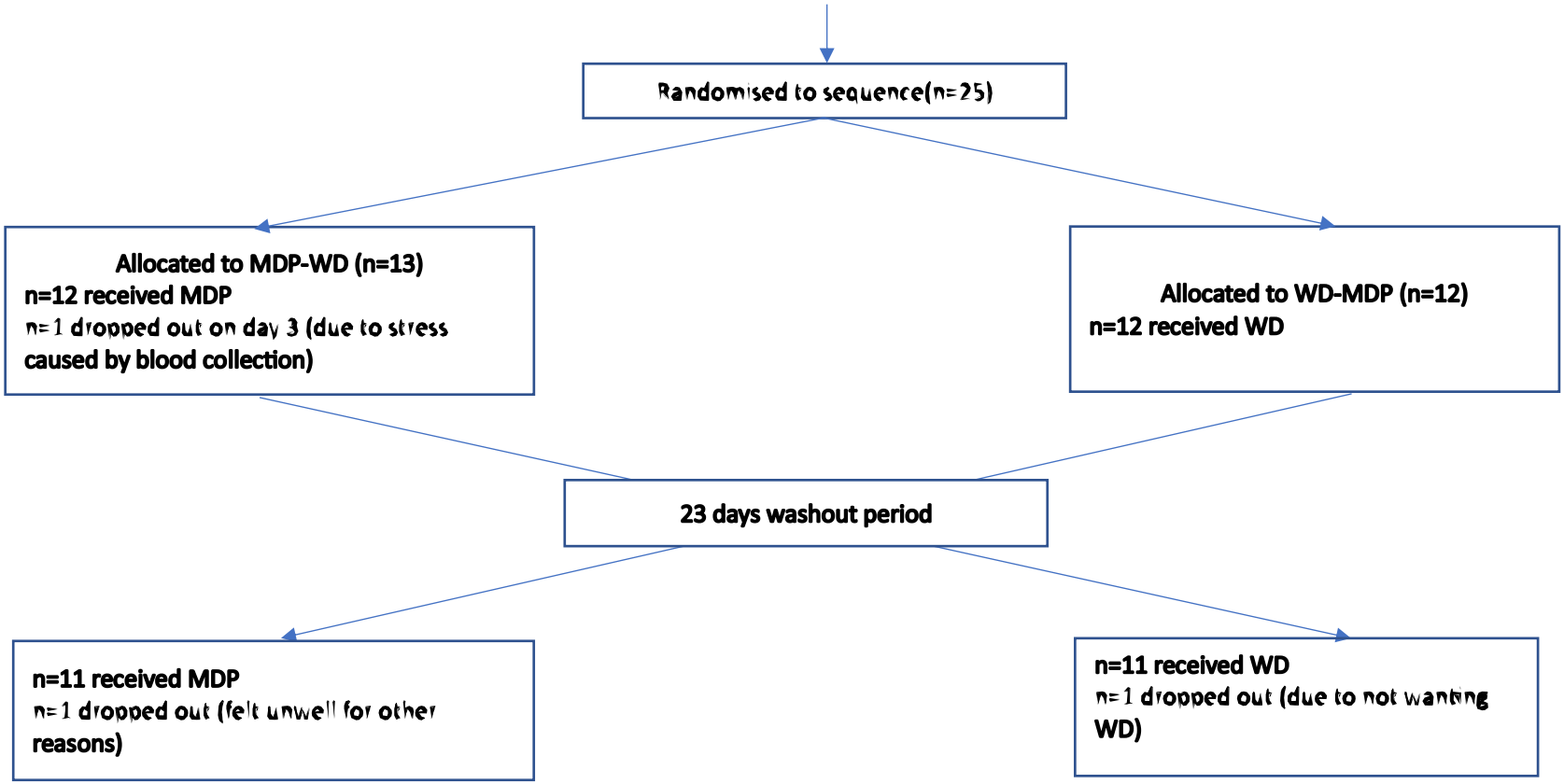


Figure 4.1. Flowchart of participant recruitment and enrolment process

Table 4.1. Participant characteristics (n=25)

Characteristic	Mean ± SD	Number (n)	Percentage (%)
Age (years)	41.6 ± 20.7	NA	NA
Sex			
Female	NA	16	64
Male		9	36
Education status			
Primary		0	0
Secondary	NA	1	4
Further		8	32
Higher		8	32
Masters/PhD		8	32
Employment status			
Student	NA	11	44
Employed		7	28
Non-employed/retired		7	28
MEDAS (score) (0-14)	5.2 ± 1.3	NA	NA
MEDAS adherence groups			
Lowest scorers (0-4)	NA	7	28
Lower scorers (5-7)		18	72
PHQ-9 (score) (0-27)	6.8 ± 2.9	NA	NA
PHQ-9 groups			
None (0-4)	NA	5	20
Mild (5-9)		15	60
Moderate (10-14)		5	20
GAD-7 (score) (0-21)	6.7 ± 1.9	NA	NA
GAD-7 groups			
None (0-4)	NA	3	12
Mild (5-9)		20	80
Moderate (10-14)		2	8
BMI ($kg/m^{2,}$ continuous)	25.3 ± 3.2	NA	NA
BMI classification	NA		
Underweight (<18.5 kg/m^2)		0	0
Normal weight (18.5-24.9 kg/m^2)		12	48
Overweight (25.0-29.9 kg/m^2)		11	44
Obese (>30 kg/m^2)		2	8
Antidepressant use			
Yes	NA	9	36
No		16	64
Smoking status			
Never smoked	NA	19	76
Current smoker		0	0
Past smoker		6	24

The values presented were taken from screening. SD: Standard deviation; MEDAS: Mediterranean Diet Adherence Screener; PHQ-9: Patient Health Questionnaire-9 which assesses

depressive symptoms. GAD-7: Generalised Anxiety Disorder-7 which measures anxiety. Both PHQ-9 and GAD-7 are often used in research and primary health care services, and are interpreted depending on the total score, which is categorised as follows; 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe for PHQ-9 and, similarly, the scoring system of GAD-7 is 0-4 no to low risk, 5-9 mild, 10-14 moderate, 15+ severe. Mild and moderate levels are recruited on to the study.

4.3.2. Study 1: Short-term (24h and 5-day) impacts of diets

Primary outcomes: Contentment and anxiety

No significant intervention effect was found for contentment (p=0.524) (Figure 4.2). Anxiety was improved by 25% after five days of MDP consumption (p=0.014), with no differences evident on day 1 (Figure 4.2).

The full results are also presented in Appendix 29.

Secondary outcomes

Further mood and anxiety domains

All are shown in Figure 4.2. A 5-day intervention effect was evident for the TMD composite score obtained from POMS, with a 40% improved score following the MDP compared to the WD (p=0.004), with no differences evident by day 1. This reflected in individual negative POMS domains (elevated scores reflect a worsened wellbeing) with decreases following a five-day MDP compared to a WD as follows; depression (p=0.007) improved by 40%, and fatigue (p=0.044) by 28%. Confusion exhibited a 11% improvement by day 1 and a 33% improvement by day 5 (p< 0.001). No effect of intervention on anger was evident (p=0.885). Among positive mood domains (higher scores reflected a better wellbeing), vigour (from POMS) increased after five days of a MDP consumption by 18% (p=0.014), and alertness (from Bond-Lader) was heightened by the MDP (p=0.028), by 12% at day 1 and 25% at day 5. Despite the enhanced calmness (from Bond-Lader) after the MDP, the difference was insignificant.

Concerning the effects of period and sequence, only calmness was affected by period with higher calmness evident in the second arm, independent of diet (p=0.007). No sequence (the order of diets) effect was found.

The full results are also presented in Appendix 29.

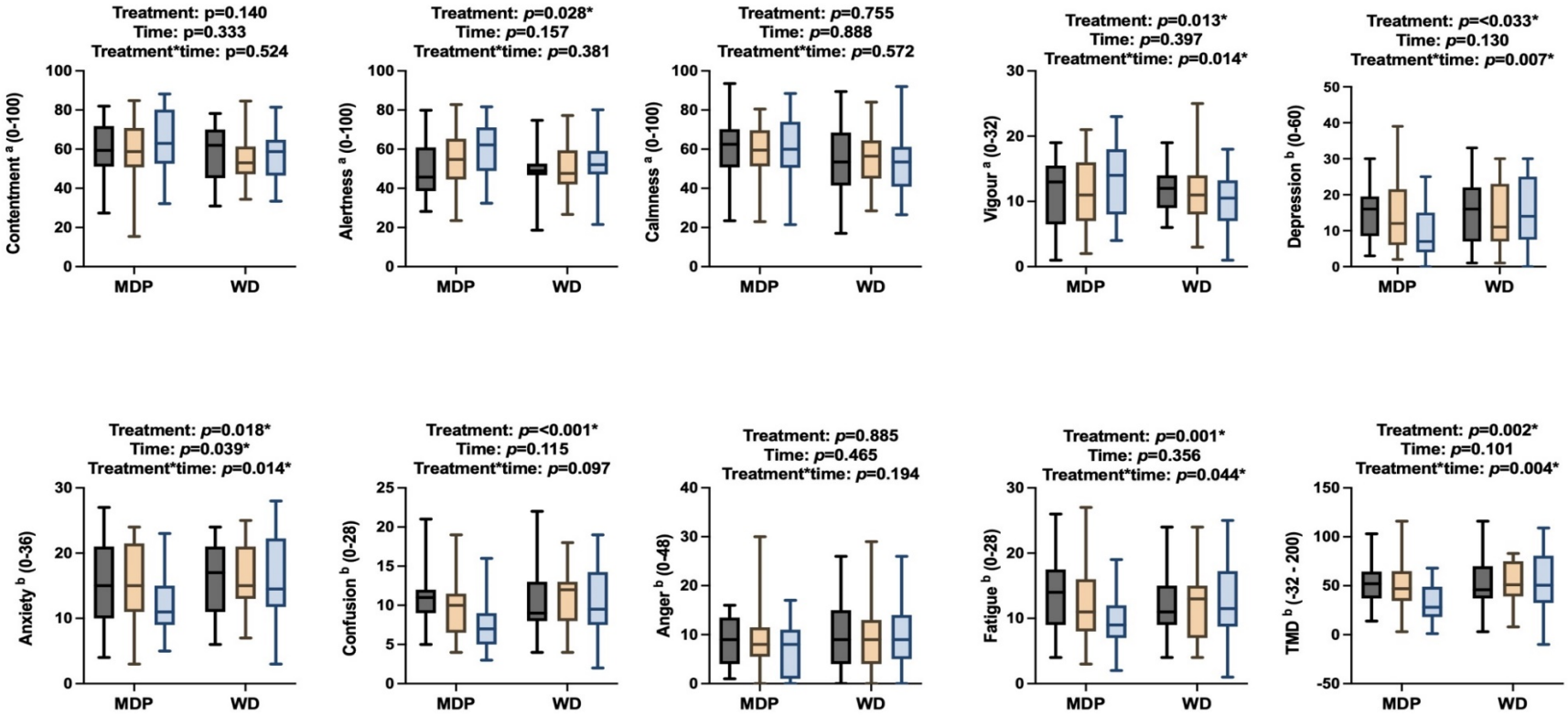


Figure 4.2. Impacts of MDP and WD interventions on mood and anxiety after one and five days

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. A linear mixed model was run adjusted for treatment, sequence and period effects. Please note that the statistical analyses were performed by taking change in scores (Day 2 – Day 1 for 24-h effect and Day 6 – Day 1 for 5-day effect). Data are presented as follows; the minimum and maximum values shown by the bars, the mean represented by horizontal lines within the bars, and whiskers indicating the Standard Deviation. *: Statistically significant effects (p<0.05). Treatment effects represent the overall main effects of diets, treatment*time interactions represent whether the treatments were effective by day 1. [a]: Higher values indicate better mental health. [b]: Lower values indicate better mental health. For depression, one extreme outlier (mean ± 3SD) was removed from WD day 6 prior to the statistical analysis.

An exploratory analysis: effect of antidepressant usage status on mood in short-term

When antidepressant use status was added to the statistical model as a covariate, the overall effects of the diets remained significant for alertness *(p*=0.015), anxiety *(p*=0.005), depression *(p*=0.008), vigour *(p*=0.005), fatigue *(p*=0.017), confusion *(p*=<0.001), TMD *(p*=0.002) and insignificant for calmness *(p*=0.356) and anger *(p*=0.441). However, the overall treatment effect became significant for contentment *(p*=0.012) (Table 4.2). Among all mood domains, the only significant interaction between diet and antidepressant use status was detected for contentment *(p*=0.028) (Table 4.2). The post hoc analysis revealed that the MDP was effective only in those who were not on antidepressant medications (n=16) *(p*=0.010) with a non-significant increased score in those who were taking a medication (n=9) *(p*=0.392) (Figure 4.3).

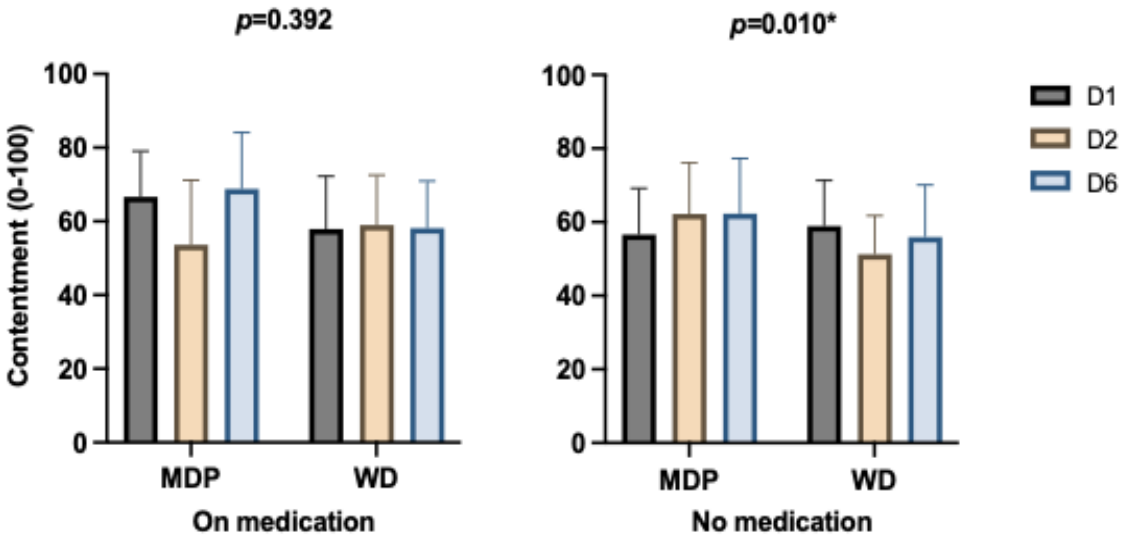


Figure 4.3. Contentment depending on antidepressant medication use status

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. Contentment is a mood domain from Bond-Lader tool. A linear mixed model was run for the statistical analyses, and was adjusted for treatment, sequence and period effects. Data are presented as follows; the mean values shown by the upper end of bars and whiskers indicating the Standard Deviation. *: Statistically significant effects (p<0.05). There was not any extreme outlier as established by mean ± 3SD method.

Table 4.2. Effects of MDP and WD interventions on mood and anxiety considering antidepressant use status

		Anti - depressant use		N	D1 morning (mean ± SD)	N	D2 morning (mean ± SD)	N	D6 morning (mean ± SD)	Overall treatment *p* value	Anti-depressant *p* value	Treatment * anti-depressant *p* value
Bond-Lader	Contentment [a] (0-100)	Yes	MDP	9	66.7 ± 12.8	9	53.6 ± 18.0	8	68.8 ± 15.8	**0.012**	0.371	**0.028**
			WD	9	57.9 ± 14.8	9	59.0 ± 14.0	8	58.2 ± 13.2			
		No	MDP	16	56.6 ± 12.8	16	62.2 ± 14.2	15	62.3 ± 15.2			
			WD	14	58.9 ± 12.7	14	51.2 ± 10.7	14	55.9 ± 14.4			
	Alertness [a] (0-100)	Yes	MDP	9	50.5 ± 15.3	9	49.9 ± 16.5	7	64.2 ± 13.0	**0.015**	0.396	0.283
			WD	9	46.7 ± 14.2	9	50.4 ± 18.5	8	52.9 ± 16.1			
		No	MDP	16	48.2 ± 12.1	16	57.7 ± 11.6	15	59.6 ± 14.6			
			WD	14	49.8 ± 7.7	14	49.2 ± 12.6	14	51.0 ± 12.8			
	Calmness [a] (0-100)	Yes	MDP	9	65.3 ± 16.4	9	56.7 ± 15.5	8	63.3 ± 15.5	0.356	0.143	0.059
			WD	9	46.7 ± 16.6	9	58.4 ± 13.7	8	50.7 ± 20.3			
		No	MDP	16	57.5 ± 14.6	16	60.9 ± 13.0	15	59.5 ± 17.4			
			WD	14	56.9 ± 16.0	14	53.8 ± 15.4	14	56.3 ± 14.2			
POMS	Anxiety [b] (0-36)	Yes	MDP	9	16.7 ± 7.1	9	19.1 ± 4.8	8	13.3 ± 3.7	**0.005**	0.534	0.130
			WD	9	20.4 ± 2.7	9	19.0 ± 4.0	8	20.9 ± 6.2			
		No	MDP	16	15.2 ± 5.5	16	13.5 ± 5.4	15	10.9 ± 5.4			
			WD	14	13.1 ± 4.7	14	13.9 ± 4.7	14	13.1 ± 5.2			
	Depression [b] (0-60)	Yes	MDP	9	17.3 ± 5.8	9	22.4 ± 10.3	8	11.3 ± 9.5	**0.008**	0.661	0.107
			WD	9	21.8 ± 7.4	9	20.6 ± 7.2	7[†=1]	20.7 ± 9.9			
		No	MDP	16	13.6 ± 7.8	16	10.6 ± 7.6	15	7.7 ± 5.9			
			WD	14	11.1 ± 7.4	14	11.1 ± 7.9	14	12.3 ± 8.0			

Anger [b] (0-48))	Yes	MDP	9	8.3 ± 4.2	9	11.9 ± 8.5	8	8.1 ± 5.6	0.441	0.898	0.142
		WD	9	13.2 ± 6.1	9	12.3 ± 8.0	8	12.3 ± 4.9			
	No	MDP	16	8.4 ± 5.3	16	7.8 ± 5.1	15	6.5 ± 5.2			
		WD	14	8.5 ± 7.5	14	8.4 ± 8.0	14	8.1 ± 6.8			
Vigour [a] (0-32)	Yes	MDP	9	11.7 ± 4.9	9	10.1 ± 4.4	8	15.0 ± 4.8	**0.005**	0.055	0.162
		WD	9	9.7 ± 2.7	9	11.0 ± 5.9	8	9.1 ± 3.2			
	No	MDP	16	11.3 ± 5.9	16	11.8 ± 6.0	15	12.7 ± 5.7			
		WD	14	13.1 ± 2.7	14	11.5 ± 4.1	14	10.4 ± 4.9			
Fatigue [b] (0-28)	Yes	MDP	9	16.3 ± 5.7	9	17.3 ± 7.2	8	10.0 ± 3.1	**0.017**	0.559	0.648
		WD	9	15.6 ± 5.1	9	16.7 ± 3.7	8	16.6 ± 5.0			
	No	MDP	16	12.3 ± 5.2	16	10.3 ± 4.4	15	9.8 ± 4.8			
		WD	14	9.4 ± 3.4	14	9.6 ± 3.7	14	10.7 ± 4.9			
Confusion [b] (0-28)	Yes	MDP	9	11.8 ± 4.3	9	11.7 ± 5.0	8	7.8 ± 4.4	**<0.001**	0.868	0.715
		WD	9	12.1 ± 4.3	9	12.1 ± 3.2	8	13.0 ± 4.7			
	No	MDP	16	10.7 ± 3.3	16	8.9 ± 3.4	15	7.3 ± 2.8			
		WD	14	9.0 ± 3.7	14	10.4 ± 4.1	14	9.2 ± 3.9			
TMD [b] (-32 - 200)	Yes	MDP	9	58.8 ± 24.9	9	72.3 ± 27.0	8	35.4 ± 21.3	**0.002**	0.719	0.222
		WD	9	73.4 ± 20.5	9	69.7 ± 14.2	8	77.3 ± 30.0			
	No	MDP	16	48.9 ± 20.7	16	39.3 ± 19.2	15	29.4 ± 19.4			
		WD	14	38.1 ± 21.0	14	41.9 ± 20.6	14	43.1 ± 24.4			

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N: number of observations with maximum possible N is being 25 as study sample consisted of 25 individuals, however N varies due to dropouts, missing data and extreme outliers. SD: Standard deviation. D1: Day 1 (baseline), D2: Day 2 (24h), D6: Day 6 (end of 5-day intervention). POMS: Profile of Mood States questionnaire. TMD: Total Mood Disturbance is an overall score generated using tension, depression, anger, vigour, fatigue and confusion scores. Bond-Lader is a visual analogue scale with each item has 0-100 mm scales. A linear mixed model was run for the statistical analyses, and was adjusted for treatment, sequence and period effects. All significant effects (p<0.05) were highlighted in bold. [a]: Higher values indicate better mental health. [b]: Lower values indicate better mental health. [†] reports the number of the extreme outliers as established by mean ± 3SD method, that were discarded prior to the statistical analysis. If not stated, that means there was not any.

Cognition

At individual cognitive abilities level, no significant impact of diets on attention, executive function, episodic memory, impulse control and visuospatial function was evident. A significant diet effect was found for variability of motor function as assessed by the SD of Reaction Time task *(p*=0.018), with motor function becoming significantly more consistent after following MDP for five days. No impact of the intervention on the composite cognitive score was evident *(p*=0.471) (Figure 4.4., Table 4.3).

In terms of the confounding effects of period and sequence variables, the Digit Span Backwards task measuring executive function and working memory was mediated by a period effect *(p*=0.032), with participants scored higher in their first arms. The difference in the change in the first arm was 14.4 ± 20.7 whilst being 0.7 ± 18.7 in the second arm. Furthermore, the accuracy of the sustained attention assessed by the number of the correct answers given for SART, was affected by the sequence *(p*=0.036), which meant participants who underwent the MDP intervention first had significantly more correct.

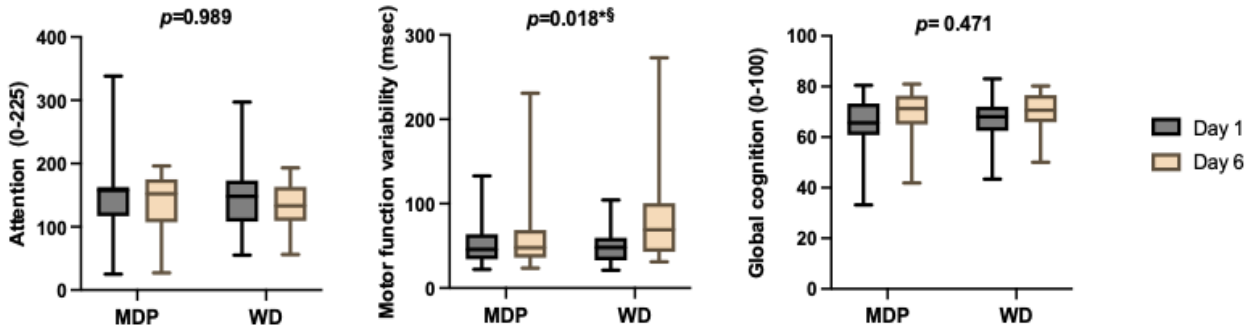


Figure 4.4. Effects of 5-day intervention on select cognitive domains

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. Attention was assessed by the number of the inaccurate answers in the Sustained Attention to Response Task, the standard number of total stimuli=225. Motor function variability was established by the standard deviation of reaction speed in the Reaction Time task, which measures the time taken as milliseconds (msec), with no upper limit. Global cognition score is generated on a 0-100 scale using all cognitive tasks. A linear mixed model was run for the statistical analyses and was adjusted sequence and period effects. Data are presented as follows; the minimum and maximum values shown by the bars, the mean represented by horizontal lines within the bars, and whiskers indicating the Standard Deviation. *: Statistically significant effects ($p<0.05$). §: Sequence affected. For attention, one extreme outlier (mean ± 3SD) was removed from MDP day 1 morning. For motor function two extreme outliers were discarded (n=1 from MDP day 1 and n=1 from WD day 6) prior to the statistical analysis.

Table 4.3. Impacts of MDP and WD interventions on cognition after five days

		N	MDP D1 morning (mean ±SD)	N	MDP D6 morning (mean ±SD)	N	WD D1 morning (mean ±SD)	N	WD D6 morning (mean ±SD)	*p* value
Motor function (assessed by RT)	Reaction speed mean (msec) [b+]	24[†=1]	306.5 ± 54.4	23	306.8 ± 52.1	23	303.2 ± 52.1	21[†=1]	319.6 ± 67.0	0.268
Sustained attention (assessed by SART)	No of incorrect answers [b+.] (0-225)	24[†=1]	144.1 ± 60.8	23	137.7 ± 45.8	23	142.3 ± 50.0	22	132.6 ± 38.4	0.989
Executive function (assessed by DSB)	Correct sequences [a] (0-14)	25	6.4 ± 3.9	23	7.8 ± 3.5	23	8.0 ± 2.9	22	8.6 ± 3.0	0.546
	Correct digits [a+] (0-85)	25	33.3 ± 23.2	23	41.9 ± 22.5	23	41.6 ± 19.8	22	47.4 ± 20.4	0.751*
Executive function (assessed by TMA)	Total interval time (msec) [b+]	24[†=1]	22560 ± 5802	22[†=1]	21626 ± 5429	23	24262 ± 8350	23	22574 ± 7903	0.540
Executive function	No of correct answers [a] (0-25)	19[†=2]	22.2 ± 4.6	15[†=1]	22.1 ± 2.7	17	23.1 ± 1.9	16	23.1 ± 2.3	0.572

(assessed by TMB)	No of incorrect answers [b] (0-25)	18[†=2]	1.6 ± 2.9	15[†=1]	1.9 ± 2.3	17	0.824 ± 1.074	16	0.938 ± 1.340	0.817
Episodic memory (assessed by WR)	Recognition memory [a] (0-100)	25	92.4 ± 7.0	22	91.8 ± 7.3	23	89.3 ± 7.9	22	90.9 ± 8.3[†=1]	0.312
	Source memory [a+] (0-100)	25	69.3 ± 19.8	23	75.7 ± 20.3	23	67.2 ± 23.8	21	76.3 ± 17.0[†=1]	0.826
Impulse control (assessed by GNG)	% of incorrect answers b[+] (0-100)	24[†=1]	3.6 ± 2.3	23	4.0 ± 3.0	23	3.4 ± 2.7	22	3.5 ± 2.8	0.596
Visuospatial function (assessed by FL)	% of correct answers [a] (0-100)	25	100.0 ± 0.0	23	100.0 ± 0.0	23	99.6 ± 2.1	22	100.0 ± 0.0	0.319

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. D1: Day 1, D6: Day 6. SD: Standard deviation. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. A linear mixed model was run, with statistical significance threshold of (p<0.05. Msec: milliseconds which measures the time taken with no upper limit. A technical error resulted in significant data loss for TMB. RT: Reaction Time. SART: Sustained Attention to Response Test. DSB: Digit Span Backwards. TMA: Trail Making A. TMB: Trail Making B. WR: Word Recognition. GNG: Go/No-Go. FL: Fragmented Letters. Overall cognition score was calculated using RT, SART, DSB, TMA, WR and GNG, with * representing the key variables used from each task, while FL was used as an eligibility criterion to be included in overall cognition score. *: period affected. §: sequence affected. [+]: the variable used to calculate overall cognition score. [a]: Higher values indicate better cognitive performance. [b]: Lower values indicate better cognitive performance. [†] reports the number of the extreme outliers as established by mean ± 3SD method, that were discarded prior to the statistical analysis. If not stated, that means there was not any.

Blood pressure and circulating biomarkers

The five-day MDP intervention reduced CRP levels by 21% whilst the opposite effect seen for the WD (57% increase) *(p*=0.038) (Figure 4.5). In contrast with our hypothesis, the WD decreased serum cortisol level (biomarker of stress) whereas MDP intervention resulted in an increase *(p*=0.024) (Figure 4.5). No impact of intervention on BP, plasma glucose, serum insulin, glucose to insulin ratio, serum lipids and serum BDNF was evident (Table 4.4).

Although there were no effects of intervention on cholesterol levels, period effects were detected, with decreases in the second arm, while the first arm displayed higher absolute values for total-, LDL- and non-HDL-cholesterol.

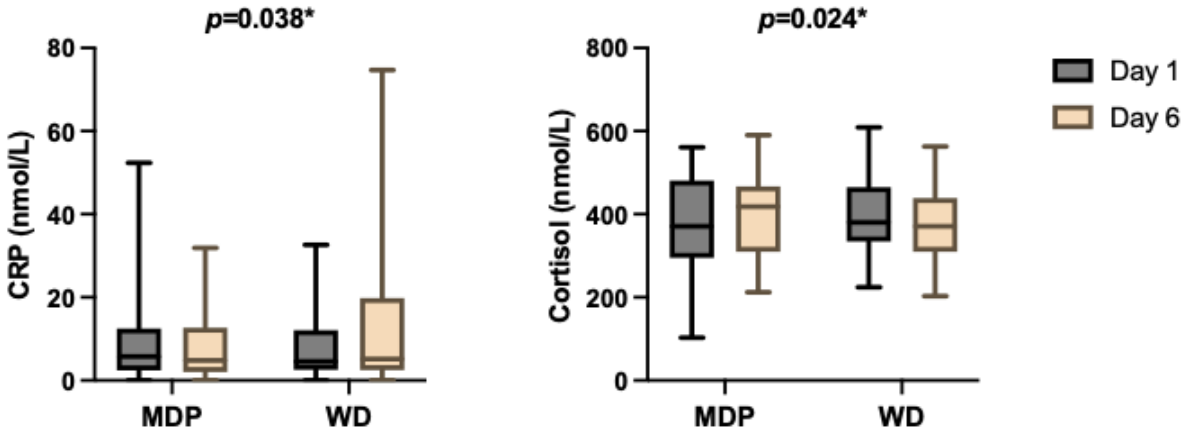


Figure 4.5. Impacts of MDP and WD interventions on CRP and cortisol

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. CRP: C-reactive protein. A linear mixed model was run for the statistical analyses and was adjusted for sequence and period effects. Data are presented as follows; the minimum and maximum values shown by the bars, the mean represented by horizontal lines within the bars, and whiskers indicating the Standard Deviation. *: Statistically significant effects (p<0.05). For the CRP analysis, 3 extreme outliers (mean ± 3SD) were removed, n=1 from MDP day 1, n=1 from WD day 1, and n=1 from MDP day 6.

Table 4.4. Impacts of MDP and WD interventions on blood pressure and circulating biomarkers after five days

		N	D1 morning (mean ± SD)	N	D6 morning (mean ± SD)	*p* value
SBP (mmHg)	MDP	25	124.4 ± 20.2	23	120.2 ± 33.3	0.333
	WD	23	125.0 ± 18.4	22[†=1]	127.3 ± 17.0	
DBP (mmHg)	MDP	25	75.2 ± 9.3	23	76.6 ± 8.9	0.244
	WD	23	77.9 ± 10.5	22[†=1]	77.2 ± 9.7	
Glucose (mmol/L)	MDP	23	4.6 ± 0.4	21	4.6 ± 0.5	0.577
	WD	21[†=1]	4.6 ± 0.3	21	4.6 ± 0.3	
Insulin (pmol/L)	MDP	22[†=1]	51.9 ± 25.1	21[†=1]	61.8 ± 49.8	0.151
	WD	22	72.5 ± 54.0	21	63.1 ± 52.0	
GIR	MDP	22	0.110 ± 0.059	20	0.099 ± 0.047	0.250
	WD	21	0.091 ± 0.042	21	0.099 ± 0.043	
Cholesterol (mmol/L)	MDP	23	5.03 ± 0.97	22	4.77 ± 0.96	0.251 *
	WD	23	5.10 ± 1.21	22	5.05 ± 1.08	
Triglycerides (mmol/L)	MDP	23	0.93 ± 0.41	21[†=1]	0.81 ± 0.23	0.206
	WD	22[†=1]	0.98 ± 0.35	22	1.00 ± 0.31	
HDL-cholesterol (mmol/L)	MDP	23	1.58 ± 0.37	22	1.51 ± 0.40	0.664
	WD	23	1.53 ± 0.37	22	1.48 ± 0.35	
LDL-cholesterol (mmol/L)	MDP	23	3.03 ± 0.82	22	2.87 ± 0.75	0.317 *
	WD	23	3.10 ± 0.95	22	3.11 ± 0.81	
Total cholesterol/HDL ratio	MDP	23	3.30 ± 0.78	22	3.30 ± 0.79	0.353
	WD	23	3.42 ± 0.76	22	3.50 ± 0.72	
Non-HDL cholesterol (mmol/L)	MDP	23	3.47 ± 0.84	22	3.31 ± 0.78	0.295 *
	WD	23	3.57 ± 0.98	22	3.57 ± 0.88	
	WD	23	401.7 ± 108.7	22	378.0 ± 92.2	
BDNF (ng/mL)	MDP	23	13.7 ± 3.2	22	13.4 ± 2.8	0.368
	WD	22	13.1 ± 3.6	21	13.3 ± 3.8	

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. D1: Day 1, D6: Day 6 (end of intervention). SD: Standard deviation. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. A linear mixed model was run with a statistical significance threshold of $p<0.05$. SBP: Systolic blood pressure. DBP: Diastolic Blood Pressure. GIR: Glucose to insulin ratio. HDL: High density lipoprotein. LDL: Low density lipoprotein. CRP: C-reactive protein. BDNF: Brain Derived Neurotrophic Factor. *: Significant period effect. † reports the number of the extreme outliers as established by mean ± 3SD method, that were discarded prior to the statistical analysis. If not stated, that means there was not any.

Anthropometric changes

A 1kg decrease in body weight was evident following 5 days of the MDP (p=0.044), with no corresponded significant change in BMI (p=0.216) (Table 4.5). The weight difference was mainly seen in females (-1.5 kg) in the MDP arm whilst the other differences (changes in MDP arm in females and in WD arm in both sexes) was less than 1 kg (Figure 4.6).

Table 4.5. Anthropometric changes after five days

		N	D1 morning (mean ± SD)	N	D6 morning (mean ± SD)	*p* value
BW (kg)	MDP	25	74.2 ± 9.4	23	73.2 ± 9.5	**0.044**
	WD	23	73.2 ± 10.1	23	73.2 ± 10.0	
BMI (kg/m^2)	MDP	25	25.8 ± 3.3	23	25.4 ± 3.2	0.216
	WD	23	25.5 ± 3.4	23	25.4 ± 3.4	

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. SD: Standard Deviation. D1: Day 1, D6: Day 6. N=25 individuals, but it varies due to dropouts. There was no extreme outlier (±3SD). Kg: kilogram. BW: Body Weight. BMI: Body Mass Index. A linear mixed model was run. Significant effects (p<0.05) were highlighted in bold.

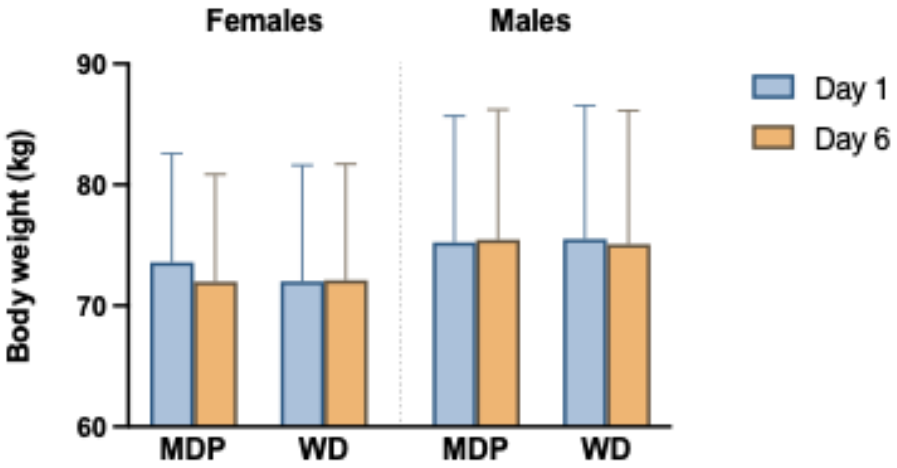


Figure 4.6. Weight change by sex

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. Kg: kilogram. Data are presented as follows; the mean values shown by the upper end of bars and whiskers indicating the Standard Deviation.

4.3.3. Study 2: Acute (postprandial) impacts of test lunch meals

Primary outcomes: Contentment and anxiety

A non-significant higher contentment score was evident after the MDP lunch compared to WD, with scores being as follows 66.5 ± 14.3 vs 63.7 ± 13.1 (p=0.136). There was no effect of lunch composition on anxiety (Figure 4.7, Table 4.6).

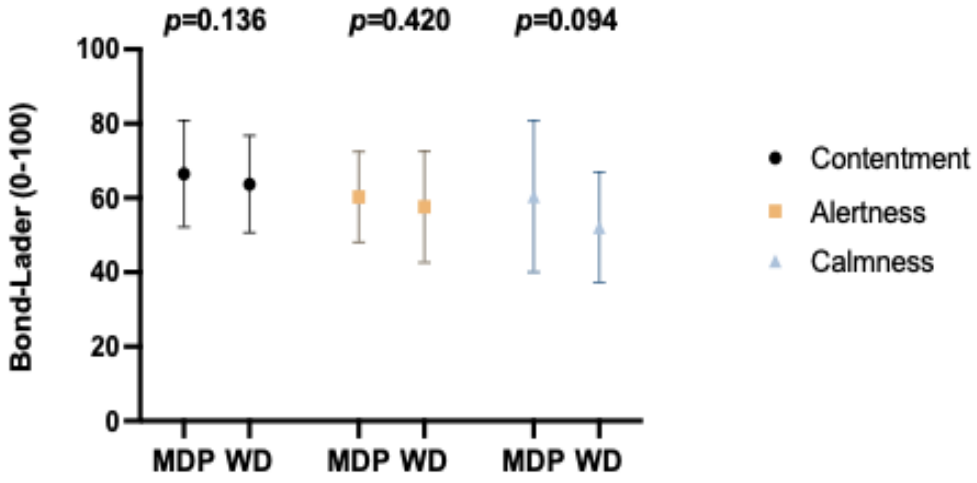


Figure 4.7. Postprandial comparison of mood domains from Bond-Lader

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts and missing data. No extreme outlier was detected (mean ± 3SD). A linear mixed model was run to compare postprandial scores with a statistical significance threshold of p<0.05, adjusted for treatment, sequence and period effects. Data are presented as follows; the minimum and maximum values shown by the lines, the mean represented by shapes within the lines, and whiskers indicating the SD.

Table 4.6. Comparisons of postprandial anxiety scores

	N	MDP (mean ± SD)	N	WD (Mean ± SD)	*p* value
Anxiety [b] (0-36)	25	15.8 ± 6.1	23	15.8 ± 6.3	0.924

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. SD: Standard deviation. N is being 25 as study sample consisted of 25 individuals, however, N varies due to dropouts. No extreme outlier was detected (mean ± 3SD). The measurements were taken after the test lunch meal on day 1 of each dietary period. A linear mixed model was run for with a statistical significance threshold of p<0.05, and the model was adjusted for treatment, sequence and period effects. [b]: Lower values indicate better mental health.

Secondary outcomes

Further mood and anxiety domains

Although non-significant, a consistent trend towards better mood profile was evident (as shown by Bond-Lader) with higher alertness and calmness scores after the MDP lunch vs WD lunch, with respectively, 60.2 ± 12.2 vs 57.6 ± 15.0 *(p*=0.420) and 60.4 ± 20.4 vs 52.1 ± 14.8 *(p*=0.094), whilst the scores generated from POMS indicating little effect of diet (Figure 4.7, Table 4.7). Confusion only was affected by period, with higher scores obtained in the first arm *(p*=0.032).

Table 4.7. Comparisons of further mood scores obtained postprandially from day 1

		N	MDP (mean ± SD)	N	WD (Mean ± SD)	*p* value
POMS	Depression [b] (0-60)	25	12.7 ± 7.2	23	14.2 ± 9.2	0.214
	Anger [b] (0-48)	25	8.5 ± 5.9	23	8.5 ± 6.7	0.656
	Vigour [a] (0-32)	25	10.6 ± 4.6	23	11.3 ± 3.1	0.491
	Fatigue [b] (0-28)	25	13.4 ± 6.2	23	12.3 ± 5.2	0.388
	Confusion [b] (0-28)	25	10.3 ± 3.5	23	10.1 ± 3.6	0.734*
	TMD [b] (-32-200)	25	50.0 ± 24.8	23	49.6 ± 24.0	0.874

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. SD: Standard deviation. N is being 25 as study sample consisted of 25 individuals, however, N varies due to dropouts. No extreme outlier was detected (mean ± 3SD). POMS: Profile of Mood States questionnaire (65 items, 0-4 scale). TMD: Total Mood Disturbance is an overall score generated using tension, depression, anger, vigour, fatigue and confusion scores. Bond-Lader is a visual analogue scale with each item has 0-100 mm scales. The measurements were taken after the test lunch meal on day 1 of each dietary period. A linear mixed model was run for the statistical analyses with a significance threshold of $p<0.05$, and the model was adjusted for treatment, sequence and period effects. *: affected by period. [a]: Higher values indicate better mental health. [b]: Lower values indicate better mental health.

Cognition

Similar to the postprandial mood profile, no significant effects of diet on postprandial cognitive performance were evident (Table 4.8). Significance was detected for the order of diets (sequence effect) on impulse control established by Go/No-Go task *(p*=0.033), with participants who underwent the MDP lunch first displayed a better impulse control.

Table 4.8. Comparison of cognitive scores obtained postprandially from day 1

		N	MDP (mean ± SD)	N	WD (mean ± SD)	*p* value
Motor function (assessed by RT)	Reaction speed mean [b+] (msec)	24[†=1]	315.1 ± 58.4	23	317.7 ± 59.7	0.871
	Variability (SD) [b]	24[†=1]	65.5 ± 33.1	23	67.7 ± 43.2	0.710
Attention (assessed by SART)	No of correct answers [a] (0-225)	25	95.8 ± 51.8	23	98.2 ± 47.2	0.649
	No of incorrect answers [b+] (0-225)	24[†=1]	133.0 ± 51.8	23	131.0 ± 45.0	0.837
Executive function (assessed by DSB	Correct sequences [a] (0-14)	25	7.0 ± 4.0	23	8.2 ± 2.0	0.087
	Correct digits [a+] (0-85)	25	37.1 ± 24.0	23	41.5 ± 14.0	0.369
Executive function (assessed by TMA)	Total interval time [b+] (msec)	25	22455.8 ± 8172.2	23	22701.7 ± 7793.0	0.873
Executive function (assessed by TMB)	No of correct answers [a] (0-25)	10	21.7 ± 5.0	9	21.6 ± 4.3	0.928
	No of incorrect answers [b] (0-25)	9[†=1]	1.0 ± 1.8	9	2.9 ± 2.8	0.173
Episodic memory (assessed by WR)	Recognition memory [a] (0-100)	23[†=1]	91.4 ± 5.2	23	90.3 ± 6.8	0.548
	Source memory [a+] (0-100)	24	65.6 ± 21.8	23	67.1 ± 22.5	0.845

Impulse control (assessed by GNG)	% of incorrect answers [b+] (0-100)	25	4.2 ± 3.1	23	3.7 ± 2.8	0.543 [§]
Visuospatial function (assessed by FL)	% of correct answers [a] (0-100)	25	99.6	23	99.1 ± 2.9	0.536
	Overall cognition score [a] (0-100)	23	66.5 ± 8.7	22	67.9 ± 6.8	0.318

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. D1: Day 1, D6: Day 6. SD: Standard deviation. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. A linear mixed model was run for the statistical analyses with a significance threshold of $p<0.05$, and the model was adjusted for treatment, sequence and period effects. Msec: milliseconds which measures the time taken with no upper limit. A technical error resulted in significant data loss for TMB. RT: Reaction Time. SART: Sustained Attention to Response Test. DSB: Digit Span Backwards. TMA: Trail Making A. TMB: Trail Making B. WR: Word Recognition. GNG: Go/No-Go. FL: Fragmented Letters. Overall cognition score was calculated using RT, SART, DSB, TMA, WR and GNG, with * representing the key variables used from each task, while FL was used as an eligibility criterion to be included in overall cognition score. *: period affected. §: sequence affected. [+]: the variable used to calculate overall cognition score. [a]: Higher values indicate better cognitive performance. [b]: Lower values indicate better cognitive performance. [†] reports the number of the extreme outliers as established by mean ± 3SD method, that were discarded prior to the statistical analysis. If not stated, that means there was not any.

Cerebral blood flow (CBF) assessed by Arterial Spin Labelling (ASL)

Although no significant effect of meal composition on cortical (frontal, temporal, parietal and occipital lobes) CBF (ml/100 g/min) was evident, there was a trend towards higher CBF in the subcortical (including amygdala, hippocampus and thalamus) grey matter areas following the MDP lunch (p=0.096) (Table 4.9).

Table 4.9. Comparison of postprandial CBFs (ml/100 g brain tissue/min)

	MDP (mean ± SD)	**WD (mean ± SD)**	***p* value**
Cortical GM	49.2 ± 10.0	47.5 ± 9.8	0.311
Subcortical GM	41.8 ± 7.2	39.8 ± 5.5	0.096

CBF: Cerebral blood flow. MDP: Mediterranean-style dietary pattern. WD: Western-style diet. SD: Standard Deviation. GM: Grey matter. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers.

Blood pressure and circulating parameters

After the MDP lunch, 12% higher glucose (p<0.001) and 33% lower insulin (p=0.005) were detected compared to the WD lunch, resulting in an improved glucose to insulin ratio of 71% (a biomarker of insulin sensitivity) (p<0.001) (Figure 4.8). No significant postprandial differences were seen for SBP, DBP, lipids, CRP, cortisol and BDNF levels (Figure 4.8, Table 4.10).

Alongside the main effects of diets, significant period effects were found, with higher SBP in the second arm (p=0.043), and higher LDL-cholesterol (p=0.008) and total cholesterol/HDL ratio (p=0.044) in the first arm, whilst a significant sequence effect was detected for DBP with lower values obtained in those who had the MDP lunch first (p=0.020).

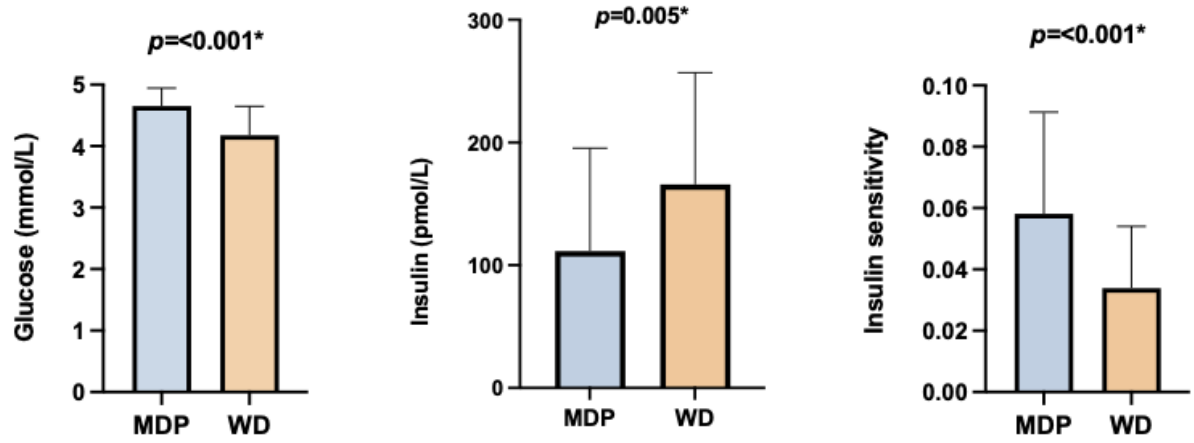


Figure 4.8. Comparison of postprandial glucose metabolism responses

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. GIR: Glucose to insulin ratio. Measurements were taken following the day 1 lunch meal. A linear mixed model was performed with treatment, sequence and period fixed factors. P value here represents the treatment effect (main effects of diets). *: Significant statistical difference (p<0.05). For the insulin analysis, one extreme outlier was removed from WD, and n=1 extreme outlier was discarded from WD for the glucose analysis.

Table 4.10. Comparison of postprandial blood pressure and circulating parameters

	N	MDP (mean ± SD)	N	WD (mean ± SD)	*p* value
SBP (mmHg)	25	115.4 ± 13.0	23	118.7 ± 14.1	0.133 *
DBP (mmHg)	25	72.5 ± 8.1	23	74.8 ± 9.0	0.170 §
Cholesterol (mmol/L)	23	5.1 ± 1.1	23	5.1 ± 1.1	0.356
Triglycerides (mmol/L)	23	1.5 ± 0.8	23	1.7 ± 0.7	0.939
HDL-cholesterol (mmol/L)	23	1.6 ± 0.4	23	1.5 ± 0.4	0.324
LDL-cholesterol (mmol/L)	23	2.9 ± 0.8	23	2.8 ± 0.9	0.504 *
Total cholesterol	23	3.4 ± 0.8	23	3.6 ± 0.9	0.924 *
Non-HDL (mmol/L)	23	3.6 ± 0.9	23	3.6 ± 0.9	0.237
CRP (nmol/L)	23	12.7 ± 16.5	21 †=1	7.8 ± 8.7	0.061
Cortisol (nmol/L)	23	167.2 ± 61.0	23	164.0 ± 51.8	0.954
BDNF (ng/mL)	22 †=1	14.1 ± 3.6	22	14.2 ± 3.4	0.784

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. SD: Standard deviation. N=25 individuals, but it varies due to dropouts, missing data and extreme outliers. SBP: Systolic blood pressure. DBP: Diastolic Blood Pressure. HDL: High density lipoprotein. LDL: Low density lipoprotein. CRP: C-reactive protein. BDNF: Brain Derived Neurotrophic Factor.

Measurements were taken following the day 1 lunch meal. A linear mixed model was performed with treatment, sequence and period fixed factors. Statistical significance threshold was set as $p<0.05$. P value here represents the treatment effect (main effects of diets). Significant differences are highlighted in bold. *: Significant period effect. [§]: Significant sequence effect. [†] reports the number of the extreme outliers as established by mean ± 3SD method, that were discarded prior to the statistical analysis. If not stated, that means there was not any.

4.3.4. Follow-up dietary behaviour change and subjective dietary assessment

The average MEDAS score increased from 5.1 to 7.5 (out of 14), which equals to a 48% increase in their MDP adherence *(p*=<0.001) at 3 months post intervention (Table 4.11).

Table 4.11. Mediterranean diet behaviour change

	N	**Screening (mean ± SD)**	**N**	**3-month follow-up (mean ± SD)**	***p* value**
MEDAS score (0-14)	17	5.1 ± 0.3	17	7.5 ± 0.4	**<0.001**

MEDAS: 14-item Mediterranean Diet Adherence Screener questionnaire. N=25 individuals, but it varies due to dropouts and missing data. No extreme outlier (mean ± 3SD) was detected. Paired t-test was performed. Statistically significance result was highlighted in bold ($p<0.05$).

In terms of subjective views on the easiness/difficultness level of following the diets, participants reported that the MDP was easier to adhere to in comparison with the WD, with inter-group differences reaching borderline significance *(p*= 0.060) (Table 4.12).

Table 4.12. Participants' scores on easiness levels of following the diets

	N	**MDP (mean ±SD)**	**N**	**WST (mean ±SD)**	***p* value**
Score	23	3.7 ± 2.0	23	4.7 ± 2.6	0.060

The single question (created by us for the study) is "Did you find following the five-day meal plan easy or difficult? Please rate on the scale from very easy to very difficult." 10 points visual analogue scale, with 1 being easiest and 10 being the most difficult. Linear mixed model was run to consider the sequence and period effects. Statistical significance threshold was $p<0.05$. N=25 individuals, but it varies due to dropouts and missing data. No extreme outlier (mean ± 3SD) was detected.

4.4. Discussion

To the best of my knowledge, this is the first RCT investigating the short-term and postprandial effects of a MDP on mood and anxiety as the primary outcomes in adults with mental health complaints. Our findings demonstrated that a MDP can improve mental health compared to a WD, by reducing TMD, tension, depression, fatigue and increasing vigour in five days, whilst diminishing confusion and enhancing alertness in 24 hours and five days. No postprandial effects of diets were evident on mood and cognition. Regarding our secondary outcomes, higher consistency in motor function, reduced CRP and increased cortisol levels were found after five-day of MDP consumption, whilst higher plasma glucose, lower insulin, evidence of an enhanced insulin sensitivity and a non-significant increased CBF were seen after the MDP lunch.

Mood, anxiety and cognition

As detailed in Chapter 2, only three RCTs (193, 194, 219) have previously examined the short-term (10 days) effects of a MDP on mood before and reported improved alertness and contentment in all three studies. Likewise, we found a positive effect of a MDP on alertness, confirming their findings and further demonstrating that alertness could be enhanced by only 24 hours of a MDP consumption. A trend toward our hypothesis occurred for contentment in our study, however, the difference did not reach the statistical significance level in five days, suggesting a longer-period (5-10 days) may be required for a meaningful change in contentment. Furthermore, those three previous studies reported improvements in individual mood domains as follows; vigour (193, 219), confusion (194), tension, anger and fatigue (219). The reason why we saw consistent improvements in almost all domains in a shorter period could be that we provided all

study foods with detailed meal plans and instructions supporting a greater MDP adherence, whilst the previous studies gave instructions only.

Our exploratory subgroup analysis revealed that improvements in mood and anxiety outcomes in MediMood were independent of medication use with the exception of contentment which was only improved by a MPD in those who were not taking an antidepressant/antianxiety medication (Table 4.3, Figure 4.3). Previously, SMILES (182), HELFIMED (183) and AMMEND (184) trials (summarised in Table 1.3) investigated 12-week effects of a MDP compared to befriending groups in those with moderate to severe depression (with the rates of people on pharmacotherapy ranging between 30-75%) and found significant improvements. However, none of these studies reported whether their statistical models were adjusted for medication use nor presented subgroup analysis results according to medication use. Nonetheless, the significant improvements in MediMood were independent of medication use with only contentment impacted by antidepressant status. Yet, it is crucial to highlight that our sample size was not powered to carry out a subgroup analysis, therefore, these results are not definitive but rather preliminary that need further exploration (Section 4.2.5).

Another relatively short-term study investigating the effects of a high fibre breakfast consumption for 14 days on digestive feelings, bowel function and general wellbeing revealed higher happiness, alertness and concentration, implying the role of bowel functions on mental wellbeing (301). We did not collect information on "stool bulking and frequency", yet improved digestion could be one of potential explanations of enhanced mood in our study, as we recruited people with sub-optimal eating habits and intervened with a MDP with a high fibre content (35g/day in MDP arm, Table 3.5) possibly providing improved defecation. Nonetheless, we collected faecal samples at baseline and after five days to assess changes in the gut microbiome species profile and metabolomics (faeces and circulation), which will provide a detailed insight into the possible effects of the microbiome in mediating the impact of the MDP on mental health outcomes.

In contrast to our mental health outcomes, no significant short-term effects of a MDP on cognition was evident except for an improved Reaction Time variability. The increased consistency in Reaction Time predicts healthier cognitive ageing and linked

with better “perceptual speed, working memory, episodic memory and crystallised abilities” (302), yet we did not observe a change in those individual domains. However, this observation is consistent with the limited available literature. The two previous 10-day MDP studies also reported mixed results from cognitive tasks (193, 194). McMillan *et al.* reported positive influence of a MDP on sustained attention, visual memory and visuospatial function and no effect of a MDP on working memory, whilst participants unexpectedly performed faster in those tasks in the control arm, which was attributed to be a potential practice effect (193). Lee *et al.* revealed improved memory recall performance and declined correct answers in working memory after MDP, with no change in other cognitive domains (194). Our data reveals that longer term interventions are required to meaningfully affect cognition.

Decreases in cognitive performance were previously stated as a result of short-term carbohydrate unavailability. A one-week high fat diet (%74 fat and %2 carbohydrate) caused worsened attention and reaction time in sedentary men (n=20, aged 36 ± 1 year) compared to baseline, with the results attributed to significantly reduced circulating glucose levels and potentially resulting in diminished glucose availability for the brain (303). Similarly, another study comparing effects of low calorie diets, either a low carbohydrate diet (complete elimination of carbohydrates in the first week, and gradual reintroduction at weeks two and three) (n=9, mean BMI=28.1) or a calorie restricted diet as recommended by American Dietetic Association (ADA) (n=10, mean BMI=30.1), measured cognition in participants aged 22 to 55 years (304). Memory was worsened after a week in low carbohydrate dieters (as there was no carbohydrate in the first week) which was restored by the reintroduction of carbohydrates (304). The carbohydrate profile of our diets (high fibre and no simple sugar in MDP vs low fibre and high simple sugar in WD) were significantly different (Table 3.3). Yet, they both still provided glucose availability for the brain as we were interested in the quality of carbohydrates rather than quantity, resulting in no extreme carbohydrate restriction which may be a reason for the lack of differences in cognitive performance.

Furthermore, a MDP contains abundant amounts of several bioactives such as long chain omega-3 fatty acids, flavonoids, carotenoids, polyphenols, antioxidant vitamins i.e. vitamin E, all known to positively influence brain functions in a long-term (305, 306), yet, there is no short-term study available examining supplementation effects

on cognition with study durations usually varying from 12 weeks (307) to 24 months (308). Otaegui-Arrazola *et al.* highlighted the inconsistent findings on those bioactives derived from RCTs, in spite of the accumulated promising evidence from observational studies (309). A review of preclinical studies reporting the salutary effects of flavonoids on cognition through "regulation of neurotransmitters and enhanced neurogenesis, synaptic plasticity and neuronal survival" also emphasised the need for further research (310). Similar to these, our study also supports the consensus regarding the lack of evidence on the relationships between the MDP bioactives and cognitive functions, and thus the need for the further research.

Concerning postprandial studies, the attention has been mainly given to meal composition (macronutrients distribution and fibre content) (311). One study investigating breakfast meals with different levels of carbohydrate (15, 30 or 50 g) and fibre composition (1.5, 6 and 13 g) in 168 female university students measured postprandial blood glucose, mood and cognition (312). Their main finding was that mood and cognitive responses were greatly influenced by the glucose tolerance (established by fasting blood glucose levels at screening with 6 mmol/L used as threshold) (312). People with better glucose tolerance displayed a better mood whilst those with poorer glucose tolerance showed an impaired memory (312). Another RCT examining the impacts of three breakfast meals with different glycaemic index (low vs high glycaemic index, both contained 50 g carbohydrate, derived from either pasta or white bread, or only water) on cognition in 21 individuals (65 ± 7.3 years) with T2D, revealed that higher blood glucose level after bread consumption (high glycaemic index meal) was negatively linked with verbal memory, whilst sustained attention did not respond to the meals (313). The higher elevation in glucose levels were associated with a poorer memory performance (313). Nonetheless, these inconsistent findings in cognitive performance that is linked with the individuals' glucose metabolism somewhat explain our results. Because we did not see a postprandial difference in mood and cognition despite the different GIs of our meals (complex carbs vs simple sugars) and higher postprandial glucose we observed. We did not collect specific information on our participants T2D status; however, our population was younger and generally healthy. As the neurological mechanisms of people with disordered glucose metabolism is more likely to be sensitive to meals acutely (313, 314), it may be one potential explanation of the absence of significant meal effects on mood and cognition in our findings. Supporting this theory and aligning with our results, in

young healthy men (n=26, 34 ± 6 years, normal weight), type of carbohydrates (simple vs complex) were reported to have a limited postprandial impact on mood in healthy men, with only fatigue increased after a simple vs complex carbohydrate breakfast (2.7 ± 3.3 vs 1.5 ± 1.7, p=0.03) (315).

Energy quantity of meals affects mood. A postprandial study comparing low- (64 kcal) vs high- (500 kcal) energy breakfasts assessed mood in 11 healthy young women (mean age 23.2 years), and decreased contentment and increased tension, irritability and lethargy levels were seen after low energy breakfast (316). The fact that our test lunches were isocaloric may help explain the lack of postprandial differences in mood and anxiety measures between a MDP and a WD in MediMood.

Furthermore, giving a test lunch rather than breakfast may have impacted the likelihood of seeing an effect of meal composition on mood and cognition due to 'biological rhythm' as the same meals are associated with different cognitive performances depending on the time of day, with the lowest performance at mid-day (317). Lunch meals were reported to associate with being drowsy (311, 318). It was also postulated that reduced mood and energy levels at mid-day, also known as 'post-lunch dip', may be solely because of time of the day independent of meal composition (319). This theory may explain why we did not see an improved performance postprandially, nonetheless, we did not see a worsened performance either.

Cerebral blood flow (CBF)

The short-term and postprandial effect of a MDP on CBF is relatively unknown. Hoscheidt *et al.* compared the impacts of four weeks of a MDP and a WD in individuals (n=87, aged 45 to 65 years) with normal cognition and mild cognitive impairment (MCI) on CBF (established by ASL) (320). The MDP and WD resulted in a higher and lower CBF respectively (p<0.01) in the whole brain in people with normal cognition, while the difference was insignificant in people with MCI (320). Lamport *et al.* examined the acute effects of a flavanone rich citrus juice versus control on CBF and cognition in healthy young adults, and demonstrated increased CBF in right frontal gyrus after 2h alongside the improved executive function, with no difference at 5h and no difference in the whole brain perfusion at neither time points, as consistent with our findings (178). Another

similar study by Lamport *et al.* using flavanol rich cocoa on CBF in 18 adults aged 50-65 years free of dementia (no information on their mental health status) demonstrated increased CBF in specific regions of brain, namely, "anterior cingulate cortex and central opercular cortex" after 2h of high flavanol drink, and no information was provided on the whole brain perfusion (321). To the best of my knowledge, no other study has been published investigating the postprandial effects of meals or bioactives on perfusion. Despite the CBF trends being in the anticipated direction, the reason why we did not see a significant difference could be our relatively small sample size (320). Besides, the vast majority of our participants were young and healthy, and with a likely optimised CBF and a potential ceiling effect to be able to detect any improved CBF induced by a MDP.

A systematic review examining the impacts of diet on brain volume, brain connectivity and cerebrovascular markers including CBF in humans, involved 52 studies, with 10 assessing whole dietary patterns and 4 a MDP with study durations beginning from 6 weeks to 13.8 years (322). It reported inadequate evidence on the effects of either MDP or a WD on multiple cerebrovascular outcomes including CBF, with a positive influence of high omega-3 PUFA intake and negative effect of "high meat, saturated fat, sugar, caffeine or alcohol consumption (except wine)", a pattern mimicking a WD, evident (322). They also stressed that CBF was a far less studied outcome compared to others, therefore the need for further research (322). Our study provided new evidence to the limited available literature, yet further research is still required as we could not assess the short-term response in the CBF to the dietary interventions, but the acute comparison only.

Circulating blood biomarkers and blood pressure

Inflammation is a critical biomarker for neurological disorders (323, 324) and further postulated to have a causative role in mood and anxiety disorders (325, 326). Human neuroimaging studies indicated bidirectional relationships between heightened amygdala activity and elevated production of inflammatory factors (327). Hence, inflammation is recommended to be a treatment target (328-330). A systematic review including studies with a minimum duration of 12 weeks revealed that a MDP can reduce CRP and interleukins (331). A cross-over RCT compared the three different 4-day diets; low-fat low-glycaemic index, low-carbohydrate high-fat, and low-carbohydrate high-fat

plus 15 mins walking, in individuals aged 48 to 72 years (223). They did not report on CRP, however, all three conditions diminished p-JNK, "a marker of cellular inflammation" (223). Regarding our CRP results, the literature suggests that potential causes may primarily include infections (332), which was not controlled for in our study. MediMood appears to be the first RCT assessing the short-term effects of a MDP compared to WD on inflammation, with evidence of reduced CRP even after a 5-day, with this indication of reduced inflammation potentially contributing to the mental health benefits observed.

Regarding the postprandial inflammatory responses, a systematic review stated that interleukin-6 (IL-6) was the only marker which consistently responded to single high-fat meals, while emphasising the robust finding on acute unresponsiveness of CRP and tumour necrosis factor (TNF) (333). Consistent with their conclusion, a study published in 2023 compared a MDP and a WD meal on oxidative stress and found no difference in CRP levels whereas significant differences in interleukins were evident (334). Thus, no difference in our postprandial CRP results align with the previous literature which also suggests that a retrospective profiling of other inflammatory biomarkers in our biobanked plasma samples such as IL-6 should be conducted in the future.

Cortisol was the other circulating biomarker exhibited a significant change in response to five-day interventions, which surprisingly was increased by 6% by the MDP and decreased by 6% by the WD. We did not measure salivary cortisol unlike the common practice, nevertheless cortisol levels in saliva and blood were reported to be highly correlated (335). One crossover RCT conducted in healthy young females tested the effect of 3-day low and high glycaemic index (GI) diets on cortisol in saliva samples, with the high GI diet increased cortisol compared to baseline and low GI diet (336), contradicting with our findings. It was discussed that cortisol may react differently in people based on metabolic conditions such as diabetes (131), obesity (337) and sex (338). Cortisol plays a role in the stress response and mood management (339). Nonetheless, the increase in cortisol in MDP did not hamper the mood improvements, suggesting cortisol may not be the primary dietary responsive mechanisms mediating the altered determining mood status. No change in postprandial level is consistent with the literature as other studies examining the different meals with different macronutrient compositions on cortisol reported no effect of food on postprandial response (340, 341).

A MDP helps regulate BP in a long-term (342). Two systematic reviews identified that higher baseline BP and longer study duration was significantly associated with reductions in BP induced by a MDP (343, 344). Consistent with our findings, Lee *et al.* did not see an effect of a 10-day MDP and suggested that changes in BP require structural alterations in large artery stiffness (194). Therefore, five days may be too short to see a change in BP.

Regarding our glucose and insulin findings, there were no changes in fasting glucose and insulin in five days despite the significant postprandial differences. Similar to our study design, Vitale *et al.* investigated postprandial and 8-week impacts of an isoenergetic MDP compared to a control arm (similar to a WD) in 29 overweight/obese adults, and found improved glucose, insulin and insulin sensitivity at both timepoints (345). Being overweight/obese was not a characteristic of our population, which may explain lack of short-term effects in MediMood. Another study comparing chickpea and wheat consumption postprandially in 19 healthy adults over six weeks found lower glucose, insulin and insulin sensitivity (measured by HOMA) levels following a chickpea based meal consumption, whereas there was no difference after six weeks (346), suggesting glucose and insulin appears to be more reactive to postprandially, supporting our findings. To the best of my knowledge, no short-term study (up to 10 days) examining a MDP on glucose metabolism has been published.

Despite the substantial fat composition differences of our diets, we saw no change in blood lipids either short-term or postprandially. One study examining two weeks effects of a calorie controlled MDP, German style diet or a fast-food diet reported no effect of diets on any of the blood lipids (347). Another study comparing a very low carbohydrate diet (10% carbohydrate, 60% total fat and 21% SFA) and low-fat diet (62% carbohydrate, 19% total fat and 6% SFA) in 10 healthy women demonstrated significant differences in total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerol in very low carbohydrate diet at weeks 2 and 4, whilst the low fat diet was linked with lowered total cholesterol, LDL-cholesterol and triacylglycerol at week 2 only (348). There is no shorter-term study available examining the impact of a MDP on blood lipids. Taken together, it may require minimum of two to four weeks to see significant alterations in blood lipids for a meaningful overall improvement, explaining our findings.

Impaired neuroplasticity associate with psychiatric and neurological disorders (133). Dietary intake is thought to be a potential modulator of BDNF concentrations, as an indicator of neural plasticity (133). A systematic review published in 2022 reported the PREDIMED study as the only MDP intervention assessing BDNF in humans (349), which observed an elevation after three years of intervention (173). A 2024 meta-analysis pooling the effects of human omega-3 PUFA interventions, a characteristic bioactive of MDP, on BDNF involved 12 studies whose study durations ranging between 4 to 26 weeks (350). They reported a significant positive effect *(p*<0.001), however, subgroup analysis revealed insignificant effect when only shorter-term (less than 10 weeks) studies were included (350), consistent with our results. Regarding its postprandial changes, studies comparing different GI breakfasts (351), and breakfasts with different macronutrient compositions (352) reported no change in BDNF levels despite the significant changes in glucose and insulin levels, consistent with our results.

Anthropometrical changes

Regarding body weight, MDP caused a 1kg reduction in weight compared to a WD, with the greatest reduction in female participants. Although we did not intend to cause a change in body weight with isocaloric diets providing 2000 (±10%) kcal per day, with our participants provided with snacks if they felt hungry, our day suggest that a MDP may be associated with weight loss. Consistent with our study, Lee *et al.* reported weight loss after 10 days MDP consumption despite no energy restriction (194). Furthermore, a study employing either low or high GI diets for three days, both with ad libitum intake, recorded a significantly lower energy intake in the low GI diet, implying the higher satiety provided by higher fibre/healthier diets (336), which may explain the weight loss observed in the MDP arm in our study. A metabolic effect of the MDP on macronutrient metabolism and energy production may underlie this weight loss.

Behaviour change

A MDP adherence range of our 25 recruited patients was between 3 and 7 at screening as 7 was used as the cut-off for inclusion (MEDAS 14-point scale). Participants' score increased to be between 5 and 12 (among 17 participants) at follow-up, resulting in

a significant improvement in their MDP behaviour. In more detail, only one participant's score remained the same at 5, with the other 16 individuals increased their MEDAS score by 1 to 5 points, with biggest rise was from 7 to 12. Considering even 1-point increment in MEDAS pyramid score is associated with 1.7 fewer years of cognitive ageing as reported by EPIC-Norfolk study (185), the reported changes are remarkably promising. Additionally, they found it easier to follow the MDP than the WD. Notably, those who did not respond to the follow-up questionnaire are likely to have less favourable dietary practices, as known as 'retention bias' (353), yet we cannot conclude with a certainty that the change would have become insignificant if they responded.

Although we did not design our study to change long-term dietary behaviour, the full food provision and detailed instructions appeared to provide them with "demonstration of the behaviour, behavioural practice/rehearsal and instruction on how to perform a behaviour", which are significant dietary behaviour change techniques (354). MediMood is the first study assessing the impact of 5-day dietary change on a longer term eating behaviour, as dietary behaviour change strategies tend to be examined in a longer term, such as minimum of 12 weeks (355). We also showed the feasibility of a high MDP adherence by non-Mediterranean individuals and that intense short-term MDP intervention with full food and food preparation instruction and provision may be an effective way to promote longer term behaviour change. This work therefore contributes to the literature exploring feasible and practical avenues to encourage non-Mediterranean populations to follow a MDP which is a hot topic in research (162, 356).

Strengths and limitations

MediMood has several strengths and limitations. Regarding its strengths:

- It is the first short-term RCT evaluating the efficacy of a MDP on mental health in individuals who are currently suffering from low mood and anxiety.
- It tests both postprandial and short-term effects of a MDP embedded in the one study.
- It employed a detailed mechanistic investigation of the main physiological and biochemical drivers of mood anxiety and cognition.
- Its crossover design eliminates the within person differences between the arms.

- It is inclusive with no exclusion criteria based on age, sex or medication use.
- It maximises the dietary adherence with full food provision, food preparation instructions and additional food for an extra person in the household.
- The primary outcome measures used are commonly used validated tools, facilitating comparability with the limited published evidence.
- The variety of cognitive tasks used allow the characterisation of the impact of a MDP on several cognitive domains.
- Daily reminder emails sent every morning aids study adherence and motivation.
- Low dropout rate at 12% compared to the literature which reports a minimum of 20% in medical RCTs (357).

In terms of limitations:

- Mood and cognition testing and biological samples collection were not conducted every day to reduce participant burden.
- Additional postprandial blood samples could not be collected on day 1 for logistical reasons, as the CRF and MRI centres were at different locations and we prioritised the MRI scan as it was a key secondary outcome, with the analysis of blood biomarkers representing a tertiary outcome.
- MRI scans could not be executed at the beginning and at the end of five-day interventions to see short-term changes due to its cost, limiting us to assessing only the postprandial effects on CBF.
- Adjustment for additional covariates could not be performed due to inadequate sample size.
- Serotonin and dopamine, primary happiness hormones, could not be analysed due to their cost. Nonetheless metabolomics analyses will quantify tryptophan which is the precursor of those hormones to amplify our understanding. Besides, biobanked samples can be analysed in future if funding is secured.
- The distance between QI CRF and UWWBIC took an approximately 20 mins walk before MRI scan, and another 20 mins before postprandial blood withdrawal, which as a form of exercise might have affected our results. However, as the participants underwent the same standardised protocol on each intervention arm (MDP or WD) any impact of our study findings was minimised.

- Our data collection spanned from June to December 2023, causing seasonal differences as weather may influence some individuals (358).

4.4. Conclusion

We conducted the first RCT examining the postprandial and short-term impacts of a MDP on brain health outcomes, namely, mood, anxiety, cognition, perfusion and sleep, alongside several cardiometabolic parameters in 25 adults with existing mild to moderate level mental health issues. Our results showed that a MDP can be effective in promoting mental health (by decreasing depressive symptoms, i.e. TMD, tension, depression, fatigue and confusion, and increasing vigour and alertness). We also detected improved motor function and inflammation after five days, alongside improved postprandial insulin sensitivity. These findings are novel, and create a good basis/rationale for further research and health policies.

4.5. MediMood contributions

The intervention was delivered by Latife Esgunoglu, Marrium Liaquat, Rachel Gillings, Juliet Hill and Rachel McGauley. The blood chemistry results were medically reviewed by Andrew Wilson. Data entry was managed by Latife Esgunoglu with inputs from Marrium Liaquat, Rachel Gillings, Juliet Hill and Rachel McGauley. Overall cognition score was generated by Latife Esgunoglu by discussions with Sol Morrissey, Michael Hornberger and Mizanur Khondoker. Statistical analysis was conducted by Latife Esgunoglu with guidance from Mizanur Khondoker and Amy Jennings.

4.6. Acknowledgements

We firstly would like to thank to all our study participants for their time and commitment. We are grateful to the QI CRF and UWWBIC personnel for accommodating our needs for the data collection, and Miss Juliet Hill and Miss Rachel McGauley for their assistance with the participant visits and the data entry. I also would like to thank to Mr Sol Morrissey for insightful discussions to analyse the cognitive data.

Chapter 5. Bidirectional relationships between fruit and vegetable intake, overall dietary quality and mental wellbeing: C-19 Wellbeing Tracker longitudinal study

(Drafted manuscript)

The C-19 Wellbeing Tracker study was started as an immediate response to the pandemic. The study involved comprehensive daily tracking of lifestyle behaviours in 1044 participants for 12 weeks and follow up assessments at 3, 6, 12 and 24 months. This chapter includes the daily tracking data collected over the first lockdown (March to June 2020) to study the short-term effects of diet on mental health.

I joined the study in April 2020 because of adaptations in my PhD plan (as a result of COVID-19 associated social lockdown and UEA and the clinical trials unit shut-down), participated in the team meetings, and contributed into the creation of the follow up surveys at 3, 6, 12 and 24 months.

5.1. Introduction

COVID-19 is a severe acute respiratory syndrome (SARS-CoV-2) caused by a virus from the coronavirus family (359). Following its severe spread starting from Wuhan, China, in December 2019, the WHO announced the unprecedented outbreak as a 'pandemic' on 11th March 2020 (360). As of 24th March, 2024, the global number of people infected was over 775 million and the death toll was more than 7 million (361). In the UK, the number of the confirmed case was nearly 25 million with over 232,000 deaths due to a positive COVID-19 diagnosis (361). As COVID-19 is a novel disease, much remained unknown about the pathophysiology, risk factors and management strategies and there was no confirmed treatment/vaccination available until 8th of December 2020 (362).

As a consequence of the COVID-19 pandemic and the absence of a targeted treatment, strict lockdown measures were implemented by governments in order to lower the spread of the disease by restricting interaction between people. In the UK, the official restrictions were put in place on the 23rd of March 2020. According to these lockdown

measures, people were allowed to leave home only for essential shopping, one form of exercise per day, any medical need and travel to and from work if there is absolutely no possibility to work from home. Furthermore, all shops, except those selling essential goods such as food and medicine were instructed to close until further notice (363). Therefore, cafés, pubs and restaurants remained unavailable. These restrictions were projected to result in significant alterations in people's daily lifestyle and health behaviours including eating behaviour, due to changes in food choices, cooking frequency and preferences.

As detailed in the introductory chapter (Chapter 1), the increasing prevalence of mental health disorders such as low mood, depression and anxiety has drawn attention worldwide. In the UK, the rate of depressive symptoms at moderate to severe level, established by Patient Health Questionnaire (PHQ-8), more than doubled during the pandemic, from 10% to 21% (before the pandemic vs early 2021) (364).

5.1.1. Chronic effects of dietary intake on mental health and sleep

A meta-analysis of observational studies assessing the risk of depressive outcomes in relation to various healthy dietary indices, namely, "the Mediterranean-style dietary pattern (MDP), the Healthy Eating Index (HEI) and Alternative Healthy Eating Index (AHEI), the Dietary Approaches to Stop Hypertension (DASH), and the Dietary Inflammatory Index (DII)", reported that the MDP displayed the strongest association with a lower incidence of depression (RR: 0.67, 95% CI 0.55-0.82), suggesting 'avoiding a pro-inflammatory' diet can be effective in the prevention of depression (365). Another meta-analysis (including 16 studies with a total of n=92,242 adults) examining the dose-response relationship between dietary induced pro-inflammation (established by the DII, a valid tool used examining inflammation level of a diet) and mental health showed a linear relationship with every 1-unit increase in DII score linked to an elevated risk of depression (OR: 1.06, 95% CI: 1.03-1.19), anxiety (OR: 1.27, 95% CI: 1.08-1.49) and distress (OR: 1.85, 95% CI: 1.43-2.40) (366).

In terms of the relationships between food groups and mental wellbeing, Gibson-Smith *et al.* (367) investigated the associations between individual food groups in the MDP and mental health outcomes using the data from the Netherlands Study of

Depression and Anxiety (NESDA) including 1634 participants. The food groups were fruits, vegetables, non-refined grains, legumes, fish, potatoes, olive oil, high fat diary, red and processed meat, poultry and alcohol, whilst the mental health outcomes were depression (assessed by Inventory of Depressive Symptomatology-Self Report), anxiety (assessed by Beck Anxiety Inventory) and phobias (assessed by Fear Questionnaire) (367). Vegetable intake was linked to lower depression (β: -0.10, 95% CI: -0.12—0.02), anxiety (β: -0.06, 95% CI: -0.11-0.01) and fear (b: -0.11, 95% CI: -0.16- -0,06), and fruit intake was linked to lower fear (β: -0.09, 95% CI: -0.14-0.04) (367). Similarly, El Ansari *et al.* (368) examined the relationships between eating behaviour and perceived stress and depressive symptoms among UK university students (n=3706). Eating behaviour was explored using a Food Frequency Questionnaire (FFQ) which captured the following groups; sweets, cakes/cookies, snacks and fast/canned food, fresh fruits, raw and cooked vegetables and salads, meat and fish, milk products and cereals (368). The Cohen's Perceived Stress Scale (PSS-4) was used to measure stress, and a Modification of the Beck Depression Inventory (MBDI) was used for the evaluation of depressive symptoms (368). Fruit and vegetable intake was associated with reduced perceived stress (β: -0.067, p=0.002 in female, β: -0.092, p=0.025 in male) and depressive symptoms (β: 0.081, p<0.001 in female, β: -0.115, p= 0.004 in male) (368).

Sleep quality is another important lifestyle factor associated with mental health (369), and alterations in sleep pattern are associated with changes in nutritional behaviours such as increased hunger and appetite (370). To date, the largest cross-sectional study investigating the associations between dietary intake, sleep and mental health symptomatology used the UK Biobank data involving 502,494 middle aged individuals demonstrated positive associations between fruit (β: 0.011, p<0.001) and vegetable intake (β: 0.001, p<0.01) and healthy sleep (established by a composite score calculated using UK Biobank questionnaire with the following components; "sleep duration, chronotype, sleeplessness, snoring and daytime dozing/sleeping"); and negative associations between fruit (β: -0.23, p<0.001) and vegetable intake (β: -0.012, p<0.001) and mental health symptomatology (assessed by a composite score created using UK Biobank questionnaire with the following elements; "mood swings, miserableness, irritability, sensitivity/hurt feelings, fed up feelings, worrier/anxious feelings, tense/highly strung, worry too long after embarrassment, suffer from nerves, loneliness/isolation, guilty feelings and risk taking") (371).

Whilst dietary intake can affect mental health status, similarly impaired mental health can worsen eating habits. In Australia, Forsyth *et al.* analysed the dietary consumption of patients (n=109) who were being treated for depression and/or anxiety in general practices (372). Participants were asked to complete a diet history (assessed through Australian Modified Healthy Eating Index (Aust-HEI)), and Depression, Anxiety, Stress Scale (DASS) questionnaires. Fruits were the most compelling groups correlated (shown by Pearson's coefficients) with lower depression (β: -0.31, $p<0.01$), anxiety (b: -0.25, $p<0.01$), stress (β: -0.38, $p<0.001$) and total DASS scores (β: -0.37, $p<0.001$) (372). Likewise, one meta-analysis pooling 58 observational studies with a total of 35481 participants, looked at the "dietary intake of people with severe mental illnesses (SMI), namely, "schizophrenia spectrum disorders, bipolar affective disorder, depression with psychosis, or other psychotic illnesses", compared to a control group and showed that poorer dietary quality was evident across all SMI groups, including lower fruit and vegetable intake and higher consumption of sugary drinks (373).

As indicated in Chapters 2-4, research investigating the impact of a MDP and mental and cognitive health is limited, with limited understanding of short-term impact of individual food groups on brain health. Therefore, the C-19 Wellbeing Tracker project provided a unique opportunity to assess the bidirectional relationship between diet and mental health outcomes.

5.1.2. Effects of COVID-19 restrictions on dietary habits and mental health in the UK and elsewhere

The aforementioned COVID-19 related lockdown restrictions influenced people's eating behaviours and mental health status, which has been the subject of research carried out in multiple countries.

In terms of change in eating behaviours, a French study (n=37,252) tracked changes in dietary intake (DI), physical activity (PA) and body weight (BW) during the first lockdown (March to May 2020) compared to before the pandemic (374). Participants were asked to complete validated questionnaires on "sociodemographic and lifestyle characteristics, health status, DI, PA and anthropometrics" (374). DI intake was measured

using 24-hour dietary records which were later followed by interviews with a dietitian and validated through plasma/urine biomarkers (374). Diet quality was assessed using the Alternative Healthy Eating Index (AHEI) which included fruits, vegetables, whole grains, sugar-sweetened beverages, nuts and legumes, red/processed meat, long chain (n-3) polyunsaturated fatty acids, total polyunsaturated fatty acids, sodium and alcohol (374). Baseline mental health status was screened using PHQ-9 and GAD-7 (374). 56.2% of the sample reported changes in their dietary intake, of which the main reasons given were life routine changes (47.6%) and increased time to cook at home (40.4%) (374). Decreased fresh fruits (17%) and vegetables consumptions (18%) were reported (374) whilst increased consumption of cakes *(p*=0.002) and cookies *(p*=<.0001) compared to pre-lockdown were evident (374).

An Italian study surveyed individuals (n=3533, aged 12 to 86 years) about their health behaviours for two weeks to make a comparison between pre-lockdown and during lockdown (375). Over half of the cohort reported a change in their appetite and fullness perceptions, and weight gain (375). As for their healthy food choices (established considering their fruits, vegetables, nuts and legumes consumptions), around a quarter kept their choices the same, 37% reported to have healthier food and 36% reported to eat less healthy food (375). Participants were also followed at individual food items level, with homemade sweets increasing the most, by over 40% (375). More prolonged sleep duration during lockdown was also evident *(p*<0.001) (375).

Regarding changes in mental health status, the first study providing insights on effects of the pandemic on mental health status in UK adults (n=3097) was conducted during the first 4-6 weeks of the lockdown (376). The outcomes of interest were depression (measured by PHQ-9, 27-point scale), anxiety (measured by GAD-7, 21-point scale) and stress (measured by Perceived Stress Scale, PSS-4, 16-point scale). Worsened mental wellbeing was reported, with scores (presented in mean) rising as follows; PHQ-9 from 2.91 to 7.69; GAD-7 from 2.95 to 6.59 and PSS-4 from 6.11 to 6.48, all significant *(p*< 0.0001) (376). The UK Avon Longitudinal Study of Parents and Children (ALSPAC) found no significant change in depression levels, but almost a doubling in anxiety compared to pre-pandemic levels (377).

With respect to the research investigating changes in both dietary behaviour and mental wellbeing status during the pandemic, a cross-sectional survey carried out in Zimbabwe (n=507) tracked a variety of health behaviours including diet, alongside stress and anxiety levels for two weeks in May 2020 to compare during lockdown to pre lockdown (378). The dietary questions measured the participants' perceptions on changes in their eating behaviour captured as overall diet quality and the following food groups; "dark green leafy vegetables, other vitamin A rich fruits and vegetables, other vegetables, other fruits, meat and meat groups, cereal breads and tubers, pulses, legumes, nuts and seeds, dairy products and eggs" and GAD-7 was used as the anxiety measure (378). 96.6% of the study population reported a change in their overall diet patterns (378). The majority (76.4%) reported higher stress and anxiety (378). Besides, elevated GAD-7 scores were associated with the lower intakes of vitamin A rich fruits and vegetables (69.1%, p=0.005), other vegetables (58.8%, p=0.001) and other fruits (80.1%, p<0.001) (378). An online survey in the UK (n=264) examined pandemic related psychological distress and its relationships with dietary behaviours alongside exercise and body image during lockdown compared to pre-lockdown (379). Over half of the cohort found the regulation of their eating behaviour more difficult (53%), more thinking about food (59%) and more concerned with their body image (49%), all of which were linked to psychological distress (respectively r=0.36, r=0.29 and r=0.41, all p<0.001), of which having a previously diagnosed mental health disorder was a significant predictor (p<0.001) (379).

5.1.3. The C-19 Wellbeing Tracker study and the purposes of the present chapter

The C-19 Wellbeing Tracker is a longitudinal cohort study developed by a multidisciplinary team at UEA, as an immediate response to the first lockdown based in the UK. The overall aim of the project was to track how a variety of health behaviours, namely, dietary behaviour, physical activity, alcohol consumption, smoking and substance use varied within and between individuals during the nationwide lockdown by tracking daily behaviour for 12 weeks in n=1044 individuals with participants additionally followed up at 6, 12 and 24 months. Mental wellbeing and sleep quality was also monitored daily. Three vulnerable groups were prioritised for recruitment, i) individuals at high-risk of COVID-19 (defined in line with the NHS), ii) individuals living

in a high deprivation area, and iii) individuals with a self-reported mental health issue. The full protocol is publicly available on an electronic database (OSF | C-19 Wellbeing Tracker study).

The initial results of the study derived from the first 30 days (early April to May 2020) have been published (380). In comparison to the pre-pandemic levels, reductions in fruit (mean difference -0.57 portion, 95% CI -0.64, -0.50) and vegetable (-0.33 portions, 95% CI -0.40, -0.25) intakes were observed, with no changes in high sugar foods (mean difference -0.03 portions, 95% CI -0.12, 0.06) and a lower self-rated diet quality (15%) reported in the whole sample (n=1044) (380). In the subgroup of people who reported an initial mental health issue, the changes were comparable to those in the group as a whole (380). Changes in some other health behaviours, namely, physical activity, alcohol intake, smoking and e-cigarette use, and substance use were also reported; however, the most substantial change was in fruit and vegetable intake (FVI) (380).

The present chapter is a sub-study of the C-19 Wellbeing Tracker study with the primary objective to investigate the bi-directional lagged associations between short term FVI and happiness. Happiness was identified as the primary variable of interest, as contentment was the factor which emerged from our systematic review as a mood domain most consistently affected by short-term dietary intake (196). Contentment as a word, is defined as "a feeling of being happy or satisfied" by the Oxford dictionary (381). In the psychology literature, contentment as a term, has been discussed as the "cognitive component of the happiness" (382, 383). The secondary objectives are to investigate the bi-directional lagged associations between short term dietary intake (FVI, high sugar foods and overall diet quality score) and mood, stress and sleep quality. All objectives were examined using daily survey data collected over 84 days (i.e. 12 weeks). We hypothesised that higher fruit and vegetable intake, lower sugar intake and a higher diet quality would be associated with a better mental health profile (higher happiness and sleep quality, lower low mood and stress levels), and vice versa.

The term 'lag' refers to the time interval between the statistical assessment points where the effects of an independent variable is tested on a dependent variable to investigate whether they predict each other. In a 'bidirectional' concept, the variables will be examined to explore whether one act as antecedent or precedent for the other. For

instance, lag 1 refers to analyses testing whether food intake from the previous day influence today's mental health or whether today's food choices influence tomorrow's mental health and vice versa, as part of the 'bidirectional' model (Figure 5.1). The lag duration was tested up to five days (days/lags 1(~24h), 2(~48h), 3(~72h), 4 (~96h) and 5 (~120h), e.g. with lag 5 testing the impact of eating behaviours on mental health outcomes and sleep five days later. Five days was chosen as the upper lag duration for two reasons. First, the gut microbiota is a major determinant of mental health through the 'gut-brain axis' (384), and greater than 80% of the whole gut transit occurs within 120 hours/5 days (385). Therefore, bioactives produced by the microbiome may take up to five days to modulate their impact on brain health. Secondly, it was to keep the theme of the present PhD thesis consistent as we previously defined the short-term as five days for the MediMood study (Chapter 3 and 4).

5.2. Methods

5.2.1. Ethics

The study was conducted by the UEA in compliance with the European Union General Data Protection Regulation (GDPR) 2018 and approved on 31/03/2020 by the Research Ethics Committee of the Faculty of Medicine and Health with the reference number 2019/20-089.

5.2.2. Sample and study design

The C-19 Wellbeing Tracker study was a longitudinal cohort study with a baseline along with daily surveys conducted over 12 weeks. All surveys were hosted on the web based Qualtrics XM software (www.qualtrics.com) and daily reminders to complete the daily survey were sent at 8 pm, 9 or 10 pm (depending on participant's preference) over the course of the survey period (12 weeks). An online platform was used to send daily message reminders (www.TextAnywhere.com).

The participant eligibility criteria were as follows; aged 18 years or over residing in the UK, had a capacity to give informed consent, and had daily access to an internet-connected device e.g. smartphone, tablet, PC, laptop. The study was advertised via social

media, existing contacts of the research team and several "organisations supporting people with conditions that make them vulnerable to suffering health complications from COVID-19". Of note, the number of participants in the abovementioned first study paper was 1044, whereas our dataset consists of 992 individuals. The reason for the discrepancy is that the data used in that paper was curated for the first 30 days of the surveys; however, the number of individuals reduced over time as the daily surveys were collected over 85 days.

The recruitment was open for 12 days, from 8th to 19th of April 2020. To collect the baseline data, participants were requested to complete a questionnaire (see Appendix 30) which had 78 demographic questions comprising contact information, age, sex, ethnicity, marital status, pre-existing health conditions, COVID-19 related health questions, employment status, average monthly income, postcode, nutrition, physical activity, mental wellbeing, smoking, alcohol consumption and drug use. Next, daily data were collected by means of Ecological Momentary Assessment (EMA) (386) which is a commonly used method in psychological research to track changes in behaviours administering repeated measurements as they happen over time in real world settings (387). EMA is suggested to be particularly useful to observe rapidly changing circumstances (388).

The daily surveys included four eating behaviours (fruit, vegetable and sugar intakes and overall dietary quality) and four mental wellbeing outcomes (happiness, stress, low mood, and sleep quality) out of a total of 30 questions (see Appendix 31). The four basic eating questions were as follows;

1) [Fruit portions]: How many portions of fruit did you eat today? (e.g. 5, 0, 1). A portion of fruit is 80g (about a handful). Fresh, frozen, canned, dried and juiced fruit all count. 30g of dried fruit is equivalent to around 80g of fresh fruit. You can include fruit juice or smoothies once. For example, if you have 2 glasses of fruit juice and a smoothie in one day, this still counts as 1 portion.
2) [Vegetable portions]: How many portions of veg did you eat today? (e.g. 5, 0, 1). A portion of vegetables is 80g (about 3 heaped tablespoons or a cup of salad vegetables). Fresh, frozen and canned vegetables all count.

3) [High sugar foods]: How many times today (e.g. 5, 0, 1) did you eat foods high in sugar such as chocolate (regular bar), cakes, biscuits (3), sweets (1 small packet), sugary drinks and jams (3 teaspoons). Include chocolate spreads (3 teaspoons), honey (2 teaspoons), table sugar (3 teaspoons), squash cordials and fruit juice.
4) [Self-rated diet quality]: How would you describe your overall diet today? Would you say: (1) Excellent, (2) Very good, (3) Good, (4) Fair, (5) Poor.

The daily mental wellbeing questions which included the sleep quality were as follows:

5) [Happiness]: Did you feel happy in general today? (0) Unhappiest, … (10) Happiest
6) [Stress]: How would you rate the amount of stress you have experienced today? (1) No stress, (2) A little, (3) Moderate, (4) A lot, (5) Extreme
7) [Low mood]: How low do you feel right now? (1) Not at all, (2) Slightly, (3) Somewhat, (4) Very, (5) Extremely
8) [Sleep quality]: How would you rate your sleep quality last night? (1) Very good, (2) Fairly good, (3) Fairly bad, (4) Very bad

5.2.3. Data preprocessing and statistical analysis

A detailed statistical analysis plan was published in an open access platform (OSF) (Appendix 32). As a primary statistical approach, Structural Equation Modelling (SEM) was employed for all primary and secondary objectives for the lagged type analyses. More precisely, the SEM model established if FVI is associated with the next day (meaning lag 1) happiness or vice versa. Due to the nature of the 'cross-type lagged panel model' analysis, both outcomes serve as both independent and dependent variables, as illustrated below (Figure 5.1). The SEM was built independently for each lag between each time point, the results of SEM were then combined using a meta-analysis model. Covariates (age, sex, BMI, mental health and IMD status) were added to both SEM and meta-analysis models. These analyses were run for each association between dietary and mental health variables for lag 2, 3, 4 and 5 alongside lag 1. The number of the repeated assessments at each lag were as follows; n=84 for lag 1, n=83 for lag 2, n=82 for lag 3, n=81 for lag 4 and n=80 for lag 5.

A p value<0.0005 was established as the significance threshold after adjustment for multiple testing (Bonferroni correction, n=100 tests). Additionally, we determined a threshold of 1% change as clinical or biological relevant, thus, associations yielding less than 1% change were deemed non-significant.

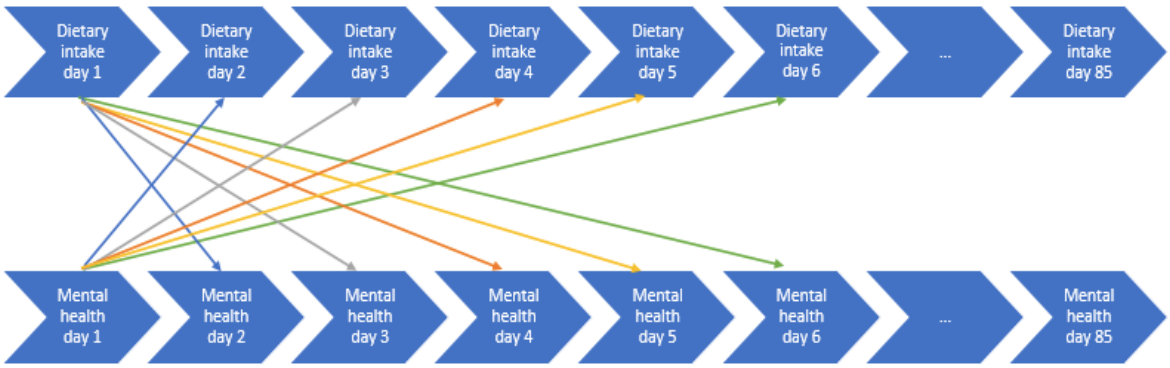
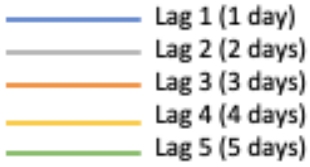


Figure 5.1. Cross-type lagged panel model for five lags



Dietary intake: fruit intake, vegetable intake, total fruit and vegetable intake, sugar consumption and overall self-rated dietary quality; Mental health: happiness, stress, low mood and sleep quality. The illustrated bidirectional associations at five different lags were repeated throughout 85 days, with the number of the repeated assessments being as follows: n=84 for lag 1, n=83 for lag 2, n=82 for lag 3, n=81 for lag 4 and n=80 for lag 5.

In addition to the primary and secondary objectives stated above, the tertiary objectives were i) to describe and to compare the adequacy of the diet of the cohort relative to dietary recommendations (5 A Day) and the Health Survey for England National Diet and Nutritional Survey (NDNS) data, ii) to report the changes in eating behaviours over the first 12 weeks, iii) to assess the linear associations between the independent and dependent variables using a cross-sectional analysis, and iv) to investigate the impact on changes in eating behaviour of selected variables (as predictors) such as initial self-reported mental health status, age, sex, BMI and deprivation status.

The other statistical methods employed in this study to meet the secondary and the tertiary objectives, alongside the primary statistical approach described above, are as follows. Descriptive statistics and frequencies were used to identify the sample characteristics. Correlation analyses were carried out among dietary variables and mental health variables in order to cross-check the quality of data. The predefined covariates,

namely, age, sex, BMI, IMD status and presence of previously diagnosed mental health issues were examined using linear and logistic regressions to understand whether they modulated dietary behaviours. In order to make comparisons between the pre-pandemic and during pandemic in dietary intake, baseline survey was taken as the pre-COVID-19 intake, and daily surveys were aggregated at individual level by taking the mean values of each participant to generate the during pandemic values. Paired t-test was used to compare the cohort's dietary intake to the NDNS data. Mean values of the variables of interest (both dietary and mental health) were aggregated for each individual (85 days), and correlation analyses (adjusted for age, sex, BMI, previously diagnosed mental health issue and IMD status) were conducted to investigate the linear cross-sectional associations among them.

The responses to the diet quality (Q4) and the sleep quality (Q8) questions were reversed to ease the data interpretation so that a higher score always reflected an 'improvement'. A composite variable named 'fruit and vegetable intake (FVI)' was created with the aim to investigate their unified impact in addition to the distinct effects of fruits and vegetables separately.

Missing data

The literature suggests that a missing data strategy should be applied if the rate of missing data is more than 10% (389). In our dataset, given the participants were asked to complete a 30-question survey every day for 12 weeks, we unsurprisingly had a higher missing data rate of 32.3%. Various techniques to deal with the missing data such as case deletion, mean imputation, multiple imputation and maximum likelihood were considered (390). In order to select the optimal strategy and to explore the missingness prior to the main analysis, several scenarios with different completion rates (in terms of the number of the days surveys were completed) were investigated. Then, the mean values of primary interest for dietary variables (fruits and vegetables) were compared for each of those scenarios (Table 5.1).

Table 5.1. Numbers of days and participants at different completion rates, with average fruit and vegetable intakes

Completion rate	Days completed	Participant number	Missing data rate (%)	Fruit intake (Mean ± SD)	Vegetable intake (Mean ± SD)	FVI (Mean ± SD)
Whole dataset	Any (0-85)	992	32.3	2.11 ± 1.54	2.91 ± 1.62	5.02 ± 2.40
90%	≥ 77	475	2.4	2.22 ± 1.24	2.98 ± 1.22	5.20 ± 2.40
80%	≥ 68	567	4.5	2.18 ± 1.55	2.95 ± 1.62	5.12 ± 2.39
50%	≥ 43	679	9.8	2.14 ± 1.54	2.93 ± 1.62	5.07 ± 2.39
20%	≥ 17	809	19.0	2.12 ± 1.54	2.91 ± 1.62	5.03 ± 2.40

Intakes were presented as Mean ± Standard Deviation (SD) and represent portions per day. FVI: Fruit and vegetable intake.

Because of the dearth of consensus regarding the handling of missing data in the published literature, we had in-depth discussions within the team (including an expert in EMA studies and a statistician) and reached the consensus to set a minimum completion threshold of 50% of days for inclusion (n=679). Thus, the rate of missing data dropped below 10%, being 9.8% (Table 4.1). The literature suggests that if the missing data rate is below 5%, it is negligible, leaving the slice between 5-10% as a grey area (391). Although less than 10% missing data is unlikely to cause a substantial bias, in order to be fully robust in our approach we decided to implement the Full Information Maximum Likelihood (FIML) strategy as it is considered to be the best missing data technique for SEM (392).

As the final step, we checked the responses of those individuals (n=679) with at least overall 50% completion rate to the daily surveys in terms of all the dietary and mental wellbeing questions on a given day. If they answered all questions of interest, their data were marked as complete data. If they had a missing answer to any of the variables, it then marked as incomplete. Thus, the final completion was defined as at least 50% completion to the daily surveys and with all diet and mental health questions answered. Therefore, our final dataset used in the data analysis included 674 participants.

Outliers

The normal ranges for the dietary continuous variables were defined as 0-10 portions per day for fruits and vegetables, and 0-20 portions for high sugar foods, while

the self-rated diet quality variable already existed on a predefined scale of 1 to 5. The outliers detected in the entire dataset (n=992) and in the 50% thresholded dataset (n=679) were minimal and remained the same in both datasets (Table 5.2). Due to the minor outlier rate, many of which belonged to the same individuals, and the fact that the majority were just over the threshold of 10 portions per day for fruit and vegetables and 20 for sugar we decided to retain outliers in the analysis.

Table 5.2. Frequencies for outliers

	Whole dataset (n=992)			**Minimum 50% completion rate (n=674)**		
	Fruits	**Vegetables**	**High sugar foods**	**Fruits**	**Vegetables**	**High sugar foods**
11-15	7	15	NA	7	15	NA
16-20	0	0	NA	0	0	NA
21-25	0	0	3	0	0	3
26-30	0	0	2	0	0	2
31-35	0	0	1	0	0	1

The normal range is for fruits and vegetables '0-10 portions', and '0-20 times' for sugary foods.

NDNS data preparation

The NDNS is a rolling programme conducted by Public Health England and collects detailed data on the nation's dietary intake since 2008 (National Diet and Nutrition Survey - GOV.UK (www.gov.uk). The most up-to-date data are available from Years 9-11 (2016/2017-2018/9). It provides information on total energy intake, macro and micronutrient intakes and disaggregated food items including FVI (number of portions), fruit (not including juice) (grams), fruit juice (grams) and vegetables (grams). To create the variables for comparison with our current COVID-19 tracker data, amounts were converted into portions. Fruit juice was added to both fruits and FVI to make them comparable to our data as the relevant question in our survey counted fruit juice as part of the total fruit consumption. NDNS presents the data for age groups and sexes. We took the average of 19-64 years and 65+ years as our study had participants over 18 years old with no upper age limit. Table 5.3 below presents the NDNS data.

Table 5.3. The conversion of NDNS disaggregated food items into portions

	Original NDNS data				Converted versions				
Population	**Fruits (g/day)**	**Fruit juice (g/day)**	**Vegetables (g/day)**	**FVI (portions)**	**Fruits (portions)**	**Fruit juice (portions)**	**Total fruit* (portions)**	**Vegetables* (portions)**	**FVI* (portions)**
19-64 years	105 ± 109	34 ± 92	206 ± 136	4.3 ± 2.6	1.31 ± 1.36	0.23 ± 0.61	1.54 ± 1.97	2.58 ± 1.70	4.12 ± 3.67
65+ years	123 ± 103	35 ± 73	183 ± 110	4.3 ± 2.4	1.54 ± 1.29	0.23 ± 0.49	1.77 ± 1.78	2.29 ± 1.38	4.06 ± 3.16
Average	114 ± 106	35 ± 83	195 ± 124	4.3 ± 2.5	1.43 ± 1.33	0.23 ± 0.56	1.66 ± 1.89	2.43 ± 1.55	4.09 ± 3.44

Data presented as mean ± standard deviation. FVI: Fruit and vegetable intake. Serving sizes used to convert amounts into number of portions: 80 grams of fruits and vegetables and 150 g fruit juice equal to one portion. *Final variables to be included in the comparison analysis

5.3. Results

5.3.1. Sample characteristics

The baseline demographic characteristics of the sample are presented in Table 5.4. Overall, 674 people completed at least 43 of the possible 85 daily surveys with complete answers to the dietary and mental wellbeing questions (minimum 50% completion rate). The mean age of the cohort was 48.9 years. The majority of participants (59.7%) were middle-aged (30 to 59 years), female (73.4%), from white ethnic background (96.7%) and married (52.7%). Approximately 60% of participants were employed (either self-employed or employed by others), of which nearly half (44.2%) held managerial/professional jobs. Nearly one fifth (17%) of the group earned less than the minimum living wage (£1500/month) and more than a quarter were living in the Index of Multiple Deprivation (IMD) quintiles 1 and 2 (most deprived). Regarding health status at baseline, the average body mass index (BMI) of the population was 27.3 kg/m^2, with almost 60% being overweight or obese. 5% reported mental health issues and around a third (31.6%) reported that they were either at increased risk (according to mainstream advice) or at very high risk (contacted by NHS to be informed) of COVID-19.

Table 5.4. The baseline characteristics of the study cohort

Characteristic	**Mean ± SD**	**Number (n)**	**Percentage (%)**
Age (years)	48.9 ± 14.9	NA	NA
Age groups (n=672)			
18-29	NA	93	13.8
30-59		401	59.7
60+		178	26.5
Sex (n=670)			
Female	NA	492	73.4
Male		178	26.6
Ethnicity (n=673)			
White	NA	651	96.7
Mixed/multiple ethnic backgrounds		11	1.6
Asian/Asian British		6	0.9
Black/African/Caribbean/Black British		4	0.6
Any other		1	0.1
Marital status (n=674)			
Single	NA	134	19.9
Co-habiting		95	14.1
Civil partnership		5	0.7
Married		355	52.7

Divorced		62	9.2
Widowed		23	3.4
Employment status (n=674)			
Not working (student/home carer/retired)	NA	172	25.5
Never worked or long term unemployed		2	0.3
Unemployed and looking for work, not due to COVID-19		12	1.8
Out of work, furloughed or given leave of absence, due to COVID-19		66	9.8
Unable to work due to sickness or disability		18	2.7
Employed		350	51.9
Self-employed/freelance		54	8.0
Occupation group (n=404)			
Routine and manual occupations	NA	13	1.9
Intermediate occupations		93	13.8
Managerial/professional occupations		298	44.2
Net household income (n=601)			
Less than £1500 (minimum wage)	NA	115	17.0
£1500-£2999		252	37.3
£3000-£4999		181	26.9
More than £5000		53	7.9
Index of Multiple Deprivation (IMD) quintile (1=most deprived) (n=662)			
1	NA	76	11.5
2		104	15.4
3		165	24.9
4		148	22.4
5		169	25.5
Body Mass Index (BMI) (kg/m^2)	27.3 ± 6.9	NA	NA
BMI classification (n= 669) *			
Underweight (<18.5)	NA	13	1.9
Normal weight (18.5-24.9)		272	40.7
Overweight (25.0-29.9)		213	31.8
Obesity class 1 (30.0-34.9)		108	16.1
Obesity class 2 (35.0-39.9)		33	4.9
Obesity class 3 (>40)		30	4.5
Mental health issue (n=674)			
Yes	NA	33	4.9
No		641	95.1
COVID-19 risk groups (n=674) **			
No increased risk	NA	461	68.4
Increased risk		163	24.2
Very high risk		50	7.4

Descriptive statistics were used to explore the population characteristics. SD: Standard deviation. The missing data for the relevant characteristics are as follows; n=2 for age, n=4 for sex, n=1 for ethnicity, n=73 for net household income, n=12 for IMD status and n=5 for BMI status. Occupation group does not have any missing data as it is consistent with the total number of 'employed and self-employed' individuals stated in the row above.

* The National Institute for Health and Care Excellence classification was used (393).

** Public Health England was taken as reference.

5.3.2. Correlations between outcomes

Associations between primary and secondary variables, namely, FVI to fruits, vegetables, high sugar and diet quality, and happiness to low mood, stress and sleep quality were assessed. FVI was positively correlated with diet quality, and negatively correlated with sugar intake (Table 5.5). Happiness was positively correlated with sleep quality and inversely associated with low mood and stress (Table 5.6).

Table 5.5. Correlations between fruit and vegetable intake and other dietary variables in 674 participants from the COVID-19 tracker study at baseline

	Fruits β **(95% CI)**	**Vegetables** β **(95% CI)**	**Sugar** β **(95% CI)**	**Diet quality** β **(95% CI)**
FVI	0.805 (0.777, 0.830) **	0.777 (0.745, 0.805) **	-0.117 (-0.191, -0.042) *	0.484 (0.424, 0.540) **

FVI: Fruit and vegetable intake. FVI was the primary dietary variable. β: Correlation coefficient; CI: Confidence Interval; *: $p < 0.005$; ** $p < 0.001$.

Table 5.6. Correlations between self-reported happiness and other mood outcomes in 674 participants from the COVID-19 tracker study at baseline

	Low mood β **(95% CI)**	**Stress** β **(95% CI)**	**Sleep quality** β **(95% CI)**
Happiness	-0.771 (-0.800, -0.738) **	-0.638 (-0.681, -0.591) **	0.565 (0.511, 0.614) **

Happiness was the primary mental health variable. β: Correlation coefficient; CI: Confidence Interval; *: $p < 0.005$; ** $p < 0.001$.

5.3.3. The predictors of dietary behaviours

Age was the most significant predictor of all dietary variables followed by BMI. Sex and mental health status predicted overall diet quality, but not individual food components. All dietary behaviours were independent of IMD status (Table 5.7).

Table 5.7. The predictors of dietary behaviours

	Age β (95% CI)	Sex β (95% CI)	BMI β (95% CI)	Mental health status β (95% CI)	IMD status β (95% CI)
FVI	0.034** (0.025,0.043)	-0.078 (-0.389, 0.233)	-0.039** (-0.058, -0.019)	-0.531 (-1,158, 0.096)	0.069 (-0.034, 0.171)
Fruit	0.024** (0.018-0.030)	-0.050 (-0.250, 0.150)	-0.014* (-0.017, -0.002)	-0.158 (-0.562, 0.246)	0.025 (-0.041, 0.091)
Vege-table	0.010** (0.004, 0.016)	-0.028 (-0.225, 0.168)	-0.025** (-0.037, -0.012)	-0.373 (-0.770, 0.023)	0.044 (-0.021, 0.108)
Sugar	-0.023** (-0.029, -0.017)	0.167 (-0.032, 0.367)	0.022** (0.009, 0.034)	0.226 (-0.177, 0.628)	-0.036 (-0.102, 0.029)
Diet quality	0.014** (0.010, 0.017)	-0.125* (-0.238, -0.011)	-0.024** (-0.032, -0.017)	-0.274* (-0.503, -0.045)	0.021 (-0.016, 0.058)

BMI: Body Mass Index; IMD: Index of Multiple Deprivation; CI: Confidence Interval; FVI: Fruit and vegetable intake. β: Unstandardised coefficient; *: p value< 0.05; ** p < 0.001 (regression analysis).

5.3.4. Changes in dietary behaviours, and their comparisons to the NDNS

Fruit, vegetable, and high sugar food intakes and self-rated diet quality were lower during the first lockdown compared with pre lockdown. The largest reduction among the original daily questions was seen in self-rated diet quality which was reported to be lower by approximately 15%. The FVI was still over 5 portions a day post-pandemic (5.08 ± 2.38) despite the decreases compared to pre pandemic levels (5.69 ± 2.41) (Table 5.8).

Table 5.8. Dietary behaviour comparison in UK adults between before the COVID-19 pandemic and the first 12 weeks of the COVID-19 lockdown (n=674)

Dietary behaviour	Pre-COVID 19 (Mean ± SD)	During COVID 19 (Mean ± SD)	Difference (95% CI)
Total FVI (portions)	5.69 ± 2.41	5.04 ± 1.83	-0.65 (-0.66, -0.64)
Fruits (portions)	2.49 ± 1.51	2.11 ± 1.19	-0.38 (-0.38, -0.37)
Vegetables (portions)	3.20 ± 1.52	2.93 ± 1.12	-0.27 (-0.28, -0.27)
High sugar food (times)	1.97 ± 1.41	1.92 ± 1.20	-0.06 (-0.06, -0.05)
Self-rated diet quality (1-5)	3.24 ± 0.95	2.77 ± 0.69	-0.47 (-0.48, -0.47)

Differences in means were calculated. Baseline survey served for the Pre-COVID 19 values; during COVID 19 were obtained by aggregating the mean values of daily surveys of 12 weeks during the first lockdown period. SD: Standard Deviation; CI: Confidence Interval, Lower - Upper Bounds; FVI: Fruit and vegetable intake.

Pre- and during pandemic FVI was also compared to national FVI using NDNS data (Table 5.9). Despite decreased consumption of fruits and vegetables of the present study's cohort relative to pre pandemic, it was still higher than the UK averages reported in the NDNS.

Table 5.9. Dietary behaviour comparison in UK adults between before the COVID-19 pandemic and the first 12 weeks of the COVID-19 lockdown (n=674)

Dietary behaviour	NDNS intake	Pre-COVID vs NDNS*	During-COVID vs NDNS*
Fruits	1.66 ± 1.89	0.83 (-2.88, 4.53)	0.45 (-3.25, 4.16)
Vegetables	2.43 ± 1.55	0.77 (-2.27, 3.81)	0.50 (-2.54, 3.53)
Total FVI	4.09 ± 3.44	1.60 (-5.14, 8.34)	0.95 (-5.79, 7.69)

*Pre pandemic (baseline) vs during pandemic (aggregated mean values of the 12 weeks lockdown period, March-June 2020) were compared to NDNS data using mean differences, presented as the Mean ± Standard Deviation. NDNS: National Diet and Nutritional Survey, Years 9-11 (2016/2017-2018/9) were used. FVI: Total fruit and vegetable intake.

5.3.5. Cross-sectional associations between dietary behaviours and mental wellbeing

Fruits and vegetable intake, either separately or together, were not correlated with mental health outcomes. Conversely, high sugar intake was negatively correlated with happiness, and positively correlated with low mood and stress. Self-reported diet quality was associated with all mental health variables, happiness, low mood, stress and sleep quality. The largest correlations were observed between diet quality and sleep quality, and diet quality and happiness (Table 5.10).

Table 5.10. Correlations between dietary intake and mental health

	Happiness β (95% CI)	Low mood β (95% CI)	Stress β (95% CI)	Sleep quality β (95% CI)
FVI	0.069 (-0.018, 0.154)	-0.005 (-0.085, 0.083)	-0.012 (-0.090, 0.069)	0.049 (-0.025, 0.124)
Fruits	0.071 (-0.006, 0.147)	0.007 (-0.069, 0.086)	-0.019 (-0.094, 0.060)	0.050 (-0.025, 0.121)
Vegetables	0.036 (-0.054, 0.119)	-0.016 (-0.100, 0.069)	0.000 (-0.082, 0.083)	0.026 (-0.045, 0.103)
Sugar	-0.099 (-0.188, -0.030) *	0.083 (0.006, 0.166) *	0.080 (0.007, 0.164) *	-0.055 (-0.126, 0.013)
Diet quality	0.366 (0.299, 0.435) **	-0.228 (-0.299, -0.151) **	-0.206 (-0.282, -0.127) **	0.387 (0.309, 0.462) **

Correlation analyses were run using the average data of 85 days. The model was adjusted for age, sex, BMI, IMD and previously diagnosed mental health issues. β: Pearson correlation coefficient; CI: Confidence Interval; FVI: Fruit and vegetable intake; *p <0.05 and **0<0.001.

5.3.6. Lagged associations between dietary behaviour and mental health status

In total, 100 bidirectional associations (5 dietary variables x 4 mental health variables x 5 lags) were examined. More specifically, the association of each dietary variable (FVI, fruit, vegetable, sugar intake and diet quality) with each mental health variable (happiness, low mood, stress and sleep quality) at lags 1 to 5 were analysed (Tables 5.11 and 5.12).

There was no significant association between FVI and happiness at any of the lags. Diet quality was positively associated with sleep quality at all lags, being linked with 1,7% improvement at lag 1 (β=0.066, 95% CI: 0.059-0.073) (Figure 5.2a), 1.6% improvement at lag 2 (β=0.064, 95% CI: 0.061-0.071), and 1.7% improvements at lag 3 (β=0.068, 95% CI: 0.061, 0.075), lag 4 (β=0.064, 95% CI: 0.059-0.074) and lag 5 (β=0.069, 95% CI: 0.062-0.076) (Figure 5.2c) (Table 5.11). Similarly, sleep quality was linked with 1.3% improvements with diet quality at all lags as follows; lag 1 (β=0.064, 95% CI: 0.054-0.073) (Figure 5.2b), lag 2 (β=0.063, 95% CI: 0.054-0.073), lag 3 (β=0.066, 95% CI: 0.056-0.075), lag 4 (β=0.064, 95% CI: 0.054-0.074) and lag 5 (β=0.064, 95% CI: 0.054-0.074) (Figure 5.2d) (Table 5.12). No other significant

associations were evident between other dietary variables (FVI, fruits, vegetables, and high sugar) and other mental health variables (happiness, stress and low mood).

Table 5.11. Associations of dietary variables to mental health from lag 1 to lag 5

		Happiness (0-10)	Low mood (1-5)	Stress (1-5)	Sleep quality (1-4)
	Lags	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
FVI (0-20)	1 day	-0.008 (-0.013, -0.003)	0.005 (0.002, 0.007)*	0.004 (0.002, 0.007)	0.002 (-0.001, 0.005)
	2 days	-0.007 (0.012, -0.002)	0.004 (0.002, 0.007)	0.004 (0.001, 0.007)	-0.001 (0.003, 0.002)
	3 days	-0.010 (-0.015, -0.005)*	0.006 (0.004, 0.009)*	0.004 (0.001, 0.007)	-0.000 (-0.003, 0.003)
	4 days	-0.011 (-0.016, -0.005)*	0.007 (0.004, 0.009)*	0.002 (-0.000, 0.005)	-0.001 (-0.004, 0.002)
	5 days	-0.011 (-0.016, -0.005)*	0.006 (0.003, 0.008)*	0.003 (0.000, 0.006)	-0.000 (-0.003, 0.003)
Fruit intake (0-10)	1 day	-0.001 (-0.008, 0.006)	0.006 (0.002, 0.010)	0.011 (-0.005, 0.026)	0.005 (0.001, 0.009)
	2 days	0.009 (0.001, 0.017)	0.004 (-0.000, 0.008)	-0.001 (-0.005, 0.004)	0.004 (-0.001, 0.008)
	3 days	0.005 (-0.003, 0.013)	0.005 (0.001, 0.009)	-0.001 (-0.006, 0.004)	0.005 (0.000, 0.009)
	4 days	0.002 (-0.006, 0.011)	0.007 (0.002, 0.011)	-0.001 (-0.005, 0.004)	0.003 (-0.001, 0.007)
	5 days	0.002 (-0.006, 0.010)	-0.011 (-0.016, -0.005)*	0.000 (-0.004, 0.005)	0.003 (-0.001, 0.008)
Vegetable intake (0-10)	1 day	-0.017 (-0.024, -0.010)*	0.003 (-0.000, 0.007)	0.007 (0.002, 0.011)	-0.000 (-0.004, 0.004)
	2 days	-0.024 (-0.031, -0.017)*	0.006 (0.003, 0.010)	0.009 (0.005, 0.013)*	-0.005 (-0.008, -0.001)
	3 days	-0.026 (-0.034, -0.019)*	0.009 (0.005, 0.013)*	0.010 (0.005, 0.015)*	-0.005 (-0.009, -0.001)
	4 days	-0.024 (-0.032, -0.016)*	0.008 (0.004, 0.013)*	0.006 (0.001, 0.011)	-0.004 (-0.009, -0.000)
	5 days	-0.025 (-0.032, -0.017)*	0.007 (0.003, 0.011)	0.007 (0.003, 0.011)	-0.004 (-0.008, 0.000)
Sugar intake (0-20)	1 day	-0.016 (-0.023, 0.009)*	0.009 (0.005, 0.014)	0.007 (0.003, 0.012)	-0.006 (-0.010, -0.002)
	2 days	-0.014 (-0.022, -0.005)	0.007 (0.02, 0.012)	0.009 (0.005, 0.014)*	-0.008 (-0.013, -0.004)*
	3 days	-0.017 (-0.025, -0.009)*	0.009 (0.004, 0.013)	0.010 (0.005, 0.015)*	-0.007 (-0.011, -0.003)
	4 days	-0.014 (-0.023, -0.005)	0.006 (0.001, 0.011)	0.009 (0.005, 0.014)*	-0.008 (-0.012, -0.003)*
	5 days	-0.012 (-0.022, -0.003)	0.005 (-0.000, 0.010)	0.009 (0.004, 0.013)*	-0.008 (-0.013, -0.004)*
Diet quality (1-5)	1 day	0.045 (0.033, 0.058)*	-0.021 (-0.028, -0.015)*	-0.014 (-0.021, -0.007)*	**0.066 (0.059, 0.073) (1,7%)**
	2 days	0.054 (0.039, 0.068)*	-0.021 (-0.029, -0.014)*	-0.022 (0.029, -0.014)*	**0.064 (0.057, 0.071) (1.6%)**
	3 days	0.054 (0.040, 0.068)*	-0.017 (-0.025, -0.009)*	-0.023 (-0.031, -0.015)*	**0.068 (0.061, 0.075) (1.7%)**
	4 days	0.053 (0.039, 0.067)*	-0.018 (-0.025, -0.010)*	-0.030 (-0.037, -0.022)*	**0.067 (0.059, 0.074) (1.7%)**

5 days	0.049 (0.035, 0.063)*	-0.017 (-0.024, -0.010)*	-0.029 (-0.037, -0.020)*	**0.069 (0.062, 0.076) (1.7%)**

FVI: Total fruit and vegetable intake. β: Coefficient. *Statistically significant with Bonferroni corrected p value<0.0005, but not clinically meaningful with effect size less than 1%. Results that have a significant p value (<0.0005) and clinically meaningful effect size (>1%) are highlighted in bold. Structured Equational Modelling was used to test associations of dietary variables to mental health. The model was adjusted for age, sex, body mass index (BMI), Index of Multiple Deprivation (IMD) status and previously diagnosed mental health issues. Effect sizes (percentage changes) were calculated using coefficients for significant associations and presented in brackets if they were greater than 1%.

Table 5.12. Associations of mental health to dietary behaviours from lag 1 to lag 5

		FVI	Fruit	Vegetable	Sugar	Diet quality
	Lags	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Happiness (0-10)	1 day	0.003 (0.005, 0.011)	0.006 (0.001, 0.011)	0.001 (-0.005, 0.007)	-0.008 (-0.013, -0.002)	0.038 (0.034, 0.041)*
	2 days	0.002 (-0.007, 0.011)	0.007 (0.001, 0.014)	-0.002 (-0.008, 0.005)	-0.008 (-0.014, -0.003)	0.040 (0.036, 0.044)*
	3 days	-0.008 (-0.018, 0.002)	0.007 (0.001, 0.013)	-0.010 (-0.017, -0.004)	-0.008 (-0.014, -0.003)	0.039 (0.035, 0.043)*
	4 days	-0.007 (-0.016, 0.002)	0.007 (0.001, 0.013)	-0.010 (-0.017, -0.003)	-0.012 (-0.019, -0.006)*	0.040 (0.036, 0.044)*
	5 days	-0.004 (-0.013, 0.006)	0.007 (0.001, 0.013)	-0.007 (-0.013, 0.000)	-0.009 (-0.015, -0.003)	0.038 (0.034, 0.042)*
Low mood (1-5)	1 day	0.021 (0.003, 0.040)	0.012 (0.000, 0.023)	0.002 (-0.013, 0.017)	0.008 (-0.005, 0.021)	-0.035 (-0.044, -0.027)*
	2 days	0.029 (0.009, 0.049)	0.012 (-0.001, 0.025)	0.008 (-0.006, 0.023)*	0.016 (0.004, 0.029)	-0.039 (-0.048, -0.029)*
	3 days	0.055 (0.033, 0.077)*	0.013 (-0.001, 0.027)	0.033 (0.018, 0.048)*	0.010 (-0.004, 0.024)	-0.030 (-0.040, -0.020)*
	4 days	0.053 (0.031, 0.076)*	0.017 (0.003, 0.031)	0.028 (0.013, 0.043)	0.020 (0.005, 0.034)	-0.034 (-0.045, -0.024)*
	5 days	0.044 (0.021, 0.066)*	-0.004 (-0.013, 0.006)	0.019 (0.004, 0.034)	0.015 (0.002, 0.029)	-0.032 (-0.042, -0.023)*
Stress (1-5)	1 day	-0.001 (-0.019, 0.018)	0.003 (-0.017, 0.024)	-0.003 (-0.017, 0.011)	0.010 (-0.004, 0.024)	-0.038 (-0.047, -0.029)*
	2 days	0.018 (-0.005, 0.040)	-0.005 (-0.020, 0.010)	0.017 (0.002, 0.031)	0.019 (0.005, 0.032)	-0.037 (-0.047, -0.027)*
	3 days	0.027 (0.008, 0.047)	-0.006 (-0.020, 0.008)	0.027 (0.012, 0.042)*	0.022 (0.008, 0.037)	-0.031 (-0.040, -0.021)*
	4 days	0.034 (0.012, 0.056)	0.003 (-0.012, 0.019)	0.026 (0.011, 0.041)	0.027 (0.014, 0.041)*	-0.029 (-0.038, -0.020)*
	5 days	0.034 (0.013, 0.055)	0.002 (-0.012, 0.017)	0.026 (0.011, 0.041)	0.017 (0.003, 0.032)	-0.022 (-0.032, -0.012)*
Sleep quality (1-4)	1 day	-0.001 (-0.022, 0.021)	0.006 (-0.008, 0.019)	-0.001 (0.017, 0.015)	-0.005 (-0.018, 0.008)	**0.064 (0.054, 0.073) (1.3%)**
	2 days	-0.011 (-0.035, 0.013)	0.003 (-0.011, 0.017)	-0.009 (-0.011, 0.017)	-0.006 (-0.020, 0.008)	**0.063 (0.054, 0.073) (1.3%)**
	3 days	-0.013 (-0.035, 0.009)	0.009 (-0.006, 0.024)	-0.016 (-0.032, 0.001)	-0.005 (-0.019, 0.009)	**0.066 (0.056, 0.075) (1.3%)**
	4 days	-0.019 (-0.042, 0.003)	0.009 (-0.005, 0.024)	-0.024 (-0.043, -0.004	-0.012 (-0.026, 0.003)	**0.064 (0.054, 0.074) (1.3%)**
	5 days	-0.003 (-0.025, 0.020)	0.011 (-0.004, 0.027)	-0.008 (-0.025, 0.009)	0.003 (-0.012, 0.017)	**0.064 (0.054, 0.074) (1.3%)**

FVI: Total fruit and vegetable intake. β: Coefficient. *Statistically significant with Bonferroni corrected p value<0.0005, but not clinically meaningful with effect size less than 1%. Results that have a significant p value (<0.0005) and clinically meaningful effect size (>1%) are highlighted in bold. Structured Equational Modelling was used to test associations of dietary variables to mental health. The model was adjusted for age, sex, body mass index (BMI), Index of Multiple Deprivation (IMD)

status and previously diagnosed mental health issues. Effect sizes (percentage changes) were calculated using coefficients for significant associations and presented in brackets if they were greater than 1%.

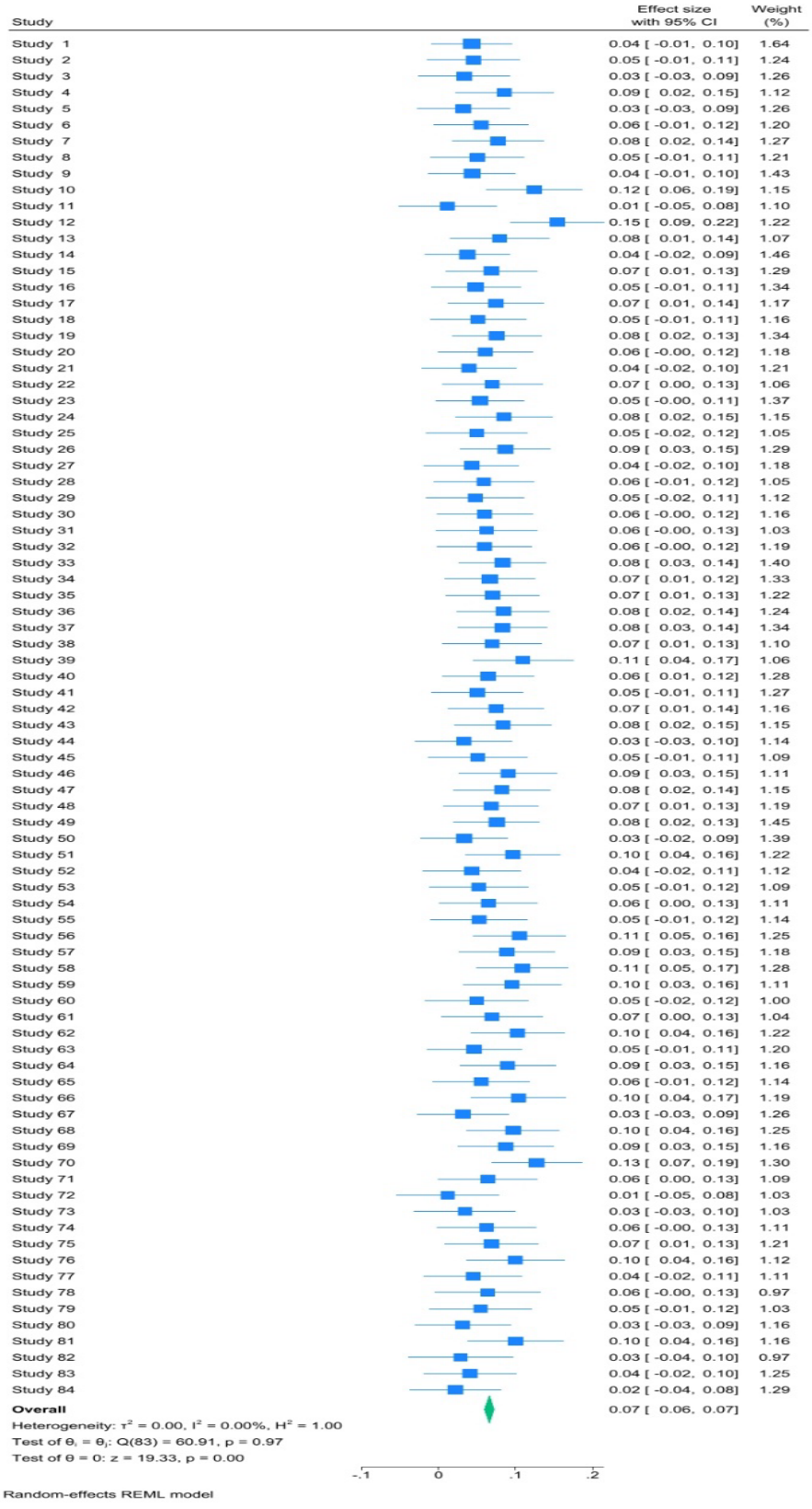
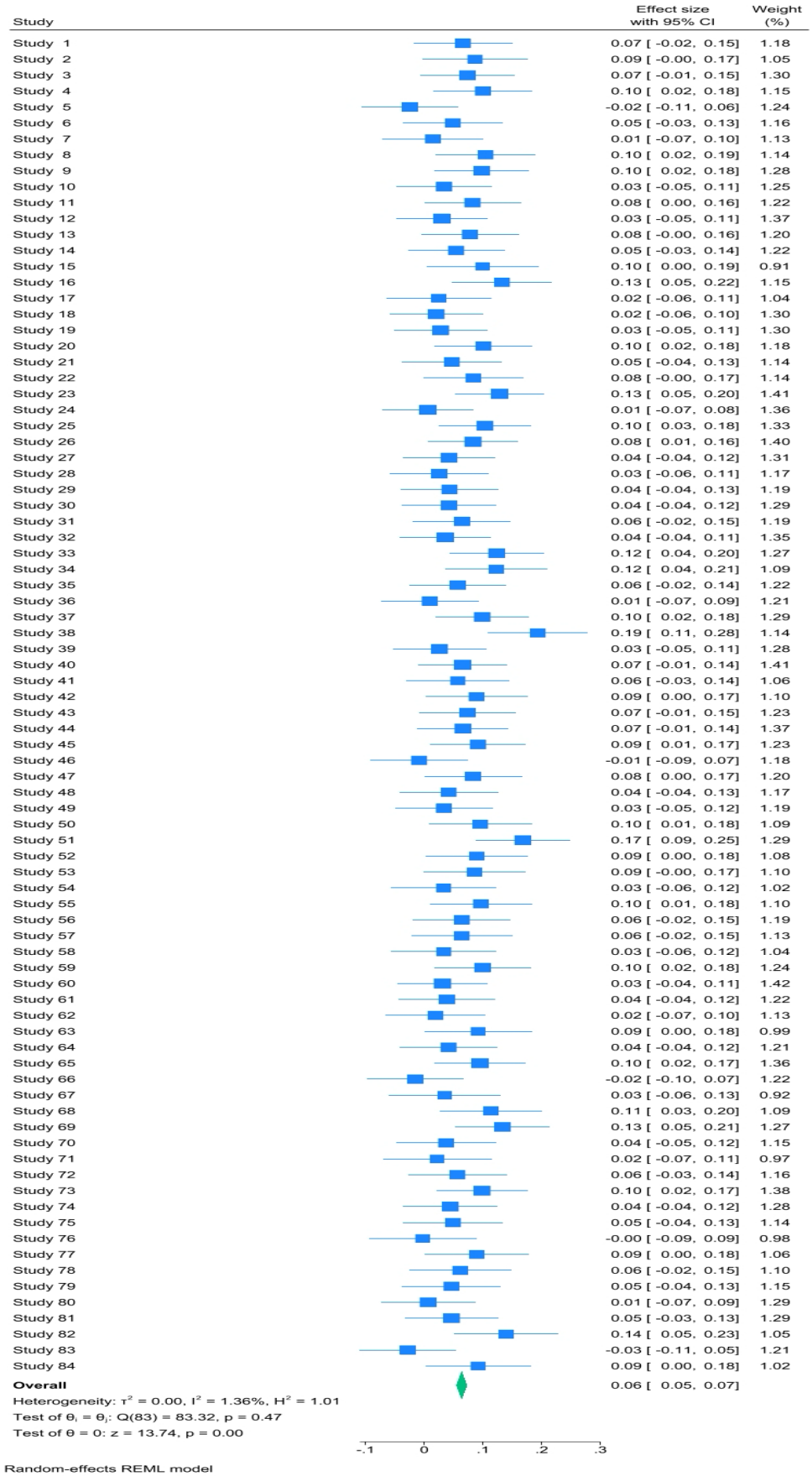


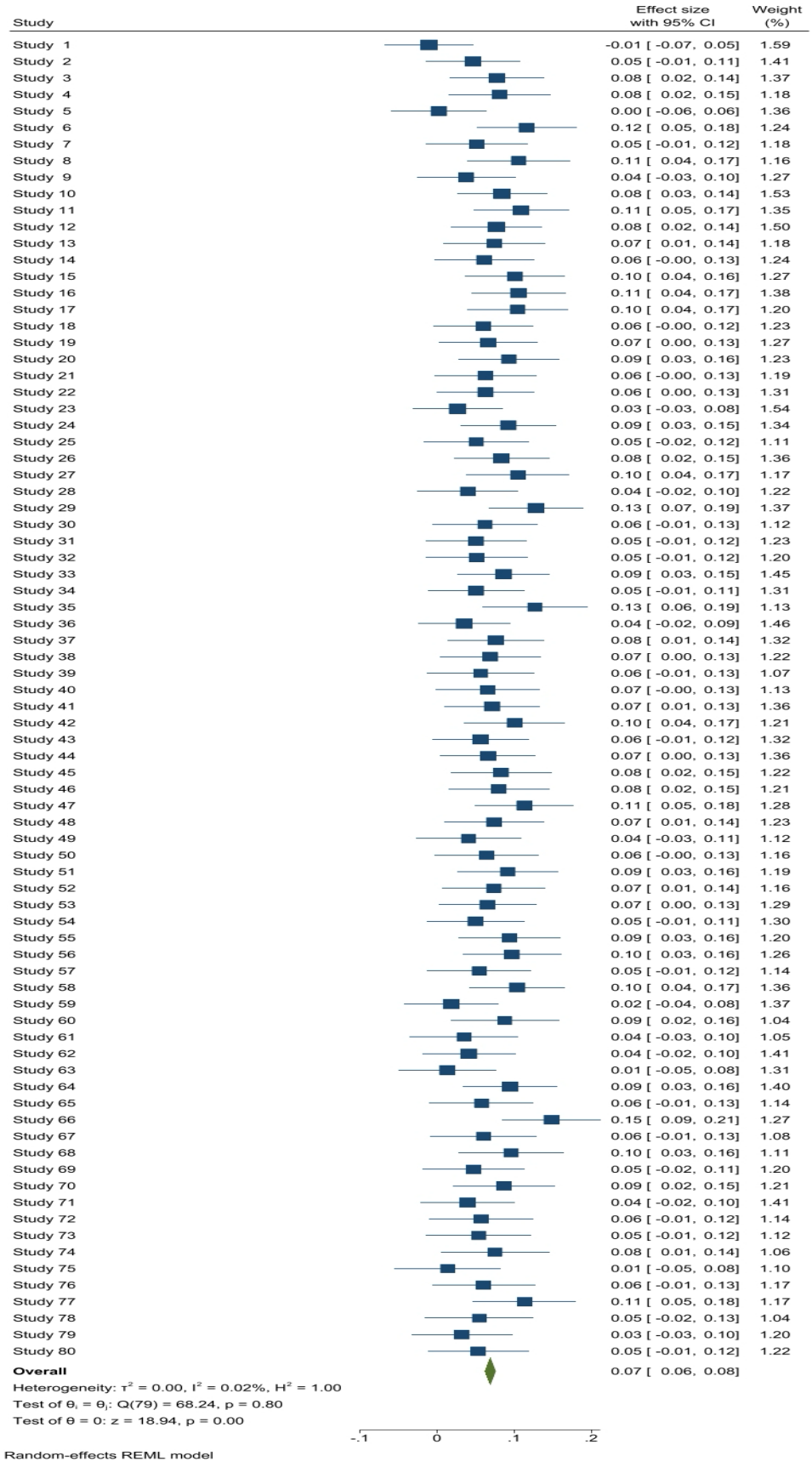
Figure 5.2. Bidirectional effects of diet quality and sleep quality on each other

5.2.a. Diet quality on sleep quality at lag 1 for each of the 85 data collection days Overall effect was calculated by averaging daily effects.



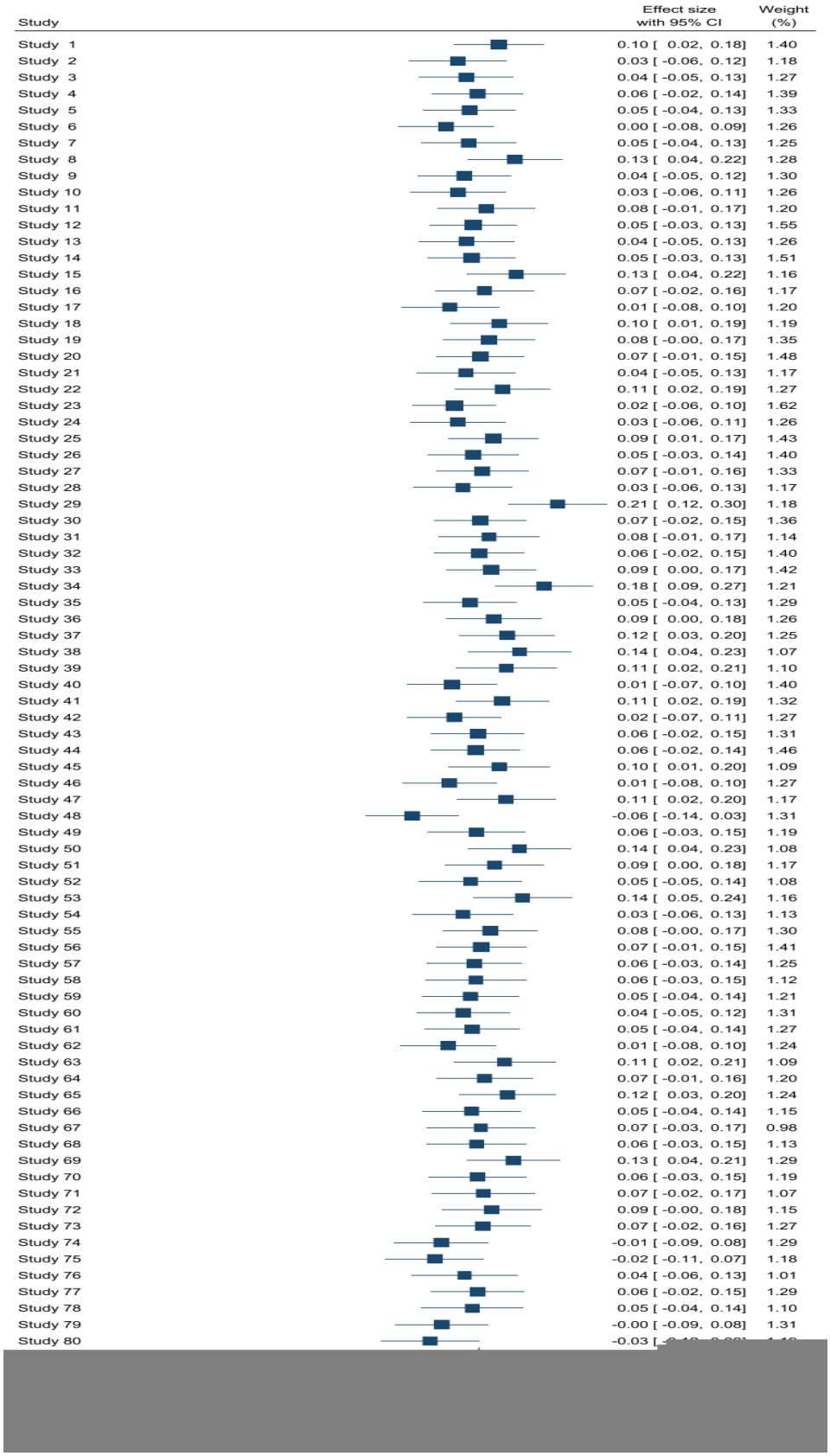
5.2.b. Sleep quality on diet quality at lag 1

Overall effect was calculated by averaging daily effects.



5.2.c. Diet quality on sleep quality at lag 5

Overall effect was calculated by averaging daily effects.



5.2.d. Sleep quality on diet quality at lag 5

Overall effect was calculated by averaging daily effects.

5.4. Discussion

The present study investigated the bidirectional relationships between five dietary behaviours, namely, fruit intake, vegetable intake, total FVI, sugar intake and subjective diet quality and four aspects of mental health, respectively, happiness, low mood, stress and sleep quality over five time-lags, one to five days, using a data collected through EMA during the first lockdown of the COVID-19 pandemic. This study applied a novel analysis approach by integrating five different time-lags to provide insight into the timing of short-term associations between diet and mental health outcomes. The findings suggest that diet quality and sleep quality are positively and consistently associated with each other in the short-term, over one to five days. Notably, the effect sizes of our findings were small, with the coefficients ranging from 0.063 to 0.069 (related to percentage changes between 1.3% and 1.7%).

Our systematic review suggested that a MDP as a whole dietary pattern can improve mood in up to 10 days (196). The current analysis did not indicate any associations between dietary intake and happiness, low mood or stress in contrast to our primary hypothesis and the literature. For example, a study surveyed university students from 28 countries from Asia, Africa and America (n= 18,522, age (mean ± SD) of 20.9 ± 2.4) and found that FVI was in a linear association with happiness and negatively linked with depression, with 6 portions of FVI per day provided the largest effect size (394) . Furthermore, longitudinal data analysis using the "Household, Income and Labour Dynamics in Australia (HILDA)", evaluated the relationships between fruits and vegetables with mental wellbeing of 12,385 individuals (395). The results demonstrated improved happiness, life satisfaction and wellbeing in association with fruits and vegetables consumption in 24 months with a peak effect at 8 portions/day (395). A UK study including nearly 80,000 individuals looked at the associations between FVI consumption and wellbeing, and they found positive linear associations in individuals consuming 5-8 portions of FVI daily (396). These chronic studies suggest 6-8 portions may be needed to see a mediating effect of FVI on mental health and the FVI of our cohort was 5.04 ± 1.83 (mean ± SD) (Table 8). In terms of acute studies, a cross-over RCT examining the postprandial effects of flavonoids through a blueberry drink in 21 adults

(18 to 21 years old) assessed mood by 'Positive and Negative Affect Schedule (PANAS)' and showed improved positive mood states with no decrease in negative mood states (397), suggesting the type of fruit consumed might be more important acutely and it may be easier to acutely meditate happiness than alleviating the symptoms of low mood and stress by means of FVI.

The potential links between eating and sleep quality and quantity have previously been reviewed (398), and evidence suggests that the composition of a diet and meal influences sleep both acutely and chronically (399). However, little empirical evidence exists. For example, a systematic review of 61 observational studies examining associations between FVI and mental health (published in 2020) reported that FVI improves mental wellbeing but also indicated that there was only one study examining the FVI and sleep quality, highlighting the research gap (400). "Personalized Responses to Dietary Composition Trial 1 (PREDICT)" study including 833 healthy adults (mean age of 46.2 years) investigated the determinants of morning alertness levels (401). Results indicated that longer sleep duration the night before and a balanced breakfast rich in carbohydrates influenced the morning alertness, of which the predictors were identified as happiness, older age, and sleep quality (401). In accordance with this, another study discussed that sleep quality could be promoted via carbohydrate quality and availability (399). In terms of the bidirectional relationships between diet quality and sleep quality, a methodologically similar study assessed sleep quality, night time eating behaviour and loss of control eating at 4 lags (lag durations were 6 months) in adolescents (11-17 years) (402). The results showed that higher night eating scores predicted poor sleep quality and loss of control eating at lag 1, 2 and 3; poorer sleep quality predicted night time eating at lag 1 and 3; and higher loss of control scores predicted higher night eating scores at wave 1 and 2 (402), showing several bidirectional associations between eating behaviour and sleep quality.

Similar to our study, Schultchen *et al.* examined the bidirectional relationships between stress and healthy eating (using a single-item scale) among 51 healthy university students (aged 19 to 29 years) (403). Data were collected using EMA with measurement frequency and durations six times/day assessing 2.5 hours lags alongside physical activity for seven days (403). They reported no effect of stress and affect with healthy eating,

whilst they found significant bidirectional associations with physical activity (403). Mason *et al.* looked at the acute (two hours) bidirectional associations between diet and mood ('affective') states among pregnant women who had low income using EMA of which the duration was four days, and the assessment frequency was 5 times/day. Women who had lower pre-pregnancy BMI, FVI and a better mood profile predicted each other (404). The authors concluded that the relationships between FVI and mood states were heavily dependent on BMI status among pregnant women (404). As we were interested in the link between dietary intake and mental health, we did not assess the bidirectional relationships of either dietary variable or mental health variables with each other. However, one study examining the daily bidirectional relationships between affect (mood) and sleep (duration, efficiency, quality) among 359 people with depression or past depression history or no depression using two-week EMA and objective (via actigraphy) and subjective (via diaries) sleep data (405). They found associations between self-reported sleep quality and mood on the same day (405).

The inverse significant associations we observed between sugar intake and mental health profiles are consistent with the literature. For example, Liao *et al.* assessed relationships of high fat high sugar (HFHS) and FVI with affective states (406). To do so, they implemented EMA structure with 2-hours lags over for a week among women (n=202) and the findings demonstrated that higher HFHS consumption was linked to sadness (406). Women who were overweight or obese also reported to have higher stress, but FVI and happiness were positively linked independent of weight status (406).

Regarding the dietary variables we utilised in our analysis and the fact that only the diet quality demonstrated significant associations may be explained by 'the superiority of whole dietary patterns over individual food items' due to synergistic effects of foods arising in whole diets (399). Furthermore, single-item overall diet quality question may be a better tool to capture self-reported dietary quality compared to individual food items (407), as individuals may have a more reliable understanding on overall dietary quality as it includes several elements, resulting in possible increased chance for participants to score it more accurately.

One potential explanation as to why only sleep quality was associated with dietary intake could be attributed to the nature of sleep. Sleeping is core to survival (408), thus may involve more direct pathways that can be easier to modulate mechanistically compared to mood-related factors. In other words, psychological factors (i.e. happiness, mood and stress) may be more complex and multifaceted, therefore they may not be physiologically as straightforward as sleep.

Change in eating behaviour between pre- and during pandemic, and NDNS data comparisons

Our study showed poorer dietary habits during the pandemic. This is consistent with the other similar studies conducted in both in the UK and in the other countries (374, 375, 378, 409). It is noteworthy that our baseline survey asked the questions with the phrase 'prior to the pandemic' which relies on longer term memory, whilst daily surveys demanded less memory skills. Therefore, the change in dietary behaviour derived from direct comparison between pre-pandemic and during-pandemic may not be of high-quality.

Regarding FVI consumption, UK public health policy promotes '5 A Day' campaign recommending at least 5 portions (400 grams) of FVI per day (410). The study cohort met the target both before and during the pandemic and consumed more fruits and vegetables than the NDNS population. It may be due to the difference between the dietary assessment methods used; the NDNS employed 4-day food diaries with estimated weights (411), whereas our study utilised isolated dietary questions which asked the number of the portions without weight estimation. Thus, NDNS is likely to have a higher quality data with higher accuracy.

Strengths:

Our study has several strengths. In terms of the study structure, our study duration (12 weeks/85 days) and sample size (n=674 participant) are superior compared to similar studies. The data collection method used, EMA, provides real time ambulatory assessment (412). Furthermore, four mental health questions assessed four separate

domains (both positive -happiness and sleep quality- and negative -low mood and stress-) as opposed to common literature which usually looks at one or two outcomes. Fruit and vegetable intakes were asked separately providing separate measures to differentiate them; besides we created a unified variable to see the composite effect likewise. Regarding statistical analysis method utilised, the number of the lags tested that were gradually increased with high number of repetitions, provided a thorough inspect on day-by-day effects. Besides, each association was tested bi-directionally which is novel.

Limitations:

We also have a number of limitations. First of all, the number of the significant associations were higher than expected that may be a result of repeated assessments over 80 observations, hence, clinically insignificant effects might have become statistically/mathematically significant. To correct for this, we corrected for multiple testing and applied a minimum of 1% effect size to ensure the results reported were statistically and biologically meaningful. Secondly, the scales used to assess mental health variables (happiness on 0-10; low mood and stress on 1-5 and sleep on 1-4) had different sizes, and we converted them into percentages to overcome the issue. However, it might still not be of great quality in terms of the comparisons as the wider scales can provide more precision. Third, the data were self-reported which is subject to reporting bias. Nonetheless, the correlation analyses (Table 5.5 and 5.6) demonstrated that the responses given were consistent supporting validity of the data.

Furthermore, the data were collected during the pandemic, therefore it reflected worsened dietary behaviours (of note, although the FVI was lower during the pandemic compared to the pre-pandemic levels, it was still above the 5-a-day recommendations (Table 5.8)) and amplified mental health complaints which may open the results to bias whether they would apply to normal/typical/regular circumstances and may restrict the generalisability of the findings. However, both dietary behaviour and mental health had worsened comparably, thus the effect size might have remained the same. Additionally, the fact that our data were collected during the pandemic may not be a 'limitation'. For instance, Schultchen *et al.* particularly selected exam period to collect their data assessing bidirectional associations between stress and healthy eating in order to ensure

considerable amount of stress was loaded to increase the quality of their results (403), hence, in our case the pandemic as a stress trigger could have served for that purpose (403, 413).

The study population lacked diversity (white ethnicity rate of 96.7%) and appeared to be an advantaged cohort compared to general public with approximately half of the participants (44.2%) stated that they had managerial/professional occupations (implying possible higher education) and 47.9% were living in upper IMD quintiles. This is a recognised limitation in the field of health research, where research volunteers tend to be from white ethnic and more affluent groups and therefore not fully representative of the UK population. For example, the UK Biobank is 94.6% white and more affluent than the general population (414). Lastly, we asked the sugar question as the number of the occasions a type of sugar snack was eaten rather than the amount (as per MEDAS questionnaire), therefore we could not compare it with the NDNS data and provide any precision rather than impact of sugar intake quantity.

Conclusion

To the best of our knowledge, this is the first study examining the short-term bidirectional relationships with five different lag durations between dietary intake and mental health using EMA methodology, and the longest study in terms of the study duration among similar studies. We found that sleep quality and diet quality are positively and bidirectionally related with each other with a consistent and significant effect lasting up to five days/lags, which we believe is a novel contribution to the literature. There was no significant relationship between individual food items (fruits, vegetables and sugar) and other mental health outcomes (happiness, stress and low mood).

5.5. C-19 Wellbeing Tracker study contributions

The C-19 study was planned and managed by Felix Naughton and Caitlin Notley, with daily nutrition questions added by Anne Marie Minihane and Amy Jennings. The data cleaning was done by Emma Ward. The research question for this analysis was developed by Latife Esgunoglu, Felix Naughton, Amy Jennings and Anne Marie

Minihane. The statistical analysis plan was generated by Latife Esgunoglu, Amy Jennings, Anne Marie Minihane and Felix Naughton. The statistical model for the primary analysis was developed by Mizanur Khondoker and performed by Latife Esgunoglu.

Chapter 6. General discussion

Due to the significance of mental health disorders and widely known health benefits of a MDP conferred in a long-term (Chapter 1), my hypothesis was that a MDP can improve mental wellbeing (mood, anxiety, cognition and sleep) in the short-term through biological mechanisms including increased brain perfusion, reduced inflammation and improved glucose control/insulin sensitivity (Figure 1.6).

6.1. Summary of main findings

We conducted the first systematic review of the short-term (up to and including 10 days) effects of a MDP on mood and cognition (Chapter 2), and found improved alertness, contentment and attention with a MDP compared to any control arm. The extensive search performed in 2020 formally identified the lack of research in the area despite the potential, with a second updated search in 2023 confirming the continuing validity of the research gap.

We designed the first short-term RCT conducted in individuals with existing mild-moderate depression and/or anxiety investigating acute, 24-hour and 5-day impacts of a MDP in comparison to a WD on brain health, particularly, mood, cognition, CBF and sleep, and investigating select underlying mechanisms (Chapter 3). MDP consumption improved mood at 24-hour and 5-days, alongside reduced variability in executive function and peripheral inflammation and increased cortisol levels at 5-days; acutely (24-hour) heightened insulin sensitivity; and led to higher MDP adherence after three months as a positive dietary behaviour change (Chapter 4).

As a change to the original thesis plan due to COVID-19 lockdown, we analysed the bidirectional short-term (up to five days) lagged associations between dietary intake (fruit, vegetable, sugar intakes and subjective overall diet quality) and mental health (happiness, low mood, stress and sleep) utilising an observational longitudinal data collected in the COVID-19 pandemic (Chapter 5). Significant relationships between overall diet quality and sleep quality were evident with effects lasting up to five days. We found no other associations in this cohort.

6.2. Overall discussion of the experimental chapters (Chapters 2 to 5)

The first systematic review on the impacts of whole dietary patterns on mood was published in 2019 and included a number of healthy dietary patterns, namely, "MDP, dietary approach to stop hypertension (DASH), vegetable-based, glycaemic load-based, ketogenic, zone and paleo diets", with no restriction on study type and duration (415). Only 18 studies (with four MDP studies) were identified with no consistent findings, highlighting the need for further studies to draw robust conclusions (415). Consequently, a narrative review (published in 2021) discussing the recent evidence regarding potential role of nutrition to prevent and to manage mental health disorders recommended that a MDP can help prevent depression and anxiety (416). The authors highlighted that this evidence was mainly retrieved from epidemiological studies, therefore, RCTs were needed to confirm efficacy and expand the knowledge on biological mechanisms (416). In 2021, Aucoin *et al.*'s review stated that the potential role of dietary interventions lack of evidence especially for those with current mental health disturbances as the rate of the studies involving those was reported to be only 10% (417). Thus, this PhD meets an important research gap in the field especially owing to its RCT component (Chapters 3 and 4).

This PhD project involved two quantitative chapters (Chapter 4, the MediMood results and Chapter 5, the C-19 longitudinal data analysis). The results from Chapter 5 favours the theory that dietary patterns as a whole are more effective to improve health status, potentially because of the synergistic effects of foods compared to single food items or isolated nutrients (418). The variety of foods consumed also has documented to confer more benefits on mental health (417). Similarly, Bhupathiraju *et al.* emphased not quantity but the diversity of fruits and vegetables play a significant role in inflammation reduction (419), which is consistent with our findings in MediMood where results from both chapters, since we the MediMood consisted of a wide range of fruits and vegetables in the MDP plan which potentially was associated with CRP levels (Chapter 4).

Furthermore, both MediMood RCT and C-19 analysis primarily aimed to assess 'healthy' foods, an overall MDP and total fruit and vegetable intake, respectively, on mood over five days. Coupled with the fact that these studies have different designs, and

analysed the extremes of dietary intake (MediMood) versus a continuum of habitual diet (C-19), the apparent differences in the findings are also likely attributable to the greater diversity of a MDP. Fruits and vegetables are composed of carbohydrates alongside fibre, with minimal fat content, whereas a MDP is abundant in MUFA and PUFA from olive oil and fish, along with other several bioactives such as phenolic acids, vitamins e.g. vitamin E and B12, and minerals such as selenium in oily fish. Therefore, it is highly likely that the high quality fat composition of a MDP contribute to its positive impact on brain health.

Regarding other potential mechanisms (in addition to those of mechanistic focus in Chapter 4) that mediated our results, altered tryptophan status may be involved. Tryptophan is a precursor of serotonin which is a neurotransmitter/hormone involves in mood, cognition and sleep regulation, and it is also linked with neuroinflammation, BDNF and gut microbiota (420, 421). As food enriched in a MDP such as white meat, nuts and bananas (422), are important dietary sources of tryptophan, and serotonin levels are set by the tryptophan availability, increased tryptophan may in part mediate the positive impact of a MDP on mood and fear (421, 423, 424). Dietary acid load (DAL) is another potential explanation how a MDP and WD influences mental and metabolic health differently as it is reported to deteriorate cardiometabolic health with heightened inflammation (425). Plant-based diets such as a MDP reduce DAL whereas WD is suggested to increase acid and thus cause metabolic acidosis, creating a challenge for the body (425). A systematic review reported worsened mental wellbeing and sleep status associated with high DAL (426).

Compared to prescribed medications and other dietary pattern interventions, a MDP also emerges as a safer approach to improve mental health. For instance, one-week ketogenic diet consumption compared to non-ketogenic diet adherers is reported to be associated with greater alertness, contentment and calmness and lowered stress, depression, anxiety and loneliness (427), with authors suggesting that it may be gamma-aminobutyric acid (GABA), a neurotransmitter, behind the improved mental wellbeing (427). The use of a combined version of Mediterranean ketogenic diets are also of interest targeting neuroinflammation (428), short-chain fatty acid production (429) and cerebral perfusion (430). Nonetheless, ketogenic diets are not compatible with national and global food and nutrient based nutrition recommendations and should be embarked upon under

the supervision of a doctor or dietitian due to its potential side effects such as diarrhoea, vomiting and fatigue (431), whereas no side effect of MDP has been reported, making it feasible for a wider application.

As highlighted by our systematic review findings (Chapter 2), there is a lack of consistency in MDP description. Although wine is a traditional element of a MDP, we decided to keep the wine consumption optional in MediMood for two reasons (Chapter 3). Firstly, we wanted the study to be inclusive of individuals who do not consume alcohol for any reason, thereby increasing the generalisability of our findings. Second, given the characteristics of our population and the comorbid links between alcohol use disorders, depression and anxiety (432), we did not want to mandate alcohol consumption for ethical reasons. The Global Burden of Disease study in 2016 recommended zero alcohol intake as the safe consumption limit that ensures prevention of any health loss (433). Consequently, Martinez-Gonzalez, a researcher involved in both PREDIMED and SUN studies, discussed the robust controversy surrounding the potential risks (including neurological harms) and benefits (obtained from light to moderate consumption) of wine (434, 435). Accordingly, a new study has been introduced to compare the relevant clinical outcomes and all-cause mortality between drinkers and non-drinkers among males aged 50 to 70 years and females aged 55 to 75 years over a 4-year follow up duration (434). In this regard, this PhD may contribute to a revised description of a MDP if required.

As this PhD focused on mood and cognition, we had an opportunity to consider the wide range of instruments measuring mood and cognition used across the literature. The common challenges faced to assess mood and cognition in nutrition research are recognised (436). For example, 'reaction time' is considered to be a gold-standard outcome measure (436), yet the best assessment method remains under discussion (437). Similarly, techniques measuring mood were also thought to be in need for advancements (438). To overcome this issue; the consensus appears to be; i) use a combination of objective and subjective tools (as we did to measure sleep in Chapter 3 and 4), ii) employ real-time assessments especially for mood research such as EMA (as we did in Chapter 5), and iii) produce a roadmap to inform cognitive measures, in particular, composite cognitive scores which are sensitive enough to quantify the changes induced by nutrition (436, 438, 439). A greater degree of standardisation of tools for the assessment of mood,

anxiety and cognition is needed to compare findings from different studies and to reach better interpretations and translation into practice, particularly considering the limited data availability in the field.

6.3. Strengths and limitations

Based upon my current knowledge, this is the first PhD project specifically focused on the short-term effects of a MDP on brain health in humans, which provide novel insights for nutrition and psychology and likely to be of interest to both disciplines. The novelty element identified in 2020, namely the 'short-term' focus remains with ongoing trials examining the impact of a MDP on mood for example having an 8-week intervention period (NCT06188754) with cognition trials being of 12-week (NCT06287489) and 12-month (NCT04990362) duration. Second, we published the protocols of each experimental chapter to enhance the credibility ("rigour, reproducibility and transparency") of our research (440, 441). Pre-registered protocols are publicly available as follows; systematic review (Chapter 2) is on PROSPERO, MediMood RCT (Chapter 3) is in the process of publication (submitted to BMJ Open) and COVID-19 data analysis (Chapter 5) is available on Open Science Framework. Next, we employed a multidisciplinary approach (nutrition, psychology/neuroscience and medical statistics) to design, conduct the research and analyse the data. Finally, the thesis has methodological diversity across the experimental chapters, including a systematic review, a human RCT including producing its protocol and ethics applications alongside the delivery of the intervention, and one longitudinal data analysis, that promoted a diversity of learning across my PhD.

On the other hand, this methodological diversity limited the cross-comparability of chapters. The common limitation of our empirical studies was the diversity of the study populations. Regarding mental health diversity; our systematic review (Chapter 2) consisted of 102 healthy young females from three 10-day studies and 26 senior people with metabolic syndrome from one postprandial study. Our RCT (Chapter 3 and 4) included 25 individuals with existing mental health complaints from various age groups with no information on their metabolic health status, and the longitudinal data analyses (Chapter 5) involved 674 individuals with only 5% of them reported to be with previous

mental health issues. Concerning ethnic diversity; the studies in Chapter 2 did not report on that. In MediMood (Chapters 3 and 4), we did not screen them for ethnicity, although the majority appeared to be white. Only C-19 study reported on ethnicity which was over 95% white as discussed in detail in Chapter 5.

6.4. Overall conclusion

This PhD sought to answer whether a MDP can enhance brain health in adults in a short-term. Our results provided the literature with several original contributions. Firstly, we highlighted the lack of knowledge on the short-term effects of dietary patterns, foods and nutrients on brain health as a research gap. Second, we found that mood, cognition and sleep can be ameliorated in one to ten days by dietary intake. Furthermore, our 5-day RCT demonstrated a significant effect on inflammation, with CRP levels reducing after MDP and rising after WD. Postprandially, we detected improved insulin sensitivity with no significant difference in CBF. One surprising finding of our RCT was the alterations in cortisol levels. Contrasting our predictions, the MDP increased cortisol levels with reduced levels after the WD. Finally, we showed that self-reported diet quality and sleep quality are positively associated with each other daily, up to five days. Overall, this PhD reveals that a MDP has a potential to elevate mood, reduce anxiety, and support cognition and sleep in adults in a short-term. The novel evidence we provided lays a foundation for future research and informs public health policies. Importantly, the sample size in MediMood study was small (although a priori power calculation was conducted), and the characteristics of the study population was heterogenous. Therefore, further research is needed for generating public health policies for the relevant populations.

6.5. Practical implications

The success rate of the conventional first line treatment formed by pharmacotherapy and psychotherapy is only 50% as reported in 2023 (141). On the other hand, the potential comparability of nutrition versus pharmacotherapy and psychotherapy against mental disorders was previously discussed (442). The International Society for Nutritional Psychiatry Research (416) and MyNewGut consortium (443) particularly suggested a MDP to be the treatment for mental health disorders, with a caution that the

evidence was mainly derived from epidemiological evidence and a few RCTs with none of them conducted in people with existing symptoms. As we have now shown, switching to a MDP, for as little as five days can alleviate disturbed mental wellbeing of adults with existing complaints, making a healthcare policy using our findings can be considered by policy makers. As MDP is widely known to be a healthy dietary pattern with no known side effect, it can be safely recommended, which is especially important for people who require extra caution with use of antidepressants for instance pregnant and lactating women (444) and those who are on other medications which are counter indicated with antidepressant-drug use (445). Widened dietary counselling, for example referral to a dietitian for a diet quality assessment and eating behaviour change support, would help realise efficacy (417, 446).

An important issue going forward which needs to be considered is affordability. Notably, the average price we paid for a MDP grocery basket in MediMood was approximately £87 for 5 days whilst the cost per basket was around £60 for the WD. Given that 11% of the UK population experience food poverty (447), and it has been even worsened by UK austerity policies (448) and the COVID-19 pandemic (449), strategies targeting affordability and accessibility of healthy food items should be prioritised for governments. When the economic burden of mental health disorders is considered, governments should invest in solutions providing financial support for all to promote healthy food consumption, which could be for example include provision of weekly/monthly allowance for MDP components, or reduction in the cost of healthy those food items' prices through subsidy schemes.

6.6. Future research directions

Although the findings of this PhD provide important insights into the short-term effects of dietary intake on brain health, some research gaps certainly remain to be elucidated.

Firstly, the study populations were diverse in the experimental chapters. Therefore, the next step should be running bigger trials with larger sample sizes that allow meaningful subgroup analyses according to for example, psychiatric medication use,

ethnicity, age and sex. The short-term efficacy of a MDP should be tested in individuals with more severe mental health disorders. It may also be worth to replicate the MediMood study in people with T2D as their neurological mechanisms may be more sensitive to the dietary interventions differently as discussed in Chapter 4.

Regarding the dietary design, using the extreme ends of the MEDAS scale (a comparison between 0 and 14) was feasible in a clinical trial setting, yet it is unclear if it would be realistic in a habitual setting. Therefore, the efficacy of more modest improvements in MDP adherence should be tested. For example, it is still unclear whether a slight increase such as from 4 to 6 could provide any benefit, or people who already have a moderate or high level of MDP adherence would confer a benefit if they increase their scores even higher, such as from 6-9 to above 10. Furthermore, a study testing mood and anxiety every day and collecting biological samples more often than we did could provide better insights into the daily metabolic responsiveness of the body to diets in the context of change in mental health and their associations.

Strategies to reduce inflammation should become more of a target for both research and healthcare practices as we have seen significant improvements in CRP and in mood, although we did not perform a correlation analysis. The effects of food on cortisol levels, and/or the role of cortisol in mental health diseases should be investigated further as our results showed improved mental health despite the unexpected rise in cortisol in MDP and a decrease in WD. To account for sex would be useful as males' and females' cortisol responses to food may differ (338). Circulating levels of ketone bodies, GABA and tryptophan as a result of a MDP and a WD and their associations to mood should be investigated in the future using our stored samples as they postulated to be associated with brain health.

Mitochondrial function is likely to mediate brain disorders including mood, anxiety, cognitive and sleep disorders and social behaviour (450, 451). It is responsible for the energy production, and disordered energy metabolism in the brain is thought to be a feature of neuropsychiatric disorders (452). Therefore, assessing the brain's mitochondrial function response to a MDP should be considered for future RCTs. To the best of my knowledge, no study has evaluated it yet. To do so, Positron Emission

Tomography (PET), a non-invasive technique, can be applied as it was previously used and recommended for brain research to measure oxidative stress and glucose metabolism as indicators of the mitochondrial function (453, 454).

Although this PhD provided some preliminary evidence on cognition, sleep and CBF, they were not the primary outcomes for this PhD. Therefore, future MDP RCTs addressing cognition, sleep and CBF as their primary outcomes should be developed to gain a deeper understanding on those as they are indispensable elements of the brain health.

Regarding health behaviour research, a Patient Public Involvement (PPI) to identify participants' views in the study design stage and a focus group to explore participants' opinions after the intervention to understand what exactly drove them to change their dietary behaviour should be included in future studies to improve design and to provide invaluable insights into intervention adherence (455).

Furthermore, although a MDP is a plant-based dietary pattern, it is still not fully vegan or vegetarian. Considering being vegan/vegetarian was the most common exclusion reason at screening (nearly 10%) for MediMood, alternative MDP versions should be developed for those individuals, to explore the best alternatives to substitute fish. Besides, we did not assess their hydration status or track their water consumption during the study, which is reported to affect mood and cognitive performance (456), hence, can be considered for future trial designs. Similarly, we did not monitor their caffeine intake that is also reported to play a significant role particularly on cognition, thus, should be taken into account for future study designs (457).

The health and longevity of 'traditional' Mediterranean citizens, the root inspiration for researchers to work on a MDP, is likely to be beyond only diet (458). An active lifestyle, 'siesta' (nap at midday), eating together, having strong social and family relationships are all recognised to be core elements of a Mediterranean lifestyle pattern alongside diet (251, 459-461). Therefore, a study holistically assessing and/or intervening as many of those components as possible along with eating behaviour/nutrition in non-

Mediterranean populations, would take nutrition and brain health research one step further.

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Appendices

Appendix 1. The 14-point Mediterranean Dietary Adherence Screener (MEDAS)

Q1. Do you use olive oil as your principal source of fat for cooking? (yes or no)

Q2. How much olive oil do you consume each day? (4 tablespoons is equivalent to 50 ml or 50 g. Include all olive oil used for frying, roasting, salad dressings, and that eaten outside the home.)

Q3. How many servings of vegetables do you consume each day? One serving is 200 g. Count salad garnishes and side servings as 1/2 serving. (Include all vegetables EXCEPT potatoes, sweetcorn, and peas (the latter count as a legume). Vegetable weights are those prepared and ready to eat.

Q4. How many servings of fruit (including 100% fruit juice) do you consume each day? One serving is 80 g, or 30 g of dried fruit, or 150 ml of 100% fruit juice. (Include fresh, cooked, frozen, canned (in fruit juice only) and dried fruit, and up to one serving of 100% fruit juice or smoothie per day.)

Q5. How many servings of red meat do you consume each day? One serving is 100-150 g. Include pork, lamb, beef, veal, venison, duck, and processed red meat products like hamburgers, sausages, and bacon. (Include all items containing red meat such as sausage rolls, meat pies, and pasties.)

Q6. How many servings of butter, margarine, or cream do you consume each day? One serving is 12 g (This includes butter or margarine used to make cakes or pastries.)

Q7. How many glasses of sugar-sweetened soft drinks do you consume each day? One glass is 100 ml. Include fizzy drinks, diluted squash, and cordial. (Do not include diet or zero-calorie drinks.)

Q8. How many glasses of wine do you consume each week? One glass is 125 ml. Include red, white, rosé, or sparkling.

Q9. How many servings of pulses do you consume each week? One serving is 150 g cooked weight. Include peas, beans (including baked beans), lentils, chickpeas, and soybeans. (Include

dried, tinned, and frozen varieties. Do not include green or French beans, or mangetout or sugar-snap peas (these count as vegetables)

Q10. How many servings of fish or shellfish do you consume each week? One serving of fish or shellfish (without the shell) is 125 g (Fish or shellfish can be fresh, frozen, or canned.)

Q11. How many times do you consume commercial sweets (such as cakes, pastries, and biscuits) each week? (Include all commercial cakes, pastries, biscuits, puddings, custard, and ice-cream. Do not include homemade varieties.)

Q12. How many servings of nuts do you consume each week? One serving is 30 g (Include all nuts, nut butters, peanuts, and seeds. Do not include salted varieties.)

Q13. Do you preferentially consume white meat instead of red meat each week? (White meat includes chicken, turkey, rabbit, and game like goose, pigeon, pheasant, partridge, and guinea fowl. Red meat includes pork, lamb, beef, veal, venison, duck, and processed red meat products like hamburgers, sausages, and bacon. If you are vegetarian or vegan, please answer 'Yes'.)

Note: in the MediMood, we added if you are vegetarian or vegan, please choose not applicable as the study required eating several meat products.

Q14. How many times each week do you consume meals prepared with sofrito (sauce made with tomato-based sauce, containing at least one of (onions/garlic/leeks) that have been sautéed in olive oil? (Include commercial tomato-based pasta sauces, passata, canned or fresh tomatoes that have had onions/garlic/leeks sautéed in olive oil added.)

Appendix 2. Published version of Chapter 2 as a full article

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Short-term effects of a Mediterranean-style dietary pattern on cognition and mental well-being: a systematic review of clinical trials

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Abstract

Although the long-term effects of a Mediterranean-style dietary pattern (MDP) on cognition and overall mental well-being have been consistently described, the short-term effects of the MDP on cognitive performance, mood and anxiety have not been as widely reviewed. Therefore, the aims of this systematic review were to synthesise the evidence from randomised controlled trials (RCT), to examine whether a MDP can alter cognition and overall mental well-being in the short-term (up to 10 d). This will also be used to identify research gaps and to inform the design of future acute RCT in the area. Ovid Embase, Ovid MEDLINE and Web of Science Core Collection were searched from inception to 8 December 2020. The data were synthesised narratively with no quantitative synthesis. The detailed protocol is available on PROSPERO, with the registration number CRD42021221085. A total of 3002 studies were initially identified. After the deduplication and screening stages, four studies (three articles and one conference proceeding) were eligible to be included. Despite the very limited data obtained, the literature suggests that a MDP can improve cognition and mood in the short-term. Specifically, improvements in attention, alertness and contentment were consistently reported. A MDP appears as a promising strategy to improve short-term cognitive and mental health. A limitation of this review is the small number of studies identified; therefore, future studies are required to confirm these initial novel findings and to provide granularity as to which domains are most responsive and in which population subgroups.

Key words: **Mediterranean-style dietary pattern: Mood: Cognition: Acute: Short-term**

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With global ageing population demographics, the prevalence of cognitive disorders has surged[1]. The number of individuals living with dementia, which is a major cause of loss of independence and disability in older age, has doubled between 1990 and 2016, reaching 50 million worldwide[1]. In the UK, dementia is now the number one cause of death, responsible for about 15 % of all-cause mortality[2]. Besides, dementia has an enormous economic burden, with the global cost expected to reach $2 trillion by 2030[3].

The prevalence of mild cognitive impairment, the transition phase prior to incident dementia, has been estimated to occur in 15–20 % of the population aged over 60 years, with 8 %–15 % progressing to dementia per year[4]. Subjective memory complaints (SMC), which are loosely defined as a state in which individuals present with 'self-reported' cognitive decline relative to their previous cognitive status (which is not diagnosed by objective standard tests), occur in 50–80 % of individuals aged 70 years or older[5]. SMC is linked to depression, anxiety and future Alzheimer's disease risk[5,6]. In addition to cognitive decline, mental disorders, including depression and anxiety disorders, are prevalent, occurring in 3–5 % of the global population[7], and are one of the top three causes of non-fatal health loss in terms of years lived with disability[8]. Depression is also a risk factor for future dementia[9].

Currently, Alzheimer's disease and other dementias are irreversible with no effective treatments available to slow or reverse the condition. Therefore, behaviours (such as altered eating behaviour and nutrition status) which can prevent or delay progression of these conditions have the potential to dramatically reduce both individual risk and the population burden of the disease[10]. A Mediterranean-style dietary pattern (MDP) is emerging as having potential positive effects on mental health status. The diet is characterised by high consumption of extra virgin olive oil (EVOO) and plant-based foods such as fruits, vegetables, nuts, legumes, whole-grain cereals; low to moderate consumption of dairy products mainly yoghurt and cheese; fish

Abbreviations: BDNF, brain-derived neurotrophic factor; EVOO, extra virgin olive oil; MDP, Mediterranean-style dietary pattern; RCT, randomised controlled trial.

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consumed two to four times a week; low amounts of red meat and moderate consumption of red wine mainly with meals[11]. EVOO, in addition to being the major component of a MDP, has been shown to independently confer neuropsychiatric and cardiovascular benefits[12], attributed to its high monounsaturated fatty acids (MUFA) and phenolic content[13].

The cardiometabolic health benefits of a MDP, first reported in the Seven Countries Study in the 1950s[14], are now well established[15–17]. An improved cardiometabolic phenotype is thought to in part underlie the emerging cognitive benefits of this dietary pattern. However, the majority of this evidence has been acquired from observational studies, such as European Prospective Investigation into Cancer-Norfolk[18], with a dearth of randomised controlled trials (RCT) which report on the causal benefits of a MDP on long-term cognitive and overall mental health. The Prevencion con Dieta Mediterranea (PREDIMED) was the first RCT testing the long-term effectiveness of a MDP in primary prevention which had incidence of CVD as the primary point[19]. In a sub-group secondary analysis, the MDP interventions enriched with either EVOO or nuts were shown to improve cognitive function[20] and depressive symptoms[21]. Available systematic reviews and meta-analysis focus on the long-term mental health benefits of a MDP, with adherence associated with an overall risk ratio of 0·79 (95 % CI 0·70, 0·90) of developing cognitive disorders[22]. Although no association was observed in the cohort analysis, data from nine cross-sectional studies indicate a negative relationship between adherence to a MDP and risk of depression (OR = 0·72; 95 % CI 0·60, 0·87)[23].

In addition to the long-term trajectory, for the ever-increasing number of individuals with pre-existing cognitive or mental health deficits and even in healthy individuals, there is a great need and interest in identifying nutrition strategies which improve cognition, mood and anxiety in the short-term, in order to improve capabilities, independence and overall quality of life. Therefore, the objectives of the current systematic review are, (i) to conduct an evidence synthesis from RCT data to scrutinise whether a MDP has the potential to alter cognition, mood and mental well-being in the short-term and (ii) identify research need and inform the design of future acute RCT in the area.

Methods

This systematic review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[24]. Our systematic review protocol is available on PROSPERO with the registration number CRD42021221085[25].

Search strategy, eligibility criteria and study selection

'Short-term' is defined as 'up to 10 days' by discussions among the authors, where effects on cognition are likely to be mediated by rapidly responsive physiological processes such as brain blood flow, inflammation and oxidative status. Ovid Emabse, Ovid MEDLINE and Web of Science Core Collection were searched[26,27] from their inception dates to 8 December 2020 by using keywords covering 'Mediterranean diet', 'olive oil', 'cognition', 'dementia', 'mood', 'mood disorders', 'anxiety', 'anxiety disorders', 'depression', 'depressive disorders' and 'well-being'. Free search terms and medical subject heading terms were combined where the databases allowed, namely Embase and MEDLINE. Final search strategies were constructed with the assistances of an expert in systematic reviews in Norwich Medical School, and the academic librarian of the Faculty of Medicine and Health Sciences, University of East Anglia. The full electronic search string used in Ovid Embase is presented in Appendix 1.

Studies were accepted eligible if they,

- had an RCT design,
- intervened with either a MDP or EVOO,
- had an intervention period of up to and including 10 d,
- assessed either cognition, mood, anxiety or depression as a primary or secondary endpoint,
- included adults over 18 years and
- published in the English language.

Observational epidemiological studies were excluded. No sex filter was applied. The reference lists of included studies were manually read in order to obtain further potential publications. Two authors (L. E. and E. S. C.) independently completed screening the titles and abstracts against the predefined eligibility criteria. Any discrepancies were resolved by discussions until an agreement was reached. EndNote X9 is used as the reference management tool.

Definition of cognitive and mental health as the primary outcomes

Cognition is defined as 'the mental action or process of acquiring knowledge and understanding through thought, experience and the senses'[28]. Memory, attention, reasoning, decision-making, visual and spatial abilities and behaviours are examples of 'cognitive functions'. Depression and anxiety are significant mood disorders; however, mild to moderate level of psychological stress can also cause substantial reductions in the quality of life. A variety of validated tools are available to assess cognition and mood, with details of the tools used in individual studies detailed below and in Table 1.

Data extraction and quality assessment

A table which recorded the authors, publication year, country where studies were conducted in, type of RCT, participant characteristics, study duration, intervention, main outcomes, assessment methods used, results (mental health status) and additional results/comments was generated to extract the data from the included studies.

A quality assessment was done using RoB2, a revised tool for risk of bias by Cochrane[29], which has five domains: bias arising from the randomisation process (D1), bias due to deviations from intended interventions (D2), bias due to missing outcome data (D3), bias in measurement of the outcome (D4), bias in selection of the reported result (D5) and plus overall bias (D6). The results of bias investigation are presented by means of a traffic light plot under low risk, some concerns or high risk.

Table 1. Study details and main outcomes
(Mean values and standard deviations)

Authors	Publication year	Country	Type of RCT	Participant characteristics	Duration	Intervention	Main outcomes	Assessment methods used	Additional outcomes	Results (Mental Health Status)	Additional results/ comments
Diekmann *et al.*[29]	2019	Germany	Crossover	*n* 26 8 Female, 18 Male Metabolic syndrome 69·9 (SD 4·7) years* BMI = 30·3 (SD 2·3) kg/m²*	4·5 h, 2-week washout periods	4 interventions (isoenergetic, 4300 kJ/meal): 1. WD + walking. 2. WD + resting. 3. MDP + walking. 4. MDP + resting	Mood, Cognition	MDMQ[34], FAIR-2[37]	Appetite, Plasma cortisol levels	MDMQ: No effect of diet	No effect of diet on cortisol.
										FAIR-2: Walking group: 1·4-fold increase in attention in MDP compared with WD. Resting group: 1·1-fold increase in attention in MDP compared with WD. ($P = 0·045$ from iAUC data, meal × time interaction NS).	VAS: No impact of diet on hunger. Satiety was higher after MDP compared with the WD ($P < 0·001$)
de Vries *et al.*[30]	2017	Netherlands	Parallel arms	*n* 53 Female 22·3 (SD 3·6) years*	10 d	MDP or control group	Mood	POMS[35], Bond–Lader[36]		Significant decreases in vigour/activity ($P < 0·001$); tension/anxiety ($P = 0·001$); fatigue/inertia ($P = 0·003$); anger/hostility ($P = 0·014$); confusion/bewilderment ($P = 0·015$) and the total mood disturbance score (p not stated), and contentment ($P = 0·001$); alertness ($P = 0·003$) in MDP compared to control group. *P* values are for the time × treatment interactions, no effect sizes are presented.	Food diaries were used over 10 d but not reported in the text. No detail given on the control group diet.
Lee *et al.*[31]	2015	Australia	Crossover	*n* 24 Female Healthy	10 d	MDP or NC	Mood, Cognition	POMS[35], Bond–Lader[36], COMPASS [38]	Cardiovascular function: blood pressure, blood flow velocity and arterial stiffness, Dietary adherence, Anthropometric measures	Confusion reduced in MDP (−1·19) and increased (1·52) in NC ($F = 6·87$, $P = 0·02$) Alertness increased in MDP (6·93) and reduced in NC (−8·31) ($F = 14·11$, $P < 0·01$) Contentment increased in the MDP group (5·35) and reduced in NC (−4·23). ($F = 6·49$, $P < 0·02$). Immediate word recall: Correct responses increased in MDP (1·14) and reduced in NC (−0·64) ($F = 8·19$, $P = 0·01$). Incorrect responses decreased in MDP (−0·32) and increased in NC (0·36) ($F = 4·83$, $P = 0·04$).	Food diaries were used over 10 d Augmentation pressure (mmHg) reduced in MDP (−1·05) and increased in NC (0·95) ($F = 6·15$, $P = 0·02$) 100 % dietary adherence to MDP BW: Reduced in MDP group (−1·77 kg) and increase in NC group (0·11) ($F = 10,81$, $P < 0·01$)

Table 1. (*Continued*)

Authors	Publication year	Country	Type of RCT	Participant characteristics	Duration	Intervention	Main outcomes	Assessment methods used	Additional outcomes	Results (Mental Health Status)	Additional results/ comments
										Delayed word recall: Incorrect responses decreased in MDP (–0·33) and increased in NC (0·71) ($F = 4·57$, $P = 0·046$).	No change in BMI
				25·6 (SD 5·1) years*						3-back task: Correct responses reduced in the MDP (–2·32) and increased in NC (4·14) ($F = 6·64$, $P = 0·02$).	
Mc Millan *et al.*[32]	2011	Australia	Parallel arms	*n* 25	10 d	MDP or NC	Mood, Cognition	65-item POMS[35], Bond–Lader[36], COMPASS [38]	Dietary adherence, Anthropometric measures	Vigour increased in MDP by 18 % (3·67) and reduced in NC by 22 % (–5·06) ($F = 11·25$, $P = 0·003$)	Food diaries were used over 10 d
										Alertness increased in MDP by 30 % (16·43) and reduced in NC group by 15 % (–9·02) ($F = 22·23$, $P < 0·001$). Contentment increased in MDP by 20 % (12·89) and reduced in NC by 15 % (–10·4) ($F = 16·634$, $P < 0·001$)	100 % dietary adherence to MDP
				Female						Numeric working memory: RT increased in MDP by 2 % (+15) and decreased in NC group by 14 % (–122) ($F = 5·05$, $P = 0·04$)	
				Healthy						Corsi Blocks task: RT reduced in MDP by 14 % (–420) and increased in NC by 27 % (837) ($F = 17·628$, $P < 0·001$)	No effect of diet on BW, BMI and WC.
				21·1 (SD 3·3) years*						Word recognition: RT reduced in MDP by 3 % (–29) ($P = 0·574$, NS) and in the NC by 20 % (–191) ($P = 0·001$). The difference between groups was significant: ($F = 5·04$, $P = 0·035$).	

RCT, randomised controlled trial; WD, Western diet that is rich in total fat, SFA, saturated fatty acids; and animal protein; MDP, Mediterranean-style dietary pattern; MDMQ, Multidimensional Mood State Questionnaire for mood; FAIR-2, Frankfurt Attention Inventory-2 for cognition; iAUC: AUC, area under the curve; VAS, Visual Analogue Scale for hunger, appetite and satiety; POMS, Profile of Mood States questionnaire for mood (tension/anxiety, anger/hostility, fatigue/inertia, vigour/activity, confusion/bewilderment, depression/rejection and total mood disturbance score); Bond–Lader Scale for mood (alertness, contentment and calmness); NC, No change in diet; COMPASS, The Computerised Mental Performance Assessment System for cognitive domains; RT, reaction time; BW, body weight; WC, waist circumference.
* Represents mean and standard deviation unless otherwise stated.

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Data synthesis

A narrative approach was used to synthesise the data. No quantitative analysis was performed due to the small number of studies.

Results

Study identification

Initially, 3002 studies were obtained from the three electronic databases. After deduplication, 2261 studies remained, with 1721 from the MDP search and 540 from the EVOO search. Of these, 2253 were excluded following the title and abstract screening for reasons such as longer study durations, irrelevant outcomes, supplement interventions, epidemiological studies, animal studies, any type of reviews, meta-analysis and protocols. Full texts were screened for the remaining eight studies. Finally, four studies, three full articles[30–32] and one conference proceeding[33], met the eligibility criteria and were included. These four papers yielded a reference list of eighty-five, which were scanned manually by LE and ESC, with no additional publications emerging for inclusion. The study identification process is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Fig. 1).

Study characteristics

All included studies were RCT, two with a crossover[31,32] and two with a parallel design[30,33]. All intervened with a MDP and were carried out in non-Mediterranean countries, two Northern European[31,33] and two Australian[30,32]. The sample sizes ranged from 24[32] to 53[33]. Three of the studies included young females only, with mean ages of 21·1 (SD 3·3)[30], 22·3 (SD 3·7)[33] and 25·6 (SD 5·2)[32] years. The remaining study[31] included both males and females with metabolic syndrome traits with a participant mean age of 70 (SD 5) years. None of the four RCT reported any previous cognitive or mental health issues in the participants. Three had a study duration of 10 d, with one[31] examining the physiological response 4·5 h after the test meal. One study[31] implemented a MDP alone or with a physical activity intervention (30 min moderate walking).

In terms of the MDP intervention, in one crossover study[31], participants were provided with their test breakfast (4300 kJ) that consisted of ciabatta, smoked salmon, muesli, fruit and vegetables which was described as rich in unsaturated fatty acids,

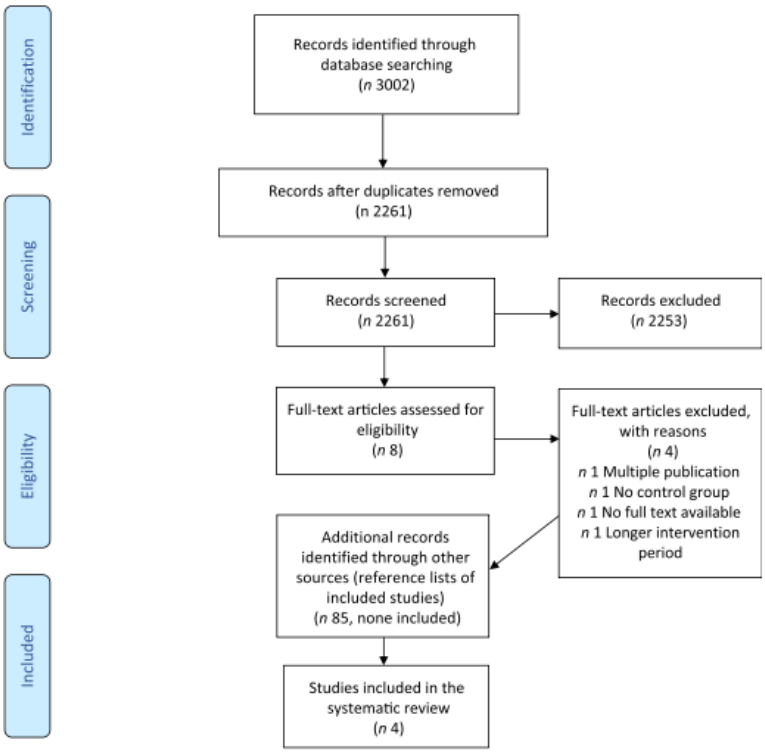

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

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dietary fibre and antioxidative compounds. The remaining three studies did not provide the study foods but rather guided participants in following a MDP. De Vries *et al.*[33] did not provide any detail of the dietary instructions provided to participants. Lee *et al.*[32] requested participants in the MDP group to increase their intake of fruit, vegetables, oily fish, low-fat dairy products and nuts with a focus on healthy carbohydrates, fats and proteins, and to exclude meat, butter, margarine, caffeinated/energy drinks, added sugars and salts, alcohol, tobacco and illicit drugs during the study period. Besides, participants were also asked to consume freshly prepared foods and to avoid processed and packaged options where possible. Similarly, McMillan *et al.*[30] asked participants to increase their consumption of fruits, vegetables, oily fish, low-fat dairy products and nuts and to combine good sources of carbohydrates (less refined carbohydrates, whole grains, legumes, fruits and vegetables), fats and proteins. Additionally, they were instructed to abstain from red meat, refined sugars, refined flour, pre-packaged and processed foods, caffeinated products, soft drinks and condiments.

Regarding dietary assessment methods, food diaries were used over the 10-d study period in order to record the dietary intake in three of the studies[30,32,33]. The remaining study provided the foods, so no self-reported dietary assessment was required[31].

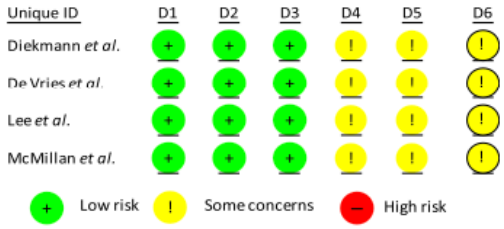
While three studies examined both mood and cognition as outcomes[30–32], one study assessed only mood[33]. The assessment methods for mood included the German version of Multidimensional Mood State Questionnaire[34] for subjective mood (good/bad mood; alertness/fatigue and ease/unease)[31], the Profiles of Mood States questionnaires[35] scoring the subscales tension/anxiety, fatigue/inertia, vigour/activity, confusion/bewilderment, anger/hostility, depression/rejection and the total mood disturbance score[30,32,33] and the Bond–Lader visual analogue scales[36] for the alertness, calmness and contentment[30,32,33]. For the assessment of cognition, the German version of the Frankfurt Attention Inventory 2 (test version A)[37] for attention[31] and the Computerised Mental Performance Assessment System[38] battery for a variety of cognitive domains were used[30,32] (Table 1).

Study quality

The study quality assessment showed that all included studies have a low risk of bias in the first three domains ((D1), bias arising from the randomisation process; (D2) bias due to deviations from intended interventions; (D3), bias due to missing outcome data), while the other two domains ((D4) bias in measurement of the outcome and (D5) bias in selection of the reported result) were assessed as having some concerns (Fig. 2).

Primary outcome measures

Cognition. According to the Computerised Mental Performance Assessment System results, increased correct responses (1·14, $F = 8·19$, $P = 0·01$) and decreased incorrect responses (–0·32, $F = 4·83$, $P = 0·04$) were seen in immediate word recall; reduced incorrect responses (–0·33, $F = 4·57$, $P = 0·046$) in delayed word recall were evident in the MDP group relative to the control,



D1: bias arising from the randomisation process;
D2: bias due to deviations from intended interventions;
D3: bias due to missing outcome data;
D4: bias in measurement of the outcome;
D5: bias in selection of the reported result; D6: overall bias.

Fig. 2. Risk of bias assessment results.

while correct responses significantly decreased in MDP treatment (–2·32, $F = 6·64$, $P = 0·02$) for the three-back task[32]. Reaction time increased for numeric working memory task in MDP by 2 % and decreased by 14 % in the control group ($F = 5·05$, $P = 0·04$); reduced for Corsi Blocks task by 14 % (–420) in MDP treatment and increased by 27 % (+837) in the control group ($F = 17·628$, $P < 0·001$)[30]. Whilst reaction times reduced in the word recognition task in both arms, it was not significant in the MDP (3 %, –29, $P = 0·574$) treatment and significant in the control group (20 %, –191, $P = 0·001$). The difference between the groups was significant ($F = 5·04$, $P = 0·035$)[30].

No overall significant effect of meal type in attention (as assessed by the Frankfurt Attention Inventory 2 method) was recorded. However, in the walking groups, a 1·4-fold increase was seen in the MDP group when compared with the WD, while this increase was 1·1-fold higher in the MDP relative to the WD in resting ($P = 0·045$ from iAUC data)[31].

Mood. Using the Profiles of Mood States questionnaire, vigour/activity ($P < 0·001$), tension/anxiety ($P = 0·001$), fatigue/inertia ($P = 0·003$), anger/hostility ($P = 0·014$), confusion/bewilderment ($P = 0·015$) and the total mood disturbance score (P value not stated) were significantly improved in the MDP arm compared with the control group[33]. Lowered confusion was observed by the MDP treatment (–1·19, $F = 6·87$, $P = 0·02$) with no other changes in the subscales of mood evident[32]. Following 10 d of MDP adherence, vigour rose by 18 % (3·67, $F = 11·25$, $P = 0·003$) in the MDP condition with no other dimensions of mood significantly affected[30].

Using the Bond–Lader scale, alertness and contentment were improved by MDP in all three studies used this scale. The results were as follows: alertness ($P = 0·003$) and contentment ($P = 0·001$)[33]; alertness (6·93, $F = 14·11$, $P < 0·01$) and contentment (5·35, $F = 6·49$, $P < 0·02$) scores[32]; and alertness (16·43 (about 30 %), $F = 22·23$, $P < 0·001$) and contentment (12·89 (about 20 %), $F = 16·634$, $P < 0·001$)[30]. No significant change was reported for calmness.

Using the Multidimensional Mood State Questionnaire test, no main effect of meal type interventions was observed for mood[31].

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Secondary outcome measures

Two of the studies reported dietary adherence. In the Lee *et al.*'s study[32], all of the participants (n 24) an average MDP adherence of 94 % was evident which ranged from 80 % to 100 %. Similarly, in the McMillan *et al.*'s study[30], a mean MDP adherence of 93 % for meals (range 80–100 %) and 95 % for snacks (85–100 %) was reported.

No significant impact of a MDP meal *v.* WD meal on plasma cortisol levels was evident[31]. Only Lee *et al.* assessed the impact of intervention on blood pressure, blood flow velocity and arterial stiffness[32]. A significant decrease (–1·05, $F = 6·15$, $P = 0·02$) in augmentation pressure (mm Hg) was observed in the MDP condition relative to the control group.

Diekmann *et al.* assessed the desire to eat[31]. The overall hunger was not influenced by meal, while satiety was higher after MDP as compared with the WD ($P < 0·001$).

Body weight and BMI were tracked in two of the studies. Lee *et al.*[32] reported a significant weight loss in the MDP (–1·77 kg, $F = 10,81$, $P < 0·01$) group. McMillan *et al.*[30] observed no significant main effect of diet on body weight, BMI or waist circumference between the two groups.

Discussion

This is the first systematic review to report the short-term effects of a MDP on cognition and overall mental well-being. The findings suggest that a MDP has the potential to affect cognition and mood in as little as 10 d. The findings have also identified important research gaps notably; there are few reported studies and of the studies available most were conducted in young people, aged 18–38 years[30,32,33] and all conducted in individuals without cognitive or mental health complaints. In addition, there was a tendency to study females with only eighteen males in the 128 participants from the four studies. Therefore, the short-term effect of a MDP on mental health status in older adults, and in particular individuals who present with evidence of cognitive or mental health decline, is currently unknown.

Specific cognitive domains improved in all of the studies assessing the cognition, although the findings were not consistent[30–32]. Attention was significantly improved after the MDP in one study, with the authors speculating that this difference may be caused by the higher glucose content of the MDP (carbohydrate content of the meals: 133 g in MDP *v.* 93·7 g in WD) as the brain uses glucose as the primary source of energy[31]. Other studies reported improvements in immediate and delayed memory recall tasks, working memory and reaction times[32], and spatial working memory[30]. Consistent with these short-term effects, previous studies have reported longer-term (8 weeks) effects of a MDP enriched with dairy foods on processing speed in adults at above average CVD risk in the MedDairy study[39].

Mood dimensions, namely, alertness and contentment, were significantly and consistently improved by MDP in the short-term in all four studies. Vigour[30,33] and confusion[32,33] were also improved following the MDP. Adherence to a MDP has previously been shown to be associated with reduced risk of depression in elderly[40], and in the MedDairy study, a reduction in depression, tension, anger, confusion and total mood disturbance score was recorded following the 8-week dietary intervention period[39]. Furthermore, polyphenols intake, which are considered an important bioactive in the plant-based MDP, has shown to reduce depressive symptoms[41].

Previous short-term studies using other dietary intervention or health endpoints provide insight into the possible mechanistic basis for the effect of a MDP on mental health. Myette-Côté *et al.*[42] examined the effects of a low-fat, low glycaemic index diet, to a low carbohydrate diet or a low carbohydrate plus post-meal walking, in type 2 diabetes on glucose levels and inflammatory factors in a RCT comprising three 4-days interventions. While improved glycaemic control was evident in the low carbohydrate diet group, plasma monocyte-derived microparticles reduced significantly in the low-fat, low glycaemic index diet group which was similar to a MDP, suggesting that cerebral hypometabolism and inflammation which are features of cognitive disorders may be positively modulated by short-term dietary strategies. Attuquayefio *et al.*[43] reported a decrease in hippocampal-dependent learning and memory following a breakfast high in saturated fat, cholesterol and added sugar and low in protein relative to an isoenergetic healthy breakfast for 4 consecutive days, findings which were subsequently confirmed over a 1-week intervention period[44]. The hippocampus is a core brain area for cognitive functions such as learning and memory[45]. Besides, the hippocampus is involved in anxiety-related behaviours[46] and major depression[47]. This evidence suggests that the hippocampus function can be affected negatively by an unhealthy eating pattern in as short period as 4 d.

The hippocampus also produces high concentrations of brain-derived neurotrophic factor (BDNF) which is important in attention, cognition and total behaviour[48]. Decreased levels of BDNF have been linked to cognitive and mood disorders, and it has been identified as a therapeutic target in neurodegenerative and psychiatric impairments[49]. In PREDIMED study, a MDP raised BDNF levels over 3 years, whilst a MDP supplemented with nuts was linked to significant improvement in serum BDNF levels in individuals with depression[50]. However, the existing literature does not provide any insight into the short-term impacts of a MDP on BDNF levels.

Blood brain barrier is a dynamic selective interface between the brain and the bloodstream, in which dysregulations are associated with cognitive (including Alzheimer's disease) and psychiatric disorders[51]. Although selected dietary components have been shown to affect blood brain barrier function such as permeability in animal models[52] and the blood brain barrier is susceptible to be impairment by a WD[53], the impact of a MDP in short- or long-term mental health is currently unknown but should be a focus of investigation. Additionally, a reduction in cerebral blood flow is associated with cognitive dysfunction[54]. Lamport *et al.*[55] investigated the impacts of high flavanones on cognition and cerebral blood flow in young healthy participants in an acute RCT. A high flavanone citrus juice resulted in a 2-h increase in cerebral blood flow and better performance in one cognitive task (Digit Symbol Substitution) was observed in the experimental group. McManus *et al.*[56] examined the acute effects of EPA or DHA, found in oily fish, on arterial stiffness

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in men at high risk of CVD. Four hours following to the test meal, vascular function was significantly improved by the DHA-rich oil. Besides, a MDP is known to chronically affect systematic vascular function[57].

The influences of the gut microbiota on cognition and overall mental well-being are well-recognised[58,59]. Therefore, nutritional strategies targeting the gut health may represent a meaningful strategy for delaying or even reversing neuropathology[60]. David *et al.*[61] demonstrated that the gut microbiota can be changed through both animal-based and plant-based diets in 5 d. Moreover, in a 1-year longitudinal study, the gut microbiota responded to daily changes in diet[62]. Hence, accumulating evidence suggests that the gut–brain axis could mediate the even short-term effects of a MDP on cognition and mental well-being.

The current review highlighted that all of the participants in the MDP treatments from the two studies tracking dietary adherence[30,32] reported high dietary adherence with no side effects. Besides, a MDP was linked to higher satiety in one study[31] and significant weight loss despite no energetic restriction in the another study[32]. Considering the fact that maintenance of healthy eating behaviours is not an easy task even in the short-term, this available evidence suggests that a MDP is an acceptable implementable approach even in non-Mediterranean countries.

The review has also highlighted a lack of consistency in how the MDP is applied. Despite the small number of included studies, none of them used the same dietary procedure, although the two Australian studies gave similar instructions to their participants[30,32]. Abdelhamid *et al.*[63] have previously reported the high inconsistencies in food and nutrient intake through when adopting a MDP. Davis *et al.*[64] also reported discrepancies in how the MDP was defined and the resulting nutrient intakes, with vegetable intakes, for example, ranged from 191 to 500 g/d in high MDP adherers. A greater standardisation in the definition of a MDP is needed in order to integrate data from difference sources and translate it in dietary recommendations focussed on improved short- and long-term health.

The main strength of the present paper is that it is the first systematic review to examine the short-term impact of a MDP on mood and cognition. Second, the database combination used ensured optimal coverage of the data[26,27] and has been shown by others to retrieve 95·9 % of available references[26]. Third, the review covers all available literature up to December 2020. As for limitations, the number of studies found was small; therefore, the conclusions are preliminary rather than robust. However, this limitation provided an opportunity to identify research gaps. The second limitation is the high heterogeneity in the dietary and mental health status assessments used. This methodological variability restricted making comparisons between studies.

In conclusion, the possible short-term beneficial impacts of a MDP on cognitive and mental health have been reviewed systematically for the first time. The results provide some initial evidence that short-term dietary interventions can confer health benefits which directly and/or indirectly improve cognitive and mental health. However, future studies are required to elucidate which cognitive and other mental health domains could be beneficially affected and what are the underlying physiological mechanism mediating the effects. Short-term strategies to improve cognition, mood and anxiety are not only of interest to improve quality of life and capabilities in those with existing mental health deficit but also in healthy individuals. The definition of the MDP in future studies should be carefully considered, with attention given to its population adoption taking into account social, geographical and cultural mediators of eating behaviours.

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A. M. M. and K. J. M. formulated the research question. L. E. and E. S. C. conducted the systematic review of the literature. L. E. and A. J. conducted the risk of bias analysis. A. M. M., A. J. and L. E. interpreted the data. L. E. drafted the manuscript with all authors contributing to the manuscript ad approving the final version.

None to report.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521002567

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Appendix 3. Published version of Chapter 2 as a conference proceeding

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Irish Section Conference, 22–24 June 2021, Nutrition, health and ageing — translating science into practice – Part A

Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials

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The long-term benefits of a Mediterranean-style dietary pattern (MDP) on cognitive(1) and other mental health outcomes(2) has been consistently reported. However, the short-term efficacy of a MDP on cognition and mental wellbeing is less researched and remains mostly unknown. Therefore, this systematic review aimed to scrutinise the data from randomised controlled trials (RCT) to investigate whether a MDP can improve mental health in the short-term. This process also aimed to identify research gaps and provide insights into the design of future acute RCTs in the area.

Systematic searches were conducted in Ovid Embase, Ovid Medline and Web of Science Core Collection from inception up to December 2020, with the keywords "Mediterranean diet", "olive oil", "cognition", "dementia", "mood", "mood disorders", "anxiety", "anxiety disorders", "depression", "depressive disorders" and "wellbeing". RCTs conducted in adults (both males and females, over 18 years), up to and including 10 days intervention were included. No additional exclusion criteria were applied. A quality assessment was done using RoB2, a revised tool for risk of bias by Cochrane. A narrative approach was used to synthesise the data. A predefined protocol was registered with PROSPERO (CRD42021221085).

In total, 3002 studies were retrieved through initial database searches. Following the elimination of duplicates and screening stages, 4 studies met the inclusion criteria, all of which conducted in non-Mediterranean countries. Three studies included only young females (18 to 38 years) and one included both genders aged 60 to 80 years. Participants had no previous cognitive and mental health complaints. Despite the limited evidence available and the heterogeneity among the methods, the findings indicate that a MDP improves cognition and mood in the short-term. In particular, increases after MDPs compared to the controls in attention (1.1-1.4 fold), alertness (_p = _0.003; $F = 14.11$, $p < 0.01$; F = 22.23, p < 0.001) and contentment ($p = 0.001$; $F = 6.49$, $p < 0.02$; $F = 16.634$, $p < 0.001$) were consistently reported.

As a novel contribution to the literature, the short-term effects of a MDP on cognition and mood were reviewed systematically for the first time. A MDP was identified as a promising nutritional strategy to improve cognitive and other mental health outcomes in the short-term. This is valuable to promote the quality of life, for not only those with existing cognitive and mental health deficits but also healthy individuals. A recognised significant limitation of this study is the small amount of evidence available to review, however, this severe limitation has provided a systematic identification of research gaps, with further studies are needed to confirm these initial findings, and to provide granularity as to which domains are most responsive and in which population subgroups.

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2. Altun A, Brown H, Szoeke C *et al.* (2019) *Neurol Psychiatry and Brain Res* **33**, 1–10

Appendix 4. PROSPERO registration

1. Review title

Short-term effects of a Mediterranean-style dietary pattern and olive oil on cognition, mood and mental wellbeing: a systematic review of clinical trials

2. Original language title

English

3. Anticipated or actual start date

15/09/2020

4. Anticipated completion date

31/03/2021

5. Stage of review at time of this submission

Preliminary searches

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11. Review team members and their organisational affiliations

Miss Latife Esgunoglu, University of East Anglia

Mrs Elizabeth Sanchia Connole, University of South Australia
Dr Amy Jennings, University of East Anglia
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12. Funding sources/sponsors

University of East Anglia
Ministry of National Education, Republic of Turkiye

13. Conflicts of interest

None

14. Collaborators

15. Review question

Is a Mediterranean-style dietary pattern (MDP) and olive oil able to provide short-term (up to 10 days) cognitive and mental health benefits in adults?

16. Searches

Comprehensive searches will be conducted in the following databases; Ovid MEDLINE, Ovid EMBASE and Web of Science with the search terms “Mediterranean diet, Mediterranean eating pattern, olive oil, cognition, cognitive disorders, dementia, mood, mood disorders, anxiety, anxiety disorders, wellbeing and depression”. Free search terms and MeSH terms will be combined where databases allow which are MEDLINE and EMBASE.

The search strategies were designed with the guidance of an expert in systematic reviews, Dr Lee Hooper and an academic librarian, Matthew Smith at the University of East Anglia (UEA).

Studies published in English language will be included. All studies exploring Mediterranean diet adherence and cognition and mental health, up to the 08/12/2020 will be included.

Reference lists of included publications will be searched for additional original publications.

17. URL to search strategy

NA

18. Condition or domain being studied

The positive association between the long-term consumption of a MDP and cognition and overall mental health has been observed in epidemiological studies and a limited number of clinical trials. Besides, olive oil either by itself or as a component of a MDP has numerous health benefits. However, there is limited evidence on whether a MDP or olive oil impact on cognition and mental health in the short-term.

19. Participants/population

Adults (over 18)

20. Intervention(s), exposure(s)

Studies involving either a MDP or olive oil in their protocol will be included.

21. Comparator(s)/control

- Any control group (no intervention, ad libitum, another type of dietary intervention)
- Baseline for single-arm studies

22. Types of study to be included

This review will include all types of clinical trials, both single-arm and multi-arms, in which either a MDP or olive oil is employed.

Epidemiological studies (cohort, cross-sectional, observational, longitudinal, quantitative), reviews and meta-analyses will be excluded.

23. Context

24. Main outcome(s)

The main outcomes of interest are measures of mental health including cognition, mood, anxiety and depressive symptoms. Cognition can either be reported as a composite cognitive score such as provided by the Neurocognitive Test Battery (NTB), Cognitive Drug Research (CDR) or Cambridge Neuropsychological Test Automated Battery (CANTAB) test batteries, or as individual measures of domains such as memory and its sub-types, executive function, spatial recognition and verbal fluency.

25. Additional outcome(s)

We will report the following outcomes where available;

- Circulating biomarkers of cognition and mental health such as brain derived neurotrophic factor (BDNF) and circulating amyloid β (Aβ)

- Dietary adherence measured by methodologies, such as Food Frequency Questionnaires, 24 hr recall, Food Diaries and any validated instrument to measure Mediterranean diet adherence such as the Mediterranean Diet Adherence Score (MEDAS).

- Cardiovascular and metabolic parameters such as blood pressure, blood lipid and glucose levels as they are linked to cognitive and overall mental health

- Body weight, BMI, fat mass, fat free mass.

26. Data extraction (selection and coding)

The search results will be imported in EndNote as the reference management tool. The inclusion criteria are as follows;

- Adults over 18 years,
- MDP or olive oil interventions with a study period up to 10 days
- A control group or reference group
- Assessing at least one of the followings; cognition, mood, anxiety or depressive symptoms
- A clinical trial.

Titles and abstracts found using the defined search strategy above will be screened against the eligibility criteria by the first and second researchers independently. Full texts of potentially eligible articles will be reviewed in detail in the second step of screening. In the case of missing data or unavailability of full texts, study authors will be contacted for further information. Any disagreement during the study selection process will be resolved by discussion among all the authors.

A data extraction table will be created including the followings; authors, publication year, country, study design, population characteristics, study duration, intervention, outcomes, assessment methods used, results and any comments.

The article will be produced in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We will report the study selection process in a PRISMA flowchart. EndNote X9 will be used as the reference management tool.

27. Risk of bias (quality) assessment

The Cochrane risk of bias tool will be employed to assess risk of bias in randomised clinical trials. The tool has 6 domains; selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The result of bias investigation will be presented in a table under high risk, low risk or unclear categories.

28. Strategy for data synthesis

The data from the individual studies will be critiqued narratively with reference to the intervention, time-scale and the size effect observed. Study characteristics will be visualised by means of a table including the following columns; authors, publication year, country, study design, population characteristics, study duration, intervention, outcomes, assessment methods used, results and any comments. As we expect the data available to be limited with high heterogeneity among the included studies in terms of study design, the assessment methods used and measurement units, we do not plan to conduct a meta-analysis. This systematic review will follow the Synthesis Without Meta-Analysis (SWiM) (462) reporting guidelines as an extension to the PRISMA guidelines.

29. Analysis of subgroups or subsets

We will evaluate the results under two subgroups which are MDP and olive oil.

30. Type and method of review

Systematic review; Mental health and behavioural conditions

31. Language

English

32. Country

England, Australia

33. Other registration details

NA

34. Reference and/or URL for published protocol

NA

35. Dissemination plans

We are planning to publish this review in British Journal of Nutrition.

36. Keywords

Mediterranean diet

Olive oil

Cognition

Dementia

Mental wellbeing

Mood

Depression

Anxiety

37. Details of any existing review of the same topic by the same authors

NA

38. Current review status

Review_Completed_Published

39. Any additional information

Systematic reviews exist on the long-term effects of a MDP on cognitive and mental health, however, there is no systematic review currently assessing it in the short-term. Therefore, this review is being conducted to address a research gap, and to provide us with the rationale for, and contribute to the planning and design of an acute clinical trial examining the impact of nutrition on mental health outcomes.

40. Details of final report/publication(s) or preprints if available

Esgunoglu, L., Jennings, A., Connole, E., Murphy, K., & Minihane, A. (2022). Short-term effects of a Mediterranean-style dietary pattern on cognition and mental well-being: A systematic review of clinical trials. British Journal of Nutrition, 128(7), 1247-1256. doi:10.1017/S0007114521002567

Appendix 5. Published version of Chapter 3 as a full article

Open access Protocol

BMJ Open

Acute effect of a Mediterranean-style dietary pattern (MDP) on mood, anxiety and cognition in UK adults with mild to moderate anxiety and depression: the MediMood randomised controlled trial protocol

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ABSTRACT

Introduction Psychological disorders including depression and anxiety are significant public health concerns. A Mediterranean-style dietary pattern (MDP) has been associated with improved mental well-being in observational studies. Evidence of the acute (defined as postprandial to 1 week) effects of an MDP on brain function, mood, cognition and important modulators, including sleep and the gut microbiota is limited. The current intervention aims to examine whether an MDP, compared with a Western diet (WD), improves mood, cognition and anxiety symptoms, postprandially, at 24-hour and after 5 days in adults with mild to moderate anxiety and depression.

Methods and analysis Twenty-five UK adults (aged 18 or over) with mild to moderate anxiety and/or depression and low adherence to an MDP were recruited to a cross-over randomised controlled trial. Each participant undergoes a 5 day MDP and a 5 day WD in a randomised order with all meals provided. The co-primary outcomes are mood and anxiety, with secondary outcomes including cognitive function, brain perfusion (as assessed by MRI), sleep quality, blood pressure, plasma glucose, insulin, lipids, C-reactive protein, cortisol, brain-derived neurotrophic factor, gut microbiota speciation and microbial metabolites including short chain fatty acids. A linear mixed model and/or paired analysis will be used to compare the effects of treatments over time.

Ethics and dissemination The study has received a favourable ethics opinion from the National Health Service London Queen Square Research Ethics Committee (22/LO/0796). The results will be disseminated through scientific journals and conferences.

Trial registration number NCT05927376.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The design of MediMood was informed by a systematic review of the literature which provided the need for, and informed the design of, the current randomised controlled trial (RCT).
⇒ MediMood is a highly controlled efficacy RCT with all food provided for 5 days with detailed food preparation instructions rather than dietary advice only.
⇒ The study quantified key physiological determinants of brain health including gut microbiota and brain perfusion quantified by MRI.
⇒ To minimise participant burden, the primary outcomes (mood and anxiety) and biological samples collection could not be conducted daily.
⇒ For logistical and costs reasons, MRI scans could not be executed at the beginning and at the end of the 5 day interventions, to assess short-term changes in brain perfusion, limiting us to assessing only the postprandial effects of dietary intervention on cerebral blood flow.

INTRODUCTION

Mental health disorders represent a major public health challenge.[1] In 2019, depression exceeded 280 million cases globally, and anxiety surpassed 300 million cases, as the two most common forms of mental health disorders.[1] Mental health disorders have constituted around 15% of 'years lived with disability' worldwide since 1990,[2] with depression predicted to be the global leading cause of disease by 2030.[3] In England, nearly 20% of adults report depression, anxiety, sleep problems, poor concentration and forgetfulness.[4]

The economic impact of mental health disorders are substantial, with an estimated annual global cost of approximately $5 trillion including loss of productivity.[5] The UK National Health Services (NHS) has allocated

a £2.3 billion budget for the years 2023–2024 for mental health services as part of its long-term plan.[6]

The main treatment for mental health disorders are antidepressant medications and psychotherapy; both can cause negative side effects,[7] stigma[8] and have poor uptake.[4] Despite increased treatment in recent decades, no decrease in the prevalence of mental disorders is evident,[9] underlining the need for alternative intervention approaches.

The WHO has highlighted the critical need for 'affordable, effective and feasible strategies to promote, protect and restore mental health', and launched several initiatives such as the 'Comprehensive Mental Health Action Plan 2013–2030'[10] and the 'World mental health report: transforming mental health for all'[11] to address these needs.

A Mediterranean-style dietary pattern (MDP) consists of high amounts of fruits, vegetables, legumes, nuts, olive oil and fish. It is low in high fat dairy, red and processed meat, carbonated beverages and free sugars, and rich in unsaturated fatty acids, polyphenols and unrefined complex carbohydrates,[12] which aligns with healthy eating guidelines in the UK and many other countries.[13]

Long-term adherence to an MDP has been consistently shown to protect mental health. Longitudinal analysis of the SUN cohort (n=10 094) reported that higher MDP adherence was correlated with a lower depression incidence after 4.4 years,[14] supported by a meta-analysis of observational studies showing a reduced risk of depression associated with long-term MDP adherence (OR=0.72; 95% CI, 0.60 to 0.87).[15] The Prevencion con Dieta Mediterranea (PREDIMED), the hallmark randomised controlled trial (RCT) in the field, reported a 41% reduction in depression among at-risk individuals with type 2 diabetes who followed an MDP supplemented with nuts for 3 years (HR=0.59; 95% CI, 0.36 to 0.98).[16] The HELFIMED,[17] SMILES[18] and AMMEND[19] trials, all of which examined the effects of an MDP on depression in adults with moderate to severe depression over the course of 3–6 months, demonstrated significant decrease in depressive symptoms. The cognitive benefits of an MDP have also been consistently reported. The PREDIMED study showed improved cognition after MDP interventions,[20] while a recent UK Biobank analysis suggested a reduced risk of future dementia associated with MDP consumption.[21] Additionally, a meta-analysis reported a linear dose–response relationship between an MDP adherence and the risk of future cognitive disorders.[22]

On the other hand, a Western diet (WD), which includes high amounts of saturated fat (SFA) and simple sugars, is associated with compromised brain health, and a higher incidence of depression, anxiety and neurological conditions.[23 24]

Our systematic review investigating the short-term effects (up to 10 days) of an MDP on brain health revealed improved mood and cognition, in particular, alertness, contentment and attention domains in the four included studies.[25] There were too few studies to draw firm conclusions, and we identified several limitations and research gaps. Three of the four studies were of 10 days duration, with no shorter term or postprandial data available. Besides, in all reviewed studies, participants were provided with dietary advice rather than the intervention diet, and adherence to the intervention was not monitored. Furthermore, mental health outcomes were not comprehensively assessed to elucidate which domains are most responsive to a short-term MDP intervention and little attention has been given to possible underlying mechanisms which could be mediating the acute effects of an MDP such as changes in inflammation, glucose regulation, cerebral blood flow (CBF) and the gut microbiota.[25]

Therefore, despite its potential benefits[25] on mental well-being and quality of life, the acute effects of an MDP are largely unknown. The overall aim of MediMood study is to examine the impact of an MDP versus a Western-style diet (WD) on mood, anxiety and cognition postprandially, at 24-hour (mood and anxiety only) and after 5 days, and to investigate underpinning physiological mechanisms.

METHODS AND ANALYSIS

This article follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[26]

Study setting

MediMood is a single-centre cross-over RCT conducted at the University of East Anglia (UEA), and the NHS Clinical Research Facility (CRF) intervention centre, based at the Quadram Institute (QI), in Norwich, UK. The data collection period spanned from June to December 2023.

Eligibility criteria

Potential participants were recruited from the general population and from the University staff and students, using advertising posters/leaflets, internal emails and social media.

Twenty-five people aged 18 years or over were recruited. Participants were eligible if they met the following conditions:

1. Had mild to moderate level depression and/or anxiety, established using the Patient Health Questionnaire (PHQ-9) (score 5-14/27)[27] and the Generalised Anxiety Disorder (GAD-7) (score 5-14/21).[28] Both measures are commonly used in the NHS settings as preindicators of depression and anxiety.
2. Were not already following an MDP, established using the Mediterranean Diet Adherence Screener (MEDAS) (score≤7/14) (online supplemental appendix 1).[29]
3. Had been on the same dosage of their medication for at least 3 months and expected to keep a stable dosage for the next 3 months (for those who are on any antidepressant/antianxiety medication).
4. Were eligible to undertake an MRI scan (eg, not having any possibility of pregnancy).

Table 1 The eligibility criteria

Inclusion criteria	Exclusion criteria
Males and females aged 18 or over	Vegan, vegetarian
Mild to moderate level anxiety and/or depression (PHQ-9 and/or GAD-7 scores of 5–14)	Allergic to any of the study components for example, nuts and fish
Low MDP adherence (MEDAS score≤7/14)	On antianxiety and/or antidepressant medication which has changed in the last 3 months or likely to change in the next 3 months
Able to have an MRI scan	Unwilling or unable to make changes to their diet for 10 days (2×5 days period)
Computer literate with internet access	Unable to attend the intervention centre
Fluent in written and spoken English	MEDAS score>7
Gave consent for the study team to contact their GP	Not fluent in written and spoken English
Willing and able to comply with all study procedures including diet	MRI unsafety
	Not agreement for the study team to contact their GP
	Not prepared to make changes to diet for 10 days (2×5 days period)

GAD-7, Generalised Anxiety Disorder (includes 7-item); GP, general practitioner; MDP, Mediterranean-style dietary pattern; MEDAS, Mediterranean Diet Adherence Screener tool (includes 14-items); PHQ-9, Patient Health Questionnaire (includes 9-item).

5. Were not vegan or vegetarian.
6. Did not have food allergies or intolerances to the food provided such as fish and nuts.

If participants reported antibiotics use in the last month, their participation was postponed until 1 month after treatment to allow the gut microbiota composition to return to its habitual status. Participants are requested to keep any probiotic supplement use and physical activity levels stable during their participation. For MRI safety, 'any possibility of being pregnant' or those with specific medical implants or devices (such as cardiac pacemakers or artificial limbs) were precluded from participating (online supplemental appendix 2, MRI Safety Screening Form). Participants were advised to discuss their participation with their general practitioners (GPs) and informed that the study researchers were going to inform their GPs about their participation (online supplemental appendix 3, Participant Information Sheet).

Table 1 lists the full inclusion and exclusion criteria.

Recruitment

Individuals who expressed an interest in the study were provided with the Participant Information Sheet and directed to the study website (https://app.mantal.co.uk/medimood), built on the Mantal platform, an online research management portal. First, participants were asked to provide consent (online supplemental appendix 4, Consent Form). Second, participants completed questionnaires to ascertain if they meet the study inclusion criteria detailed above. Those meeting the criteria were enrolled in the study and randomised to either an MDP or a WD for arm 1 of the study, by using random number generator in Microsoft Excel.

The study stages are displayed in figure 1.

Safeguards for maintaining psychological well-being of participants

Enrolled participants' GPs are notified about their patients' participation and provided with their PHQ-9 and GAD-7 scores. The GPs of participants who are ineligible due to severe levels of anxiety and/or depression were also notified. All participants are signposted to mental health and well-being support.

Interventions

The experimental arm is a 5 day MDP, with a 5 day WD comparator arm. Both diets are designed to provide approximately 2000 kcal/day (±10% flexibility per day, ranging between 1800 and 2200 kcal). The MDP diet scores 14 (or 13 if no alcohol is consumed) on the MEDAS scale (maximum score 14) on each of the 5 days. Conversely, the WD scores zero points on the MEDAS scale on each of the 5 days. The full meal plans are presented in the online supplemental appendix 5.

The total macronutrient (carbohydrates, fat and protein) composition, and free sugars, fibre, SFA and monounsaturated fat content of the diets have been designed to ensure that they represent typical MDP and WD. For the MDP, the PREDIMED diet was used as the reference standard[30] and for the WD, the nutrient profile was based on extreme nutrient intakes (lowest or highest 2.5%) of the UK population using the UK National Diet and Nutrition Survey (NDNS) data (https://www.gov.uk/government/collections/national-diet-and-nutrition). Table 2 represents the nutrient compositions of the test lunch meals, and table 3 represents the nutrient compositions of the full 5 day diets.

To capture their habitual dietary intake prior to the study, the participants are asked to complete the European Prospective Investigation into Cancer and Nutrition study Food Frequency Questionnaire (EPIC FFQ; https://www.epic-norfolk.org.uk/about-epic-norfolk/nutritional-methods/ffq/) before their baseline visit. To promote adherence, all study foods are delivered to participants' homes using a supermarket delivery service, with extra food provided for the evening meals for one other person at home. Participants are provided with booklets (online supplemental appendix 6), with guidance as to

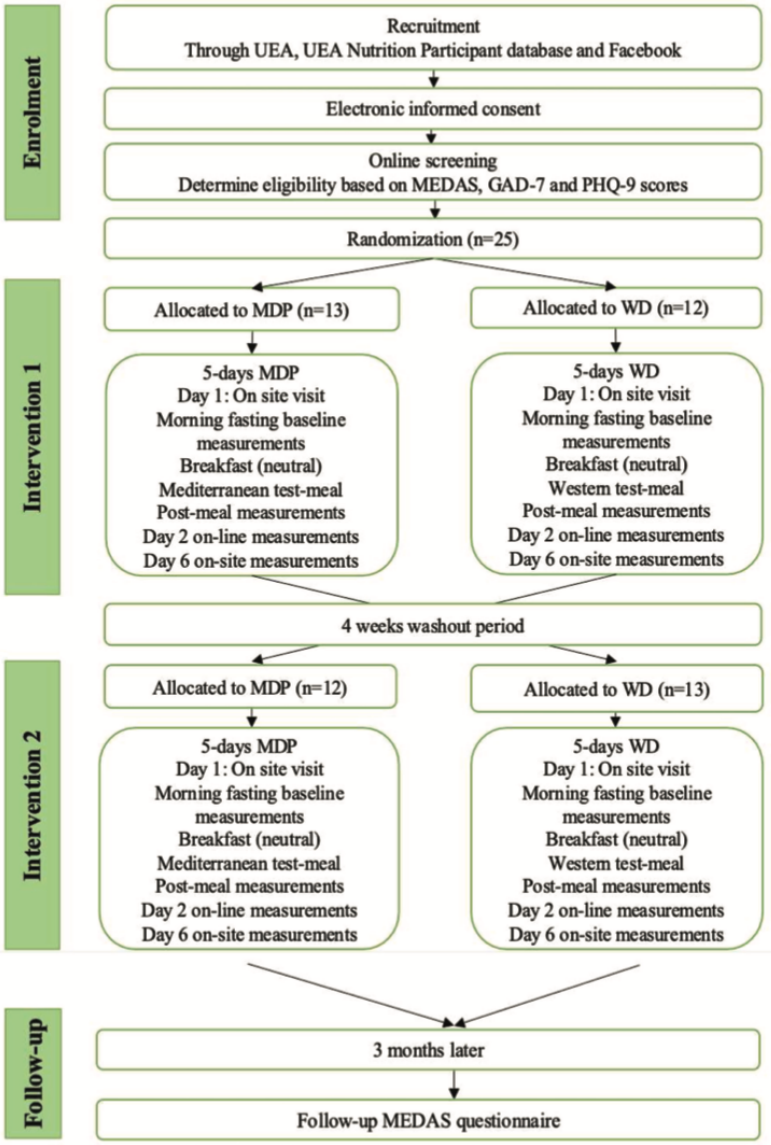

Figure 1 Study flow diagram. GAD-7, Generalised Anxiety Disorder (includes 7-item); MEDAS, Mediterranean Diet Adherence Screener; PHQ-9, Patient Health Questionnaire (includes 9-item); WD, Western-style diet.

how to store and prepare the meals and which additional foods and snacks can be consumed if hungry. The snacks are chosen to ensure they do not affect the MEDAS score of the study arm. To track dietary compliance, participants are asked to record all foods and beverages on the daily checklists in the booklets and provide notes and feedback. Participants are contacted daily to encourage dietary adherence.[31]

Participants are asked to visit the intervention centre on day 1 (figure 2), from 08:00 until approximately 15:30. Before their arrival, they are required to collect a urine and faecal sample at home using sample collection kit provided at least 2 days prior to their day 1 visits. The kit includes a stool sample catcher, two plastic tubes with scoop, a biohazard bag, a sealable bag, a urine sample collection pot with a sealable bag, a pair of disposable gloves, an insulated cool bag, two freezer blocks with two sterile outer bags and instructions. They are asked to collect the faecal sample within 24 hours prior to their clinical visit, and the urine sample as the first pass on the

Table 2 Nutrient composition of the lunch test meals (day 1) taken from the product labels

		Mediterranean diet	Western diet
Energy	Kcal	1013	984
Carbohydrates	g	45	123
	%	18.3	50.3
Free sugars	g	0	83
Fibre	g	10.6	2.9
Proteins	g	60	37.5
	%	24.3	15.3
Total fat	g	63	37.3
	%	57.4	34.4
SFA	g	8.8	15.2
	%	7.8	14

%, contribution to the total daily energy intake as per cent; g, grams; kcal, kilocalories; SFA, saturated fatty acids.

morning of their visit (day 1). Participants arrive at the intervention centre in a fasted state (fasted from 20:00 the night before). On arrival, anthropometric (weight and height) and blood pressure (BP) measurements are taken. A nurse collects the baseline blood sample. Participants are then provided with a honey and oat cereal bar. After 15 min rest, participants undergo the mood, anxiety, cognition and sleep testing via the study website; 90 min after completing these tests, participants are served either an MDP or a WD test meal (at 11:30)

Table 3 Nutrient composition table of the 5 day test diets

		Mediterranean diet (mean±SD)	Western diet (mean±SD)
Energy	Kcal/day	1878±46	2027±79
Carbohydrates	g/day	154.2±16.2	230.8±24
	%	32.8±3.0	45.5±4.6
Free sugars	g/day	0.3±0.6	35.7±10.4
Fibre	g/day	34.8±6.4	10.6±2.9
Proteins	g/day	80.8±19.1	64.6±11.4
	%	17.1±4	12.7±2.3
Total fat	g/day	105.0±8.9	94.2±11.2
	%	50.3±4.6	41.8±4.6
SFA	g/day	16.1±2.0	37.1±3.9
	%	7.2±1.0	16.5±1.3
MUFA	g/day	43.5±6.1	5.0±2.6
PUFA	g/day	16.9±7.5	2.6±3.0
Omega-3 PUFA	g/day	2.4±1.5	0.7±0.1
Omega-6 PUFA	g/day	9.3±6.6	0.6±0.7

%, contribution to the total daily energy intake as per cent; g, grams; kcal, kilocalorie; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

depending on the arm they are randomised to. Following the meal, participants' BP is measured at 12:45 and start postprandial mood and cognitive testing at 13:00. At 14:00, they undergo the brain MRI scan and provide a postprandial blood sample at 15:15. Afterwards, participants are provided with an afternoon snack before leaving the unit and consume their day 1 dinner at home. On day 2 morning, participants complete online mood and anxiety testing at home after having a honey and oat cereal bar. On days 2–5, participants complete a sleep diary. An actigraphy is worn throughout the intervention period. On completion of the 5 day intervention, participants return to the intervention centre on the morning of day 6 (08:00–10:00) to repeat the morning assessments, as carried out on day 1 (figure 2).

As menstruation-related hormonal fluctuations can cause disturbance in mood,[32] neurocognitive functions[33] and sleep,[34] a wash-out period of 23-days was chosen to ensure female participants are on the same phase of their menstrual cycle on each intervention arm (ie, 28 days between arm 1 day 1 and arm 2 day 1).

Outcomes

All outcome measures are summarised in table 4.

Primary outcomes

Mood and anxiety

Mood and anxiety levels are monitored using two scales. The primary outcome measure is the Profile of Mood State score (POMS)[35] with mood also scored using the Bond-Lader questionnaire.[36] The former has 65 items measuring 6 elements of mood (namely anxiety, anger, confusion, depression, fatigue and vigour); while the latter has 16 items (alert, drowsy, calm, excited, strong, feeble, muzzy, clear-headed, well-coordinated, clumsy, lethargic, energetic, contented, discontented, troubled, tranquil, mentally slow, quick witted, tense, relaxed, attentive, dreamy, incompetent, proficient, happy, sad, antagonistic, amicable, interested, bored, withdrawn, gregarious) under four categories (1. mental sedation or intellectual impairment, 2. physical sedation or bodily impairment, 3. tranquillisation or calming effects and 4. other types of feelings or attitudes) or three mood factors (alertness, contentment and calmness). Both are commonly used in research including three of the four studies included in our systematic review,[25] allowing a direct comparison of our findings with the limited published literature. The primary outcomes are the 'contentment' domain from Bond-Lader and the anxiety domain from POMS.

Secondary outcomes

Cognitive performance

Changes in cognition are assessed using a cognitive battery administered using the NeurOn online platform (https://neuropsychology.online). The following tests are included the following:

1. Reaction Time Test for motor function.
2. Digit Span Test for executive function.

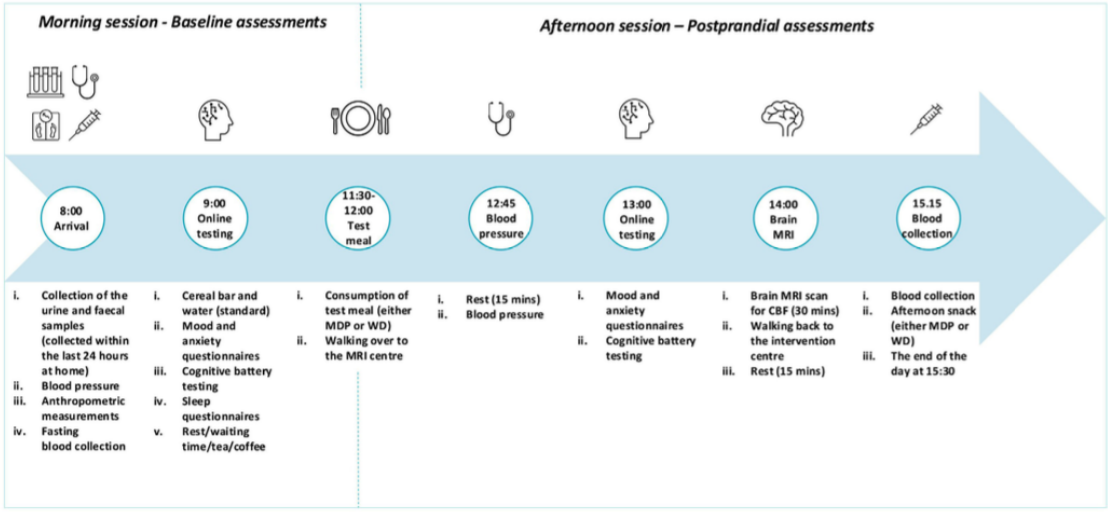

Figure 2 The protocol for the intervention centre visits. On the day 1 visit, participants undergo the full protocol. On day 6 visit, participants undergo the morning session only. CBF, cerebral blood flow; MDP, Mediterranean-style dietary pattern; WD, Western diet.

3. Trail Making Test (Trails A and Trails B) for executive function.
4. Sustained Attention to Response Test for executive function and attention.
5. Word Encoding for episodic memory.
6. Word Recognition for episodic memory.
7. Go No-Go for executive function and impulse control.
8. Fragmented Letters Test for visuospatial function.

Attention is an important secondary outcome as it was shown to improve in the short-term in our systematic review.[25] Attention is measured by the Sustained Attention to Response Task (SART).[37] In the SART test, participants have a visual presentation of 225 digits on a computer screen in a random order over a 4.3 min period (1150 ms between the onsets of digits) and are expected to respond with a key press except when they see the digit 3.[37 38] It is a commonly used measure in research and is postulated to be sensitive to everyday attention tasks in traumatic brain injured patients as well as normal (control) individuals.[37 38]

Cerebral blood flow

CBF, also known as brain perfusion, can be affected by macronutrient composition[39 40] and bioactives such as polyphenols,[41] which are abundant in an MDP. Furthermore, reduced brain energy glucose metabolism and CBF is evident in major depressive disorders[42] and cognitive decline,[43 44] which is affected by food intake. An effect of intervention on CBF is proposed to partly underpin the effect of intervention on mood, anxiety and cognitive outcomes. We hypothesise a greater CBF after the MDP meal compared with the WD meal. MRI is considered the gold standard CBF measurement,[41] with the following sequences used:

1. Time of flight angiography to determine the labelling plane to be used with pseudo-Continuous Arterial Spin Labelling (p-CASL).
2. P-CASL which provides a means of quantifying regional CBF.[45]
3. Magnetisation Prepared Rapid Gradient Echo (MPRAGE) for routine whole brain imaging using rapid acquisition.[46]
4. Fluid-Attenuated Inversion Recovery (FLAIR) to visualise the white matter hyperintensities (WMH).[47]

MPRAGE and FLAIR sequences help to eliminate potential confounders influencing CBF in the present study such as atrophy and WMH.

Resting state functional MRI (rs-fMRI) is used to explore resting neural activity and connectivity between different brain regions including those that are concerned with self-referential processing and salience networks.[48] During the scan, participants wear a pulse oximeter and respiratory belt to record the influence of cardiac and respiratory processes on measured signal. The scan parameters are taken from the UK-Biobank protocol,[49] allowing a comparison to this large cohort. Analysis utilises physiological noise modelling, white matter/CSF signal regression and spatial independent components analysis to define resting state networks. Seed-based analysis utilises regions of interest (ROIs) for example, insular cortex, to determine whole brain connectivity. As part of a more extensive analysis, we will employ a Functional Connectivity Multivariate Pattern Analysis approach. This methodology allows us to rigorously test hypotheses across the entire functional connectome as it encompasses all voxel-to-voxel functional connections throughout the entire brain. This exploratory approach complements

Table 4 Summary of the outcome measures

	Measurement	Tool used	Time point	Time per measurement point	Location
Screening	Mood	PHQ-9	Prebaseline	9 min	Home
	Anxiety	GAD-7	Prebaseline	6 min	Home
	Initial dietary habits	MEDAS	Prebaseline	10 min	Home
During interventions	Initial dietary profile	EPIC FFQ	Baseline	30 min	Home
	Mood and anxiety	Bond-Lader VAS, POMS	Baseline, postprandial, 24 hours, day 6	30 min	Home (24 hours) and intervention centre (baseline, postprandial and day 6)
	Cognitive functions	NeurOn battery	Baseline, postprandial, day 6	30 min	Intervention centre
	CBF	MRI	Postprandial	30 min	UWWBIC
	Blood pressure		Baseline, postprandial, day 6	5 min	Intervention centre
	Blood samples		Baseline (≥10 hour fasting), postprandial, day 6 (≥10 hour fasting)	15 min	Intervention centre
	Urine and faecal samples		Baseline, day 6		Home collection kits are provided
	Weight and height	SECA scale	Baseline, day 6	5 min	Intervention centre
	Initial sleep profile	PSQI	Baseline	10 min	Intervention centre
	Sleep quality	Actigraphy KSD KSS	Over 5 days	Continuously (for actigraphy) 5 min (for KSD and KSS)	Home
	Subjective dietary review score	Non-validated single question	Day 6		Intervention centre
Follow-up	Dietary behaviour	MEDAS	3 months	10 min	Home

CBF, cerebral blood flow; EPIC FFQ, European Prospective Investigation into Cancer and Nutrition study Food Frequency Questionnaire; GAD-7, Generalised Anxiety Disorder-7; KSD, Karolinska Sleep Diary; KSS, Karolinska Sleepiness Scale; MEDAS, Mediterranean Diet Adherence Screener tool (includes 14-item); PHQ-9, Patient Health Questionaire-9; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; UWWBIC, University of East Anglia Wellcome-Wolfson Brain Imaging Centre; VAS, Visual Analogue Scale.

the seed-based method as it does not require a predetermined parcellation of the brain into ROIs.[50]

Blood pressure

Brachial BP is measured with the participant seated and following a 5 min rest period. Measurements are taken using an automatic BP monitor (Omron, 705IT) with an appropriately sized cuff. BP is measured three times and averaged in accordance with published guidelines.[51]

Biological samples

Blood, urine and faecal samples are collected at baseline (on day 1) and on completion of the 5 day intervention (on day 6 morning). Postprandial blood samples are collected after the day 1 test meal; 30 mL of blood is collected in three separate tubes (EDTA, Heparin, SST). Several blood biomarkers of mental and cognitive health as well as cardiometabolic health will be assessed including but not limited to plasma glucose, lipids, cortisol and select inflammatory markers and brain-derived neurotrophic factor. On arrival of the day 1 and day 6 mornings, the urine and faecal samples are frozen at −80°C for later analysis.

Gut microbial profile

The link between the gut microbiota and anxiety, depression,[52] and cognition[53] is evident through the gut–brain axis. Diet composition is an important modulator of microbiome composition and metabolism.[54] The gut microbiome will be profiled using 16S rRNA Amplicon-based Metagenomic Sequencing of faecal samples.[55]

Metabolomics profile

Metabolomics are a tool for providing mechanistic insight into the response to dietary interventions.[56] The influences of interventions on the metabolomics signature in serum and/or faecal samples will be explored using 1H-NMR-based untargeted metabolomics approach.[57]

Targeted metabolomics by Liquid Chromatography Tandem Mass Spectrometry will be used to measure both straight and branched short chain fatty acids, which are important mediators of gut–brain communication.[58]

Sleep timing, quality and quantity and circadian rest-activity rhythmicity

Due to the multidirectional relationship between sleep and circadian disturbances, anxiety and depression,[59–61] cognition including alertness and attention[62] and food intake,[63] we will investigate the short-term effects of diet on sleep and circadian rhythmicity. By doing so, we also aim to eliminate the confounding effect of low sleep quality on mood and anxiety. The Pittsburgh Sleep Quality Index (PSQI) will be used to establish the initial sleep profile to detect sleep disturbances on day 0.[64] Sleep quality is tracked during the two 5 day intervention periods using the Motion Watch 8, which is a wrist-worn actigraphy device. This will allow for the estimation of sleep timing, duration and quality as well as the amplitude and stability of circadian rest-activity rhythmicity known to be interlinked with mental well-being. The Karolinska Sleep Diary (KSD) is a subjective measure and used to estimate the duration, timing and quality of all sleep periods and will complement the actigraphy data to increase the accuracy of the objective sleep quality estimation.[65] The Karolinska Sleepiness Scale (KSS) is administered every morning during the interventions alongside the KSD, to subjectively measure sleepiness. The KSS is a 9-point scale and asks the user to circle the number that represents the sleepiness level during the immediately preceding 5 min.[66]

Dietary behaviour

Participants will be sent the MEDAS questionnaire, 3 months after completing both arms to see if they have made any long-term change to their diets compared with the screening phase. They were also asked to rate how they found following the diets on a scale of 1–10.

Statistical methods: data collection, management and analysis

Sample size calculation

The sample size calculation was based on data from a previous cross-over trial of the effect of MDP adherence in a young healthy adult group.[67] Assuming an error rate of 0.05 and 90% power, we would require 15 and 20 participants to complete each arm for the primary outcome, which is the contentment, a mood domain from the Bond-Lader scale (9.6 unit expected difference, SD 10.3). To account for up to 20% dropout between random allocation to treatment sequence and study completion, we recruited 25 individuals.

Analysis

The main aim of the trial is to test if mood and anxiety can be improved over 5 days of intervention. The primary outcome analysis will use two-way repeated measures analysis with paired analysis taking mean change-scores.

CBF data analysis steps

1. Data preprocessing: raw data will be converted into the Brain Imaging Data Structure format for standardised data organisation.
2. Structural processing: individual subject-level processing includes structural image processing and segmentation and normalisation to enhance the quality of anatomical data.
3. Single-subject ASL processing: specific processing steps tailored for ASL data will be applied at the individual subject level, including motion correction, registration, partial volume correction and quantification of perfusion.

Group-level analysis: group-level processing through template creation producing a group-average image and subsequent atlas-based ROI statistical analyses.[68]

Machine learning analysis

Machine learning holds considerable potential for identifying biomarkers and enhancing clinical decision-making in varied contexts and is effective in discerning clinical interventions. Our study will use the Random Forest algorithm to enhance the interpretability of the heterogeneous data. This is a supervised machine learning approach recognised for its adeptness to handle missing values, alleviate data noise and mitigate the risk of overfitting making it a robust choice for our analytical framework.[69]

Monitoring: incidental findings and adverse events

Measurements that are deemed to be outside the normal clinical range will be reported to GPs as incidental findings. Potential incidental findings may be noted from PHQ-9 and/or GAD-7 questionnaires, blood sample analysis or the MRI scans. Due to the nature of the intervention, that is, commercially available food products, no adverse events are expected. If participants feel in anyway adversely affected by any foods or the principal investigator feels an AE necessitates cessation, the participant will be advised not to continue, and the appropriate measures will be taken. All AE's will be recorded and handled in accordance with Good Clinical Practice guidelines.

Patient and public involvement

None.

DISCUSSION

The MediMood study is an efficacy trial which will provide evidence and mechanistic insights into the acute and short-term effects of an MDP on mental health and cognitive performance in UK adults.

MediMood is the first RCT examining the acute (postprandial up to 5 days) effects of an MDP on mood and anxiety as the primary endpoint. Its strengths are as follows: (1) its controlled intervention design informed by a systematic review,[25] with standardised meals supported

by full food provision and detailed preparation instructions, rather than dietary advice only, (2) its cross-over design,[70] (3) assessment of several biological mechanisms which are hypothesised to mediate the effects of diet on mental and cognitive health, (4) combination of both objective and subjective assessment/measurement methods, (5) its focus on at-risk individuals for future major psychological and neurological disorders, (6) involvement of adults with no upper age limit as people suffer from mental disorders at every life stage and (7) considers the effects of the menstrual cycle on the study outcomes.

The main limitation of the study is that, to reduce the participant burden, we do not measure mood, anxiety and cognition every day. Second, our MRI scan is in a different location, which causes a delay in the postprandial blood collection. Given the nature of the diets, it is not possible to conduct a double-blinded intervention as participants know which diets they are following which may lead to an 'expectation bias'.[29] All clinical data, including MRI and biological samples will be anonymously analysed. Cross-over design requires participants to undergo two interventions which may cause attrition.[70] However, as our intervention duration is only 5 days, we think it is a low risk for the MediMood study.

Day-to-day low mood, anxiety and poor cognitive performance can adversely affect quality of life for not only those with pre-existing mental and/or cognitive health complaints but also healthy individuals. Therefore, there is a need to identify safe and accessible approaches impacting short-term brain health, which is the focus of the MediMood intervention, which also has a strong mechanistic component. The results will help inform future management strategies and policies for individuals with mental health complaints and in the early stages of age-related cognitive decline.

ETHICS AND DISSEMINATION

Research ethics approval

The study has been approved by the London Queen Square, NHS Research Ethics Committee and Health Research Authority (22/LO/0796). Informed consent is provided by all participants in the presence of certified research personnel.

Dissemination policy

The findings of the study will be disseminated through peer-reviewed publications, conference presentations, public outreach events, local and national news and academic blogs such as www.conversations.com for public members.

Data deposition

Anonymised data may be made available on request for additional analysis, by contacting AMM (senior author).

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Contributors LE, AJ, ES and AMM designed the study. The authors expertise and contributions are as follows: LE, AJ, RG and AMM for the postprandial study day design; AJ for the sample size calculation; LE, ML, AJ and AMM for the selection of blood biomarker analysis and blood sampling protocols; LE, ML, RG and AJ for the meal plans, booklet production and the website design; LE, ML and RG for the delivery of the intervention; MH and ALe for the design of cognitive function and mental health assessment; MH, JB and WP for neuroimaging. SS for MRI data analysis. ALa for the sleep assessment. ML for the gut profiling and metabolomics. ALe for the safeguards of mental well-being of the participants. All authors drafted and revised the manuscript with LE, AJ and AMM taking the lead role. All authors approved the final version of the manuscript. AMM is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 6. Published version of Chapter 3 as a conference proceeding

DOI: 10.1002/alz.074649

PUBLIC HEALTH

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PREVENTION (NONPHARMACALOGICAL)

Effects of a short-term Mediterranean diet on mental health, cognition and cerebral blood flow in UK adults: MediMood study protocol

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Abstract

Background: Dementias and mental health disorders (i.e. depression, anxiety) are significant public health challenges. Chronic consumption of a Mediterranean diet (MD) has been associated with lower incident dementia, improved cognitive performance, and reduced brain atrophy. Yet, short-term studies and randomised clinical trials (RCT) are lacking. Our systematic review of RCTs showed that in only four available studies, a MD can improve attention, alertness and contentment in up to 10 days (1). In a controlled efficacy study with all foods provided, we aim to explore postprandial, 24-h and 5 days impacts of a MD and a Western diet (WD) on mood, anxiety and cognition, cerebral blood flow as assessed by MRI.

Method: MediMood is an efficacy crossover RCT. Individuals (n = 25) over 18 years with mild to moderate anxiety and/or depression will complete a 5-day MD and a 5-day WD intervention with a 4-week wash-out period, with foods, meal plans and instructions provided. Biological samples (blood, urine, faeces) will be collected. The primary outcomes are mood and anxiety assessed using Bond-Lader and POMS questionnaires. Secondary outcomes include cognitive outcomes assessed through computerised neuropsychology tests, brain perfusion assessed by MRI, select cardiometabolic and inflammatory biomarkers, ketones, brain-derived neurotrophic factor, several hormones (e.g. serotonin, dopamine), gut microbiome speciation, sleep quality and behaviour change. The assessment time points during each arm are baseline (day 1 morning), postprandial (post day 1 lunch), 24-h (day 2 morning) and day 6 morning.

Result: NA

Conclusion: This will be the first well-controlled RCT examining the acute and short-term impacts of a MD and a WD on mental health and cognition in a targeted risk group. MediMood considers interfaces between sleep quality and the gut-brain axis as modifiable determinants of mental health. We expect the findings to provide novel insights in efficacy of a MD on daily and short-term well-being in those with existing mild-

Appendix 7. NHS HRA ethics application

IRAS Form | Reference: 22/LO/0796 | IRAS Version 6.3.4

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Acute effects of a Mediterranean diet on mood and anxiety

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Ionising Radiation for combined review of clinical trial of an investigational medicinal product

( ) Ionising Radiation and Devices form for combined review of combined trial of an investigational medicinal product and an investigational medical device

( ) Clinical investigation or other study of a medical device

(•) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (•) No

b) Will you be taking new human tissue samples (or other human biological samples)? (•) Yes ( ) No

c) Will you be using existing human tissue samples (or other human biological samples)? ☐ Yes ◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

- ☑ IRAS Form
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR MedTech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

○ Yes ◉ No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

☐ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

☐ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

☐ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

☐ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

☐ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

☐ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Acute effects of a Mediterranean diet on mood and anxiety

Please complete these details after you have booked the REC application for review.

REC Name:
London - Queen Square Research Ethics Committee

REC Reference Number:
22/LO/0796

Submission date:
06/10/2022

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

MediMood: A randomised controlled trial investigating the acute impact of a plant based Mediterranean-style dietary pattern (MDP) on mood, anxiety and cognition in UK adults with mild to moderate mental health complaints

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Anne Marie	Minihane
Post	Head of Nutrition and Preventive Medicine		
Qualifications	BSc Nutrition and Biochemistry PhD Nutrition		
ORCID ID	0000 0001 9042 4226		
Employer	University of East Anglia		
Work Address	University of East Anglia Norwich Medical School BCRE Level 2 Norwich		
Post Code	NR4 7UQ		
Work E-mail	a.minihane@uea.ac.uk		
* Personal E-mail	a.minihane@uea.ac.uk		

Work Telephone	01603592389
* Personal Telephone/Mobile	01603592389
Fax	01603593752

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title Forename/Initials Surname
	Mrs Sarah Ruthven
Address	University of East Anglia
	Research & Innovation Services
	Norwich Research Park
Post Code	NR4 7TJ
E-mail	s.ruthven@uea.ac.uk
Telephone	01603592389
Fax	01603593752

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	R211670
Sponsor's/protocol number:	NA
Protocol Version:	2.0
Protocol Date:	28/09/2022
Funder's reference number (enter the reference number or state not applicable):	NA
Project website:	NA

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

☐ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Depression, anxiety and age-related cognitive decline are leading global public health problems. A plant-based Mediterranean-style dietary pattern (MDP) includes olive oil as the main source of fat, fresh fruits, vegetables, seafood, legumes and nuts and a low consumption of red and processed meat, confectionary, and high-sugar drinks. A MDP promotes both physical and mental wellbeing and brain function. However, most studies to date have examined the impact of a MDP on health over months or years. As several underpinning biological mechanisms are likely to be responsive within hours or days, examining the short-term effect of a MDP on mental health outcomes is important.

In this study we aim to test whether a MDP can enhance mood, anxiety and cognition (brain function) following a meal (postprandial) and over 5-days in adults over 18 years with mild to moderate mental health problems (low mood and anxiety). Participants who are already following a MDP or have unstable use of antidepressant and/or antianxiety medications (i.e. medication has changed over the last 3 months, or the likely to change over the course of the study) will be excluded. Participants will be assigned to both a MDP and a Western diet (WD) for 5-days in a random order with a 4-week break period. We will conduct several computer-based tests measuring mood, anxiety and cognitive performance over the five days, brain imaging (MRI), and collection and analyses of blood, urine and faecal samples will also be carried out. The study will be conducted in the NHS Clinical Research Facility (CRF, Quadram Institute) by the Norwich Medical School, University of East Anglia (UEA) and Norfolk and Norwich University Hospitals (NNUH). As low mood, anxiety and stress disorders affect daily functioning and reduce the quality of life significantly for many, we believe the findings have wide public health application.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

PURPOSE AND DESIGN
The aim of the present study is to examine the effects of a MDP on mood and anxiety by comparing it to a WD.

A MDP is rich in fresh fruits and vegetables, olive oil, fish and nuts and has been traditionally followed in Mediterranean countries for centuries. It has been repeatedly proven to be healthy. A WD refers to the poor quality diet (high saturated fat, high free sugar and low fibre) that is followed in Western countries including the UK. A WD may harm health in long term.

Both diets have been designated using National Diet and Nutrition Survey (NDNS) data, from which extreme ends (top 2.5% and bottom 2.5% of population intake) were taken as the references, thus, it is ensured that the the interventions will overlap with the nations' dietary behaviour and stay in the frame of the latest nutrient profiles of the UK population. For the MDP arm, PREDIMED (the largest Mediterranean diet intervention conducted to date) (1) had been used as a reference diet in the intervention design.

Although long term consumption of the WD would not be recommended, we have based the intakes on NDNS data, so the nutrient profile is reflective of poor diets currently consumed by adults in the UK. The two interventions will be delivered using commercially available whole foods, and no supplements will be involved. We do not expect any significant risk, side effects or ethical issue with either intervention arm.

A cross-over RCT model will be used where participants perform as their own controls, reducing participant numbers. While designing the study, a number of discussions were held with different experts. Professor Anne Marie Minihane and Dr Amy Jennings are expert in the design and the delivery of dietary interventions. Professor Andrew Scholey (Swinburne University, Melbourne, Australia) advised on mood testing. Professor Michael Homberger advised on cognitive tests and brain imaging sequences while Dr Alpar Lazar advised on sleep assessment. Thus, ensuring that

the study is well planned in terms of; recruitment, inclusion and exclusion criteria, the safety of participants, acceptability of interventions, assessment methods, selection and validity of measures that have been planned to use, and the overall efficacy of the study.

The previous version of this application (IRAS Project ID was 314156) was not approved. The main reason was that the Committee was concerned that there was no clinical psychology input to deal with any potential acute exacerbations of anxiety/depression in our participants. In response to this, a Clinical Consultant Psychologist, Dr Adrian Leddy, has joined our research team. GPs of participants will be informed about their mental health status and participation in the study. This has been now made clear in all study documentations. Participants who do not consent GP contact will be excluded. Relevant charities such as MIND and Samaritans have been signposted in the PIS. Additionally, the language used in PIS in describing MDP and WD has now been more balanced. Participants are now clearly informed that a WD might have some mild side effects. The remuneration (£50) that will be given to participants to reimburse their time and effort has been removed from the 'benefits' section in both PIS and IRAS forms.

1. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E, Predimed Investigators. Benefits of the Mediterranean diet: insights from the PREDIMED study. Progress in cardiovascular diseases. 2015 Jul 1;58(1):50-60.

RECRUITMENT
The study will be advertised at UEA using social media accounts and internal email lists to invite students and staff. Recruitment posters and leaflets will be circulated on campus. All recruitment material will be submitted to REC for approval. Individuals who took part in previous studies run by our department, Nutrition and Preventive Medicine, and gave consent to be invited for future studies will also be contacted. If needed, recruitment might be broadened to the local media and relevant charities. No data will be collected until potential participants give their informed consent to take part in the study. No GP database will be involved.

INCLUSION/EXCLUSION
No participant will be excluded on the basis of race, gender, appearance or religion. The health and welfare of those not wishing to be involved will not be compromised by declining the invitation to participate. It will be made clear at all times that involvement in the study is entirely voluntary and that withdrawal can be initiated at any time and without giving a reason. Recruitment material will make no therapeutic promises. Inclusion and exclusion criteria have been designed solely to minimise confounders that may affect the validity of the outcome measure.

Overall we will recruit individuals who

- Have mild to moderate level of depression and/or anxiety as this makes them at risk population for future mental and cognitive diseases, and also likely to be responsive to the intervention.
- Do not normally follow a MDP in order to increase the chance of seeing the improvements provided by the intervention as the study duration is short.

People who are currently taking medication (antidepressant/antianxiety) of which has changed in past or next 3 months (i.e. study duration including recruitment) will be excluded to prevent a shadowing effect on the intervention effects. Vegan and vegetarians will be excluded as a MDP includes fish, and encourages consumption of more white meat (e.g. poultry) than red meat. Designing a novel alternative vegan/vegetarian MDP is beyond the scope of the current research. As our study will include questionnaires, people who are not fluent in English language will be excluded. Lastly, people having allergies to any of the study components such as fish or nuts will be excluded for their own safety.

CONSENT
People initially will be provided with the ethics committee approved Participant Information Sheet such that they can fully appraise themselves of the purpose and nature of research. Electronic consent process will be in place. Those who express an interest to taking part in the study will be contacted to arrange an online videoconference session via Zoom where the study will be explained in detail, such as the dietary interventions i.e. what they will eat, how the foods will be delivered, stored and prepared, and their questions will be answered. If they wish to proceed, informed electronic consent will be taken using the Consent Form approved by the ethics committee.

Consent forms will be completed in the presence of a researcher from the study team, who will take the participant through each point of the form, thus ensuring that they understand what is being asked. Both researcher and participant will use a simple electronic signature. A copy of the form will be made and given to the participant. If the study team have any doubt as to the ability of the participant to give informed consent then they will not be able to participate. All consent literature will be photocopied for their records and participants will have a minimum of 72 hours between consent and future involvement in the study. At each stage the participant will be reminded that their involvement is entirely voluntary and that they may withdraw at any time without giving a reason, and that such withdrawal will not in any way impact on their future healthcare.

RISKS, BURDENS AND BENEFITS

As mentioned above, no significant risks of the intervention are expected. However, as mentioned above, in case of any acute aggravation of existing mental health complaints, we will contact our clinical psychologist for the advice. In case of any discomfort or adverse effect (e.g. stomach bloating or wind as a result of increased fibre intake in the MDP), it will be monitored and documented immediately, and participants will be advised not to continue. The design has been carefully considered to minimise participant burden. For example, day two mood assessment will be done online instead of in the CRF to reduce the participant burden and all food will be delivered to participants home, via a supermarket delivery.

CONFIDENTIALITY
The General Data Protection Regulations (GDPR) 2018 and Data Protection Act (DPA) 2018 will be fulfilled to protect individuals' personal data. The handling of personally-identifiable data in the study will be conducted in compliance with the Caldicott principles, and under the new GDPR 2018 and DPA 2018 regulations, such that only relevant study-relevant information and data will be collected or measured. All data collected in the study will be pseudonymised by assigning a numerical code to participants and their associated data and biological samples. Participants will be made aware at their consent visit that their data will be anonymised and that only group mean (and not individual) data will be presented and published.

CONFLICT OF INTEREST
All study researchers declare no conflict of interest.

USE OF TISSUE SAMPLES IN FUTURE RESEARCH
Human tissues, blood and faecal samples collected as part of this study will only be used in this study for the purposes outlined in the research protocol. However these samples could be invaluable for future research in this area, and so during the consent process volunteers will be asked if they consent to the data and samples being stored to be used for future research projects. These samples will be de-identified and labelled with only their study ID. This information is available at the Participant Information Sheet.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply:*

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☑ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

Can a plant based Mediterranean-style dietary pattern (MDP) improve mood and anxiety after a meal (postprandial), at 24-hour and over 5 days in UK adults with mild to moderate mental health problems?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

If a MDP (compared to a Western Diet) can modulate:
- cognition (brain functions)
- cardiometabolic health (blood pressure and plasma lipid, glucose and insulin)
- circulating hormones regulating mood, anxiety and stress
- circulating biomarkers of mood and cognition regulation
- circulating ketone body profile which are the only alternative energy source for the brain
- the gut profile including gut microorganisms and hormones
- improve sleep quality which is a major determinant of mental and cognitive health
- response to treatment in accordance with baseline APOE genotype status will be investigated.
- dietary behaviour at 3 months

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

A MDP has been associated with decreased depression and anxiety symptoms, and the risk of future cognitive disorders such as dementia. However, this evidence is obtained from observational studies which do not explain causality. Besides, those studies were long-term, conducted over many months or years. Evidence looking at the acute impact of a MDP on mental health is extremely limited.

Considering that millions of people suffer from depression and anxiety worldwide, creating a huge personal, community and health care provision burden with direct (treatment costs) and indirect costs (loss of productivity due to inability to work), it is essential to discover safe, quick and accessible approaches to support individuals suffering from mental health problems. Such approaches would have wider application and associated with improved mental health, cognitive performance and overall quality of life in healthy individuals.

Our systematic review investigating the short-term impact (up to 10 days) of a MDP on mood and cognition (1) demonstrated that only 4 randomised clinical trials (RCT) are available with none conducted in the UK. Despite this very limited data, a MDP showed some indications of being beneficial in the short term.

Our systematic review identified several research gaps. Firstly, three of four studies provided dietary instructions rather than controlling the diet fully. Second, the same three studies out of four were conducted in young and healthy individuals. The remaining RCT was a single test meal and included people over 65 years with metabolic syndrome, with no mental and/or cognitive health complaints. Overall, the day-to-day impact of a MDP in individuals with current mental and/or cognitive health complaints remains unknown. In addition, none of the studies assessed hormones, biomarkers, ketones, gut profile and sleep quality, which are needed to establish the mechanism underlying any mental or cognitive health benefits.

The proposed study is therefore designed to understand the postprandial, 24 hour and five day effects of a MDP on mood and anxiety using a well-controlled diet that is habitually achievable. To the best of our knowledge, this study will be the first to do so.

1. Esgunoglu L, Jennings A, Sanchia Cornole E, Murphy KJ, Minihane AM. Short-term effects of a Mediterranean-style dietary pattern on cognition and mental wellbeing: A systematic review of clinical trials. British Journal of Nutrition. 2021 Jul 8.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Participants will be recruited, provide informed consent, and screened remotely, using a combination of questionnaires sent through the post or emailed, along with an online Zoom meeting, where there will be the opportunity to discuss the study at length with the study researchers. Once recruited participants will be invited to undergo two x five-day periods of intervention (MDP and WD) in a random order separated by a four-week washout period. All food will be delivered to participants by supermarket delivery along with detailed instructions on how to store, prepare and record the food consumed. During each five-day period participants will be requested to collect a faecal sample the day before, a urine sample on the morning of day one and attend the CRF after 12h fast. The day one schedule will be approximately 8-8,5 hours in total and include a 60 ml (30 ml x 2) blood sample, mood and cognitive questionnaire, a test lunch (MDP or WD) and a brain scan (MRI) post meal to assess brain blood flow. On day two participants will be asked to complete online mood and cognition questionnaires at home, on day five to collect a faecal sample and on day six, collect a urine sample and attend the CRF to provide a blood sample (30 ml) and conduct the final mood and cognitive testing.

The null hypothesis is that relative to a Western Diet (WD) "a MDP will not improve mood and anxiety compared over the course of five days in adults with mild to moderate levels of depression or anxiety.

The alternative hypothesis of the study is that relative to a WD, a MDP will improve mood and anxiety over the course of five days in adults with mild to moderate levels of depression or anxiety.

A detail description of the schedule as to what participants will be expected is given below.

POTENTIAL PARTICIPANTS
1. Send Participant Information Sheet (prior to the consent meeting, at least 5 days ago), 10 mins to read
2. Detailed information, questions and answers session, informed electronic consent via an online meeting, 45 mins
3. Screening via an email: PHQ-9, GAD-7, MEDAS questionnaires, and MRI safety screening form 20 mins

RECRUITED PARTICIPANTS

Participants will be given the equipment for urine and stool sample collections at home.
A wrist-worn actigraphy watch will also be given to be worn throughout the interventions 1-3 days prior to the study start.
Participants will be asked to complete a food frequency questionnaire capturing their habitual dietary behaviour.
All study foods will be delivered to the participants' addresses.

Day 1

8 am: Arrive at Clinical Research Facility (CRF)
Baseline measurements: Weight, height and blood pressure (15 mins), Venous blood collection (30 ml)(15 mins), Urine sample (will be done at home, the first pass of the day), Faecal sample (will be done at home prior to the 24 h), Sleep questionnaires (10 mins)
8.40 am: Simple breakfast (cereal bar and water) (10 mins)
9 am: Mood and cognitive measurements, a set of computerized tests (60 mins)
12 pm: Lunch (test meal) (30 mins)
2 pm: Mood and cognitive measurements (60 mins)
3 pm: Venous blood sample (30 ml) and blood pressure measurement (15 mins)
3.15 pm: MRI scanning (30 mins)
4.00 pm: End of the day 1 in CRF

Day 2
At home 9.00 am: The same simple breakfast (cereal bar and water) as day one (10 mins)
9.15-10.15 am: Mood measurements (30 mins)
10.15-10.20 am: Sleep questionnaires (5 mins)

Day 3,4,5 Sleep diaries will be kept daily (5 mins)

Day 6
8 am: Arrive at CRF
Baseline measurements: Weight, height, blood pressure (15 mins)
Venous blood collection (30 ml) (15 mins)
Urine sample (at home, the first pass of the day)
Stool sample (at home prior to the 24 h)
Single question asking their view on the diets, i.e. how easy/hard did they find following to the intervention?
8.40 am: Simple breakfast (cereal bar and water) (10 mins)
9 am: Mood and cognitive measurements, a set of computerized tests (60 mins)

4 WEEKS WASH OUT PERIOD

2ND ROUND, ALL STEPS REPEATED

Follow-up: A MEDAS questionnaire will be sent by an email 3 months after the study ends (15 mins).

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research

- [ ] Analysis of results
- [ ] Dissemination of findings
- [x] None of the above

Give details of involvement, or if none please justify the absence of involvement.

The described study is an efficacy RCT. Its design has been influenced by the feedback received from Norwich Institute of Healthy Ageing (NIHA) co-production partnership, and its lead Anna Sweeting.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [x] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [x] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [x] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- Male and female, aged 18 years or over
- Mild to moderate level of depression and/or anxiety. The former will be established using the 9-item Patient Health Questionnaire (PHQ-9) while the 7-item Generalised Anxiety Disorder (GAD-7) will be applied for the establishment of the latter. Both questionnaires are interpreted according to the total score. The classification of scores are: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe for PHQ-9 and, similarly, 0-4 no to low risk, 5-9 mild, 10-14 moderate, 15+ severe. Individuals will be included if they score 5-14 from PHQ-9 and GAD-7.
- Low habitual adherence to a MDP. A 14-item Mediterranean Diet Adherence Screener (MEDAS) questionnaire will be used to assess this criterion. People scoring 7 or less on a 14-point scale will be included.
- Access to, and able to use, the internet/computer/tablet device
- Understands and is willing and able to comply with all study procedures, including changes to diet
- Fluent in written and spoken English
- Willing and able to provide written informed consent

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Use of antidepressant/antianxiety medication if it has changed in the last 3 months or expected to change in the next 3 months (end of the second arm).
- High adherence to a MDP at present (scoring more than 7 on MEDAS)
- Being vegan or vegetarian
- Having a food allergy to any of the MDP elements such as fish or nuts
- Not giving consent to GP contact.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Online consent	1	0	45 minutes	By the study researchers. Via videoconferencing
Online screening	1	0	20 minutes	Results will be assessed by the study researchers. An email or paper copies will be sent.
Dietary interventions (MDP and WD)	2	0	10 days (5 days x 2)	Participants will follow their assigned diets for 10 days, with 2 5-days periods with a 4-week wash-out period.
Initial sleep profile assessment	1	0	5 minutes	Participants will be guided by study researchers. At CRF, at day 1 visit
Sleep diary	10	0	5 minsx5=25 mins	By participants. Day 1 and 5 at CRF, day 2,3,4 at home.
Wearing an actigraphy watch	2	0	2x5 days=10 days	By participants during the interventions
Mood and anxiety questionnaires	8	0	15 minutes	By participants. The 3rd one at 24-h will take place at home. The remainings will be done at CRF.
Cognitive tests	6	0	45 minutes	By participants in the presence of the study researchers at CRF.

Online follow-up questionnaire	1	0	10 minutes	By participants via an email

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Weight-height measurements	4	0	5 minutes	By the study researchers at CRF
Blood pressure measurement	6	0	5 minutes	By the study researchers at CRF
Venous blood collection (30 ml)	6	0	15 minutes	By nurses/phlebotomists at CRF
Urine sample	4	0	The first urine pass	By participants at home
Faecal sample	4	0	24hrs prior to day 1	By participants at home

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

☐ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

128 days = 2 x 5 days interventions + 4 weeks washout + single 3 months follow-up question

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

We do not foresee any significant side effect/risk with this research as the study will test a whole diet approach consisting of foods which are commercially available commonly consumed food items.

WESTERN DIET (WD): In the long term A WD may aggravate the existing mental health complaints of participants. Although we do not expect a significant impact over the 5 days intervention period, a Clinical Consultant Psychologist is part of the research team, who can advise if such an event happens. GPs of participants will be informed about their patients' participation in the study with the study overview and patients' mental health assessment results provided. In addition, the PIS includes signposting to relevant charities.

TRAVEL: Participants will have to travel to the UEA for the purpose of this study, which may represent an inconvenience to them. We hope to minimise the inconvenience by remunerating the participants, which may permit more convenient forms of travel - train, bus, or taxi.

BLOOD SAMPLING: Blood samples will be taken by venepuncture as part of this project which introduces a slight risk of bruising and infection. To minimise this risk, all blood samples will be collected by personnel who have been trained in these blood sampling techniques, and standard aseptic techniques will be employed to protect against cross-infection. Should values be outside of normal clinical limits the necessary clinical follow-up (similar to that outlined below for MRI findings) will be in place.

MAGNETIC RESONANCE IMAGING: A number of theoretical risks are associated with the magnetic resonance imaging (MRI) scans. Heating and peripheral nerve stimulation can occur, but only at power levels much greater than found in normal use: protections in the machine prevent safe levels being exceeded. the presence of pacemakers, surgical clips, and other implants is a contraindication to scanning; subjects will be asked to complete the standard MRI form identifying these. Scanning can be very loud; however, subjects will be provided with earplugs and/or headphones to reduce sound levels to a comfortable volume. It will be made clear that the subject can abandon the examination at any stage that they wish to, without prejudicing payment of expenses.

INCIDENTAL FINDINGS: There is a small chance that the examination may demonstrate an incidental abnormality. In such an event, it will be the Principal Investigator's responsibility to organise the necessary clinical follow-up, which will include informing the subject and their GP by mail and possible referral to an appropriate physician, as well as the organisation of further investigations. As for incidental findings emerging from MRI, it will be University of East Anglia Wellcome Wolfson Brain Imaging Centre (UWWBIC) Head or their delegate's responsibility to contact participants' GP.

TIME COMMITTMENT: The first on-site visit will be full day. Participants will be provided with rest periods in between the procedures. We moved the 24 hour mood assessment online to reduce the participant burden. The last visit of each day (at day 6) will be a short duration, approximately 2,5 hours with no extensive periods of waiting. The research team will be mindful of maintaining a pace which is to the comfort of the participant. Participants will be asked regularly if they are happy to continue before progressing to the next stage.

FASTING: Participants will be asked to fast for 12-hours prior to the two on-site clinical visits. Participants will be instructed to maintain hydration with water on the testing days.

Cognitive testing is designed to be slightly challenging so that an improvement in performance can be detected, which we explain to all participants. However, some participants can feel somewhat deflated if they feel they have not done well. We have designed our cognitive testing by placing the Fragmented Letters test last. Participants generally find this test relatively easy, so finish with a sense of 'success'.

We have selected the shorter validated sleep diaries, and incorporated the dietary instruction session in the consent meeting to keep the researcher-participant interaction to a minimum in order to save time for participants.

We put our best effort into meal planning to ensure the meals are acceptable, easy to prepare and enjoyable in both arms during the dietary design process. We will deliver all the required foods to their homes, to avoid the inconvenience of grocery shopping.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☐ Yes ◉ No

A24. What is the potential for benefit to research participants?

There are no obvious direct benefits to participants for taking part in the study. However, they may observe some improved health and wellbeing during the MDP arm.

Participants will contribute to the development of a better understanding on how a MDP and WD affect mental wellbeing, and therefore, future directions in research and policy making.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

No intervention will be available after the trial, but on request participants will be signposted to reliable source of dietary information.

A26. What are the potential risks for the researchers themselves? *(if any)*

The safety and wellbeing of the researchers is the utmost priority to us. However, as the intervention will take place at CRF and a few online assessment at participants' home on their own, we do not expect any risk for our researchers.

Some members of the research team will be handling and processing potentially infectious human biological samples, namely urine, faeces and blood. These individuals will be trained in Good Clinical Practice and will also be familiar with the joint standard operating procedures (SOPs) of the the University of East Anglia (UEA) and the Norfolk and Norwich University Hospitals (NNUH).

Risk assessments will be carried out and all study staff will be immunised against hepatitis B if appropriate to their role.

The analysis of samples will take place in the Bob Champion Research and Education Building (BCRE) at the UEA, and all staff will be trained in the laboratory procedures for handling biohazard samples and work to strict SOPs and Control of Substances Hazardous to Health (COSHH) guidelines and forms.

All clinical measurements will be held within the CRF, Quadram Institute, and nonclinical assessments may be held in small interview rooms within the BCRE building. Two researchers will be present for all study days as far as possible, and SOPs for safe working will be devised.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

We will send out an invitation email to all relevant individuals on our existing participant database (Department of Nutrition and Preventive Medicine, UEA). We will display recruitment posters around the campus and advertise the study through UEA social media platforms and local media. If needed, we will contact local relevant charities. This process will be carried out by our research team, mainly two PhD students. No other person outside our research team such as GP, any NHS centre will be involved in this. We will not use GP or hospital records to identify potential participants.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☐ Yes ☑ No

Please give details below:
Only information we will have will be potential participants' name and contact details during the recruitment. No other personal information will be collected until they give their informed consent, after which screening will take place.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☑ Yes ☐ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).
Posters will be displayed in various locations within the University of East Anglia.

A29. How and by whom will potential participants first be approached?

An initial invitation email, including the participant information sheet will be sent to potential participants who have expressed an interest in MediMood by contacting us using the study email address (medimood@uea.ac.uk) which will also be placed on recruitment posters. The principle of voluntary basis of the participation will be considered throughout the study. We are not planning to identify potential participants through GPs, therefore, no health care member will be involved in the first approach to participants.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(•) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

The researchers will obtain the informed electronic consent via a videoconference using Zoom. The researcher will explain each item, and will ask the participant if they have any further questions. They will also emphasise that they are free to withdraw at any time without giving in a reason for doing so. Participants will have been given the Patient information Sheet in the mailout detailed previously, and during the online consent process, and will have the opportunity to re-read this in the presence of a member of the research team prior to their consent being taken. Participants' GPs will be contacted in the event of any results outside the normal range being observed during the study. This provision will be detailed on the consent form. The consent form will be signed by both the researcher holding the meeting and the participant. Both researcher and participant will give a simple electronic signature. A printed version of signed consent forms will be stored.

As our target sample is adults who are able to give consent, we will not be handling with the procedures related to vulnerable groups.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

( ) Yes (•) No

If No, how will it be recorded?

We will obtain consent electronically. A researcher will go through the consent form with the potential participants online. Once participants give their consent, they will be emailed an online copy of the Consent Form for their records. Research team will also keep an online copy for the record.

A31. How long will you allow potential participants to decide whether or not to take part?

Potential participants will be given up to 48 hours to make their decision whether or not if they are happy to proceed with consenting. For those who do not provide on-line consent, another Zoom session will be offered to help completing the Consent Form.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

( ) Yes
(•) No
( ) Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

No arrangements have been made for translation of materials to any language other than English, or for the provision of interpreters. Due to the nature of the intervention (e.g. use of online platforms, questionnaires), a good understanding of written and verbal English is a requirement for participation the study, and will be detailed in the screening questionnaire.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

We do not expect any new information to emerge which have a potential to affect their participation. However, the research team will keep themselves up-to-date of any developments in the literature relevant to the study. Information with implications for risk or benefit of participation, or affecting the method of study delivery, will be assessed by the research team and disseminated to participants immediately as necessary.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ☐ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ☐ The participant would continue to be included in the study.
- ☐ Not applicable – informed consent will not be sought from any participants in this research.
- ☐ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

In the unlikely event of loss of capacity, as soon as the research team became aware that a participant had lost the capacity to consent, that participant would be fully withdrawn from the study due to both nature of the study and the ethical issues involved, and no further samples collected or tests undertaken. Any data already collected would be fully anonymised and retained for analysis.

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)

- [x] NHS computers
- [ ] Social Care Service computers
- [ ] Home or other personal computers
- [x] University computers
- [ ] Private company computers
- [ ] Laptop computers

Further details:
Our screening questionnaire will be circulated using Microsoft Forms link as a platform. Personal details such as email addresses and telephone numbers will be required such that we are able to contact, screen and book participants in for study sessions. Paper copies of information will be kept locked in a filing cabinet and will not be accessible by anyone outside of the research team, and will also be uncoupled form subsequent data through the deidentification process detailed elsewhere. Electronic study data will be deidentified at the point of collection, and where each participant is to be assigned a unique study code. Data will be stored solely on computers of the research team, namely password protected designated testing PCs, on which the various parts of the cognitive test battery will also be located, and on the password protected work (office) PCs of the team, again situated onsite at UEA and inaccessible except via swipe cards/door codes. Where data is collected at the CRF (NNUH facility), de-identified data will be collected either as hardcopies into the case report forms or on computers that will be situated in the CRF. Only the study team will have access to these folders. MRI data will be transfered to UEA computers via magnetic or optical media. Magnetic media will always be encrypted, and files will be deidentified prior to transfer.

A37. Please describe the physical security arrangements for storage of personal data during the study?

The personal data of participants will be stored in accordance with the General Data Protection Regulation (GDPR) 2018 and Data Protection Act (DPA) 2018. Safeguards will be taken to ensure about the security. Paper copies of personal data will be kept locked in a filing cabinet and will not be accessible by anyone outside of the research team. Electronic data will be stored on password-protected office computers situated on-site at UEA, backed-up onto secure servers regularly, and supported by security provided by each institution's IT team. Physical access to and filing cabinets computers will be via swipe cards/door codes. Study computers on which the various parts of the cognitive test battery will be located will be password protected and stored safely in locked cupboards when unattended.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The Data Protection Act 2018 and General Data Protection Regulation 2018 will be followed. Participants will be assigned random codes as their study identifications to deidentify their real identities. This will be done by a person outside our research team within the department to blind the study researchers. Participants will not be identifiable in publications with research findings presented as the average data of the cohort. Any identifiable information will not leave the research sites, nor appear in any reports or papers published by the research team.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Only members of the research team will have access to this data, to be stored in a highly secure manner as detailed previously. Participants will be made aware that their anonymised data may be subject to audit procedures but will remain confidential. Only GPs will be advised of a participant's personal data in the event of obtaining study data that indicates a potential risk to the participant. This will be detailed on the consent form so participants are comfortable with this arrangement.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Some of the biological samples (glucose, lipids and cortisol using blood samples) will be analysed at the NHS Norfolk and Norwich University Hospital (NNUH). All data will be analysed in the UEA by the research team, on UEA password protected computers and data storage systems. The data will not be transfered either outside the UK or EEA.

Data will be analysed by members of the research team at UEA. Any physical or electronic data will be secure, password-protected and encrypted where relevant, in accordance with guidelines from IT department and in accordance with GDPR.

A42. Who will have control of and act as the custodian for the data generated by the study?

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	Professor	Anne Marie	Minihane
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Work Telephone	01603592389		
Fax	01603593752		

A43. How long will personal data be stored or accessed after the study has ended?

- ☐ Less than 3 months
- ☐ 3 – 6 months
- ☐ 6 – 12 months
- ☐ 12 months – 3 years
- ☑ Over 3 years

If longer than 12 months, please justify:
Personal data of participants who consent to being contacted for future studies will be stored on the UEA Department of Nutrition and Preventive Medicine database and maintained in accordance with approved procedures.
For those who do not consent to being included in the database, once study has been published and all participants have been sent copies of the study outcomes, personal data will be deleted.
Volunteers will be asked if they agree to their anonymous samples being stored for future analysis as part of the consenting process.

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

The data generated via the questionnaires will be stored online where the UEA owned cloud location and the files will be password protected. Paper-based data will be stored within the same rooms, within locked filings cabinets which again will only be accessible by the research team. As for the biological samples collected, they will be de-identified, with only study ID on, and will be stored securely in the university freezers (-80) until the study end date, after which they will be transferred to the biorepository to be stored for up to 10 years. Approved personnel will have access by a swipe card.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

(●) Yes ( ) No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Participants will receive £50 as a voucher upon completion of both interventions of the study as a recognition of their participation.
Study foods will be purchased and delivered participants' addresses by the research team with no cost to participants.
All travel expenses will be reimbursed on presentation of receipts (public transport, taxis) or at current site-specific mileage rates (private vehicles) up to a 30 mile radius. Car parking fees will also be reimbursed.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (●) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (●) No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

(●) Yes ( ) No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

(●) Yes ( ) No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

(●) Yes ( ) No

Please give details, or justify if not registering the research.
As soon as the ethical approval is obtained, a public registry will be completed. The study will be registered on ClinicalTrials.gov.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [ ] Publication on website
- [x] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

News on local or national media, www.theconversation.com

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

To maintain anonymity, participants will be allocated a numerical identifier. After consent is obtained, only these numbers will identify participants. All raw and analysed data from tests and questionnaires will be assigned a code number and will not contain information that could enable identification of individual participants. In all publications and findings, the average values will be reported, the upper and lower bounds can be stated as only numbers with no identities participants will be anonymous.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
A summary report of the findings produced in a lay language will be sent to the participants in a paper-based letter form to their addresses.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [ ] Independent external review
- [ ] Review within a company
- [ ] Review within a multi-centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [x] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
Review was conducted by the research team in consultation with internal and external colleagues in the field.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☑ Review by a statistician within the Chief Investigator's institution
- ☑ Review by a statistician within the research team or multi-centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title Forename/Initials Surname
	Dr Amy Jennings
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E-mail	amy.jennings@uea.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Profile of Mood State (POMS) questionnaire which has 65 items.

A58. What are the secondary outcome measures? *(if any)*

Bond-Lader scale will be the co-primary outcome measure for mood and anxiety.
A composite score generated through a neuropsychological test battery will be used for the cognition. The Sustained Attention to Response Task (SART) will be the measure for the attention outcome which is also an important parameter for our study.
Other secondary outcome measures will include cardiometabolic profile markers (blood pressure, insulin, glucose, lipids and inflammatory markers such as C-Reactive Protein), hormones (adrenaline, cortisol, serotonin, dopamine and thyroid hormones), brain-derived neurotrophic factor (BDNF), tryptophan (precursor of serotonin and melatonin) and choline, APOE-4 genotype status, ketones (beta-hydroxybutyrate (β-HBA) and acetoacetate (AcAc)), neuroimaging using MRI to assess regional blood flow.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	25
Total international sample size (including UK):	
Total in European Economic Area:	

Further details:
The study design is a two-armed cross-over design, therefore, participants will complete both arms and act as their own controls.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Our sample size calculation was based on data from a previous cross-over trial of the effect MDP adherence in a young healthy adult group (1). Assuming an error rate of 0.05 and 90% power we would require 15 and 20 participants to complete each arm for mood (9.6 unit expected difference, SD 10.3) and cognition (0.7 unit expected difference, SD 0.9), respectively. To account for dropouts between random allocation to treatment sequence and study completion we will aim to recruit 20% more participants per group; thus, we will recruit 25 individuals.
1. Lee J, Pase M, Pipingas A, Raubenheimer J, Thurgood M, Villalon L, et al. Switching to a 10-day Mediterranean-style diet improves mood and cardiovascular function in a controlled crossover study. Nutrition. 2015;31(5):647-52.

A61. Will participants be allocated to groups at random?

(•) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Yes, participants will be randomised to a study arm, minimizing for sex (M/F) to ensure maximum possible balance across arms.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Our statistician will advise on statistical analysis plan finalisation, randomisation of participants, data management and data and statistical analysis.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title Forename/Initials Surname
	Miss Latife Esgunoglu
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	Title Forename/Initials Surname
	Miss Mamun Liaquat
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Title	Forename/Initials	Surname
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Post	Professor
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
Dr	Cristina	Razquin Burillo

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Title	Forename/Initials	Surname
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Post	Professor
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Title	Forename/Initials	Surname
Dr	Amy	Jennings

Post	Senior Research Fellow
Qualifications	Doctorate

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Title	Forename/Initials	Surname
Dr	Adrian	Leddy

Post	Clinical Associate Professor, Clinical Psychologist
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Telephone	0 1603 456161
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A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ☐ NHS or HSC care organisation
- ◉ Academic
- ☐ Pharmaceutical industry
- ☐ Medical device industry
- ☐ Local Authority
- ☐ Other social care provider (including voluntary sector or private organisation)
- ☐ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation: University of East Anglia

Given name	Sarah
Family name	Ruthven
Address	Norwich Medical School, BCRE Level 2

Town/city	Norwich
Post code	NR4 7UQ
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Telephone	01603592389
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E-mail	s.ruthven@uea.ac.uk

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)
Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU

Contact person

Name of organisation
Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	MRC UK Research and Innovation
Address	58 Victoria Embankment

London

Post Code EC4Y 0DS
Telephone 01793 298 902
Fax
Mobile
Email corporate@mrc.ukri.org

Funding Application Status: (•) Secured ( ) In progress

Amount: £30,000

Duration
Years: 1
Months: 6

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
Existing MRC consortium grant NuBrain: UK consortium for optimal nutrition for healthy brain ageing

Organisation Commonwealth Scholarships Commission UK
Address Woburn House 20-24
Tavistock Square
London
Post Code WC1H 9HE
Telephone +44 (0)207 380 6700
Fax
Mobile
Email press@cscuk.org.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: £10,000

Duration
Years: 2022
Months: 2025

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Organisation Ministry of National Education, Republic of Turkey
Address Ankara
Turkey

Post Code 06460
Telephone 90 312 413 16 93
Fax
Mobile
Email burslu_londra@meb.gov.tr

Funding Application Status: ◉ Secured ○ In progress

Amount: £10,000

Duration
Years: 2020
Months: 2023

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

◉ Yes ○ No

If Yes, please give details of each rejected application:

Name of Research Ethics Committee or ethics authority:	London South East Research Ethics Committee
Decision and date taken:	25 July 2022
Research ethics committee reference number:	22/LO/0499

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
Rowe	Felicia	Rowe

Organisation: Norfolk & Norwich University Hospital
Address: Norfolk & Norwich University Hospital
Clinical Research Facility Quadram Institute
Rosalind Franklin Road, Colney, Norwich
Post Code: NR7 0MG
Work Email: felicia.rowe@nnuh.nhs.uk
Telephone: 01603 647322
Fax:
Mobile:

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 31/10/2022
Planned end date: 30/09/2023

Total duration:

Years: 0 Months: 10 Days: 0

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

The last interaction with the participants will be the follow-up questionnaire that will be circulated 3 months after the study ends.

A71-1. Is this study?

- (•) Single centre
- ( ) Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study

Does this trial involve countries outside the EU?

( ) Yes (•) No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	1
[ ] NHS organisations in Wales	
[ ] NHS organisations in Scotland	
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[x] Educational establishments	1
[ ] Independent research units	

☐ Other (give details)

Total UK sites in study: 2

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

☐ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The standards that are set out in the Research Governance Framework will be followed in the monitoring and auditing the conduct of the study. In order to comply with Good Clinical Practice (GCP) guidelines, monitoring and auditing procedures will be followed. The study will be monitored at regular intervals to ensure compliance with the study protocol, GCP and legal aspects. This may include on-site checking of the case report form (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. Standard Operating Procedures (SOPs) will be in place to ensure the trial is conducted in accordance with GCP. Additionally, there will be an SOP for administering and scoring each task to ensure production of quality data. The PI will routinely monitor the trial and ensure the trial is being conducted in accordance with the protocol and GCP requirements. Additionally, the principal investigator and research team members involved in this study will have weekly meetings to discuss progress and any issues which arise during the course of the study.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

Participants will be asked to contact the study team immediately in the event of experiencing an adverse (AE) or serious adverse event (SAE), no matter how unlikely it seems that this would relate to the intervention

We have not established a Data Monitoring Committee as this is a short term study and we do not predict any high morbidity or mortality, or unknown or uncertain risks.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

In the event that concern be caused through a high number of adverse events being reported, clinical staff may terminate the study with immediate effect.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** In this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

UEA insurance shall apply.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

UEA insurance shall apply.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

UEA and NHS insurances shall apply.

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

☐ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

☐ Yes ◉ No ☐ Not sure

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Blood:
A fasted blood sample of no more than 30 ml will be collected three times at day 1 (two times) and day 6 (one time) in three separate tubes (EDTA, Heparin, Serum).

Urine:
A fasted midstream urine sample will be provided at the day 1 and day 6 on-site visits to measure selected plant bioactives as markers intake of foods specific to the MDP. All participants will be asked to provide the first morning void and to collect at least 100 mL of urine in a provided 200 mL container. Urine samples will be aliquoted in the laboratories and acid stabilisers added (i.e. hydrochloric acid, ascorbic acid).

Faeces:
Within 24 hours of the baseline and outcome measurement, a faecal collection will be made. From a passed stool, 4 pea sized aliquots of faeces will be removed (equipment provided) and added to sample tubes (n=2 tubes, with 2 pieces of faeces in each tube) containing RNAlater® RNA Stabilisation Solution (Invitrogen, UK) and silicone dispersion beads, and then inverted vigorously. Samples will then be placed in a sealed container (provided) on top of ice (ice cube sheets made by participant with material provided) and then returned to the research facility for freezing at -80° C until further analysis.

2. Who will collect the samples?

Blood will be collected in the Clinical Research Facility (CRF) by research nurses or Trust approved phlebotomists. Urine samples will be collected by the participant at home and brought to the CRF during the two on-site visits. The appropriate urine collection kits will be provided with instructions on their use. Faecal samples will also be collected by participants at home, using the equipment provided by the research team, and brought to the CRF during the on-site visits. Instructions on safe sample collection and appropriate storage conditions will be provided to participants in advance.

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?
(•) Yes ( ) No

In future research?
(•) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be stored: *(Tick as appropriate)*

In fully accoyonised form? *(link to donor broken)*
( ) Yes (•) No

In linked accoyonised form? *(linked to stored tissue but donor not identifiable to researchers)*
( ) Yes (•) No

In a form in which the donor could be identifiable to researchers?
(•) Yes ( ) No

If Yes, please justify.
Samples will be stored in the de-identified form by having participants' study IDs on, thus, the samples can be linked back to individuals using their study IDs. The PI and the researchers named by the PI will have access the study IDs.

9. What types of test or analysis will be carried out on the samples?

Blood: The plasma/serum will be stored for future analysis of pre-intervention/pre-existing inflammatory and cognitive decline risk biomarkers.

Urine: to measure selected plant bioactives as markers intake of foods specific to the MDP.

Faeces: will be assessed for gut bacterial speciation and short chain fatty acids.

10. Will the research involve the analysis or use of human DNA in the samples?

(•) Yes ( ) No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

(•) Yes ( ) No

12. If so, will arrangements be made to notify the individuals concerned?

( ) Yes (•) No ( ) Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

APOE gene status will be assessed, which is one of the most significant genetic risk factors for the dementia. Neither participants nor relatives, will be notified about the results as, (1) yet there is no available interventions which can with any certainty mitigate the increased risk and (2) the genotype is predictive rather than deterministic, with the majority of carriers never developing dementia.

Participants will be asked to consent to the results of their medical screening (and any other relevant details, determined by the clinical advisor) being forwarded their GP. This is to ensure the primary health care provider (GP) has access to any pertinent clinical data regarding their patient. No clinical opinion will be given by the research team on the basis of a one-of test result. The GP of the volunteer may decide to pursue the matter with subsequent test to establish the importance of the finding.

During the MRI scan procedure, there is the potential that an abnormality may be detected, which the participant is unaware of. These occurrences are generally infrequent. However, in the event of this happening, the Chief Investigator will highlight this finding with the participant primary care provider (GP), to ensure that the necessary clinical follow up may be pursued.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

All samples will be collected in CRF and stored in -80°C freezers at CRF. Before analysis, samples will be transferred to the Bob Champion Research and Education Building (BCRE), UEA according to approved human tissue schedule of works attained for each procedure. Faecal samples will initially be stored at -80°C within CRF. Access to all stored samples in the CRF and BCRE is restricted to staff as delegated by the CRF management (holding an approved research passport). The BCRE has swipe-card access and the freezer room, and each individual freezer, is locked when not in use (with keys held in a code protected key press (access to key-press code is limited to authorised personnel). Samples are stored in a pseudonymised format (i.e. numerical code) and linking codes to connect subjects to numerical codes will have restricted access (delegated by the Principal investigator). All samples will be stored at the biorepository for a maximum of 10 years from the collection of the last sample from the last volunteer. Samples will then be disposed of or transferred to the NNUH Human Tissue Bank for long term storage and potential use for further analyses within this research or in future research. The samples will be kept there in the name of the Principal investigator and access will be restricted to the Principal investigator and researchers named by the Chief investigator only. The Principal investigator is responsible for the custodial arrangements.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☑ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

The samples will be stored for up to 10 years to use for future research purposes, in order to analyse the biological samples for any new emerging biomarkers of health and dietary exposure. Participants will be informed about this possibility on the Participant Information Sheet as well as the Informed Consent Form.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site	Investigator Name
IN1	☐ NHS/HSC Site ☑ Non-NHS/HSC Site	Forename: Anne Middle name: Marie Family name: Minihane Email: a.minihane@uea.ac.uk Qualification (MD...): PhD Country: United Kingdom
	Institution name: University of East Anglia Department name: Wellcome-Wolfson Brain Imaging Centre (UWWBIC) Street address: School of Psychology Town/city: Lawrence Stenhouse Building Post Code: NR4 7TJ Country: United Kingdom	
IN2	☑ NHS/HSC Site ☐ Non-NHS/HSC Site	Forename: Latife Middle name: Family name: Esgunoglu Email: l.esgunoglu@uea.ac.uk Qualification (MD...): MSc Country: United Kingdom
	Organisation name: NORFOLK AND NORWICH UNIVERSITY HOSPITALS NHS FOUNDATION TRUST Address: COLNEY LANE COLNEY NORWICH Post Code: NR4 7UY Country: ENGLAND	

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.
3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.
10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.
11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.
12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [x] Chief Investigator
- [ ] Sponsor
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

- [ ] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Anne Marie Minihane on 04/10/2022 17:16.

Job Title/Post:	Prof of Nutrigenetics
Organisation:	UEA
Email:	a.minihane@uea.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mrs Sarah Ruthven on 06/10/2022 14:33.

Job Title/Post:	Research Manager
Organisation:	University of East Anglia
Email:	researchsponsor@uea.ac.uk

Appendix 8. ClinicalTrials.gov registration

Study overview

Brief summary: Observational studies and a limited numbers of RCTs have observed that habitual Mediterranean-style dietary pattern (MDP) consumption is associated with improved mental health and cognition. Yet, its efficacy in a short-term has not been studied in well-controlled intervention settings.

MediMood is a cross-over RCT aiming to test whether a MDP can affect mood and anxiety following a meal (postprandial) and over 5-days in adults over 18 years with mild to moderate mental health problems relative to a Western diet (WD).

Detailed description: Depression, anxiety and age-related cognitive decline are leading global public health problems. A plant-based Mediterranean-style dietary pattern (MDP) includes olive oil as the main source of fat, fresh fruits, vegetables, seafood, legumes and nuts and a low consumption of red and processed meat, confectionary, and high-sugar drinks. A MDP promotes both physical and mental wellbeing and brain function. However, most studies to date have examined the impact of a MDP on health over months or years. As several underpinning biological mechanisms are likely to be responsive within hours or days, examining the short-term effect of a MDP on mental health outcomes is important. The overall goal of the present study is to understand the effects of a MDP on acute/sub-chronic brain health and its underpinning mechanisms.

MediMood is a randomised cross-over efficacy trial. Participants will be assigned to an isocaloric MDP and a Western diet (WD) for 5-days in a random order with a 4-week wash-out period. All foods, meal plans and detailed dietary instructions will be provided. In addition to the primary outcome measures (mood and anxiety), the impact of intervention on cognitive performance, sleep, cerebral blood flow (MRI) and a selection of biomarkers of brain function will be measured in biological samples over five days.

As low mood, anxiety and stress disorders affect daily functioning and reduce the quality of life significantly for many, the investigators believe the findings will have wide public health application.

Official Title: MediMood: A Randomised Controlled Trial Investigating the Acute Impact of a Plant Based Mediterranean-style Dietary Pattern (MDP) on Mood, Anxiety and Cognition in UK Adults With Mild to Moderate Mental Health Complaints

Conditions: Depression/Anxiety

Intervention/ Treatment:

Behavioural: Mediterranean diet

Behavioural: Western diet

Other study ID Numbers: R211670

Study start (Actual): 2023-08-01

Primary completion (Actual): 2023-12-15

Study completion (Estimated): 2024-06-30

Enrolment (Actual): 25

Study type: Interventional.

Location: Norwich, Norfolk, UK

Participation criteria

Eligibility criteria:

Inclusion criteria:

- Male and female, aged 18 or above
- Is willing and able to comply with all study procedures, including changes in diets
- Has access to and able to use the internet/computer/tablet device
- Mild to moderate level of anxiety and/or depression symptoms, assessed by Generalised Anxiety disorder (GAD-7) score and Patient Health Questionnaire (PHQ-9), scores 5 to 14 on both questionnaires
- A habitual MEDAS score of ≤ 7/14
- To be fluent in English

Exclusion Criteria:

- MEDAS score >7
- Vegan/vegetarian
- Allergies to one of the study components i.e. nuts, fish
- On antidepressant or antianxiety medication where dosage is likely to change over the next 3 month
- Factors precluding MRI scanning such as suffers from claustrophobia or has metal implants
- Not fluent in English
- Not agreement for the study team to contact the participants general practitioner about trial participation and screening results

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: Yes

Study plan:

Design Details

Primary Purpose: Prevention

Allocation: Randomized

Interventional Model: Crossover Assignment

Masking: Single (Outcomes Assessor)

Arms and Interventions:

Participant Group/Arm:	Intervention/Treatment
Experimental: Mediterranean-style dietary pattern A Mediterranean-style diet (as a whole diet, no supplements	Behavioural: Mediterranean diet • All foods, meal plans and instructions provided.
Active Comparator: Western-style dietary pattern A Western-style diet (as a whole diet, no supplements)	Behavioural: Western diet • All foods, meal plans and instructions provided.

Primary Outcome Measures:

Outcome Measure	Measure Description	Time Frame
Change in mood	Established by the Bond-Lader visual analogue scale (includes 16 items each having antonyms on two ends, on a scale of 1 to 100, 50 being the neutral point)	Baseline (morning of day 1), Postprandial (after lunch on Established by the Bond-Lader visual analogue scale (includes 16 items each having day 1), 24-hours (morning of day 2), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in anxiety	Established by the Profile of Mood States (includes 65 items on a 5 point Likert scale)	Baseline (morning of day 1), Postprandial (after lunch on day 1), 24-hours (morning of day 2), day 5 (morning of day 6 upon completion of 5 full days intervention)

Secondary Outcome Measures:

Outcome Measure	Measure Description	Time Frame
Change in cognitive performance	Established by a neuropsychological test battery (https://neuropsychology.online) which assesses the following measures; attention, motor function, executive function, episodic memory, impulse control, visuospatial function	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Cerebral blood flow	Measured using MRI	Postprandial day 1
Change in blood pressure	Measurements of brachial artery blood pressure (both diastolic and systolic pressure)	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in gut microbiota speciation	Faecal samples will be analysed for the gut microflora using 16sRNA sequencing.	Baseline (morning of day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma short chain fatty acids (SCFA)	Acetate, propionate and butyrate	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in untargeted metabolomics	Analysed through faecal samples using 1H-NMR-based untargeted metabolomics approach.	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Habitual sleep quality profile assessed by the Pittsburgh Sleep Quality Index	The Pittsburgh Sleep Quality Index is a 10-items validated questionnaire, which is based on 'the last month'. It will be used to establish usual sleep habits (before the interventions) and to	Baseline (morning of day 1)

	identify sleep disturbances if there is any.	
Change in subjective sleep quantity	Assessed using the Karolinska Sleep Diary (KSD). The KSD is a series of questions, with 5 possible tick box options, which characterise the efficiency and the duration of last night's sleep.	Each morning, days 1-6
Change in subjective sleep quality	Assessed using the Karolinska Sleepiness Scale (KSS). The KSS is a single item, 9-point scale, assessing the sleepiness level at a particular time of day.	Each morning, days 1-6
Change in objective sleep quality	Assessed using the MotionWatch 8. The MotionWatch 8 is a medical-grade actigraphy watch which can be used to monitor sleep, circadian rhythm and physical activity. Its software (The Motion Ware) will provide two objective measures of sleep quality, namely sleep efficiency and sleep fragmentation.	Each morning, days 1-6
APOE4 genotype status	Assessed through DNA genotyping	Baseline (day 1)
Participants subjective overview of the intervention	Assessed through a non-validated single question	Upon completion of 5 full days

Other Outcome Measures:

Outcome Measure	**Measure Description**	**Time Frame**
Change in dietary behaviour	Through the Mediterranean Diet Adherence Screener (14 items food questionnaire, MEDAS) questionnaire, with a minimum score of 0 and a maximum of 14. A	Screening and 3 months upon the completion

	higher score indicates a higher diet quality which is a better outcome	
Change in plasma insulin	Measured using ELISA	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma glucose	Measured by autoanalyser	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma triglycerides	Measured by autoanalyser	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma cortisol	Measured by autoanalyser	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma brain derived neurotropic factor	Measured by ELISA	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)
Change in plasma serotonin	Measured by ELISA	Baseline (morning of day 1), Postprandial (after lunch on day 1), day 5 (morning of day 6 upon completion of 5 full days intervention)

Collaborators and Investigators

Sponsor: University of East Anglia

Collaborators: Newcastle University

Investigators: Principal Investigator: Anne Marie Minihane

Appendix 9. Participant information sheet

5-day plant based Mediterranean style and Western style diet on Mood and Anxiety in UK adults

PARTICIPANT INFORMATION SHEET

13/12/2022, version 2.1, IRAS ID: 320471

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

We would like to invite you to take part in a research study conducted by the University of East Anglia (UEA). Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully, and do not hesitate to contact us if anything is not clear or if you would like more information.

This study is organised by Professor Anne Marie Minihane (the Principal Investigator) and Miss Latife Esgunoglu.

Members of the study team who can be contacted are:
Miss Latife Esgunoglu and Miss Marrium Liaquat.

To contact the study team:
Tel: +44 (0) 1603591949

Email: medimood@uea.ac.uk

Before deciding whether or not you would like to take part, you may wish to talk about it with a relative, friend or your local doctor.

If you decide to take part in the research project, you will first be asked to provide consent to participate in the study. You will be asked to sign and return a consent form either electronically or by post which a researcher will check via videoconferencing software (e.g., Zoom). A copy of the signed consent form will be provided to you. By signing it you are telling us that you:

- understand what you have read in this information sheet
- consent to take part in the research project
- consent to have the tests and treatments described
- consent to the use of your personal and health information as described.

An expression of interest does not commit you to take part.

Why are we doing this research and why is it important?

Mental health issues such as anxiety and depression are common problems worldwide at all stages of life. Although some effective medications and psychotherapies are available to treat depression, these can take time to work, may be expensive, and do not suit everyone.

Scientific evidence shows that what you eat plays an important role on your health, including mental and cognitive (brain function) health. Both a Mediterranean-style diet and a Western-style diet are among the most studied dietary patterns associated with mental health. A Mediterranean-style diet is high in olive oil, fish, fruits and vegetables, nuts, legumes while a Western-style diet is high in processed foods, refined sugar, saturated fat, and salt.

To date, most of the studies examining the impact of diet on mental and cognitive health have been carried out over many weeks or months. We aim to compare the effects of a Mediterranean-style diet and a Western-style diet on mental health and overall quality of life in the short term (over the course of five days)

What is the MediMood study?

The MediMood study is designed to explore the short term (5 days) effect of eating a Mediterranean-style diet and a Western style diet on mental and cognitive health in adults. Both diets have been designed by an expert nutrition team. Using dietary profiles based on national intakes in the UK population. The study is funded by MRC-NIHR Nu/Brain Consortium Grant, PhD scholarships of The Republic of Turkiye, and The Commonwealth Scholarship Funds.

Who can take part in the study?

We aim to recruit 25 volunteers aged 18 years or over, fluent in English, who have a mild to moderate level of anxiety or depression which we will determine through a questionnaire.

Unfortunately, you will not be able to volunteer if you:

- have high levels of depression or anxiety
- are on antianxiety and/or antidepressant medication which is likely to change over the next 3 months
- are already following a Mediterranean diet
- are vegan or vegetarian
- have allergies to any of the study components e.g., nuts or fish
- are not fluent in English language
- are not able to have an MRI scan (e.g., have a pacemaker, suffer from claustrophobia)
- are not prepared to make changes to your diet for 10 days (2 x 5 day periods)

- do not agree your GP to be contacted about your participation and with your screening results.

If you are unsure whether you meet the criteria for our study, please get in touch with the study team and we can talk to you about your suitability.

Do I have to take part in the study? Can I withdraw after consenting?

Participation in this research is entirely voluntary. If you decide to take part, you will be free to withdraw at any time and without giving a reason. If you choose to take part, or withdraw from the study, this will not affect your future health care. An expression of interest (for example, contacting the study researchers via telephone or email for further details) does not commit you to participation. If you withdraw, we will keep the data you have given us up to that point.

Where is the study based? Who is involved?

The study will take place in the Norfolk and Norwich University Hospitals (NNUH) Clinical Research Facility (CRF) in the Quadram Institute, based on the Norwich Research Park. The study is being conducted by researchers and PhD students at the University of East Anglia (UEA), Norwich. The study also involves research nurses who will take your blood samples.

What will happen if I agree to take part?

This study will involve two 5-day dietary intervention study periods blood, urine and faecal samples collected on day one and six of each study periods, computerised psychological and brain function-related tests administered on day one, two and six of each study period, and an MRI scan taken on day one of each study period.

The figures below (on the next page) summarise the stages of the study:

1. Consent to the study (online, 45 minutes)

If you are interested in taking part, we will arrange an online videoconference using Zoom (or a phone call, depending on your choice) where a member of the study team will go through the details of the study including dietary instructions with you and answer your questions. When you are satisfied with the information provided and you remain interested in taking part, we will ask you to complete and sign a consent form either electronically or using a print-out version which you can post to the study team. If you prefer, you can take an extra 48 hours to decide to consent and proceed with the study.

2. Online screening (30 minutes)

After you consent the study, we will ask you to complete four short questionnaires to establish your eligibility for the study. of the first of these questionnaires will be about your food preferences and how often you currently eat certain foods, and the second and the third will assess certain aspects of your mental health, the final questionnaire will assess your suitability for an MRI scan of your brain. We will also ask you if you are currently on any antidepressant or antianxiety medication. The screening can be done either electronically or paper based, depending on your choice.

Once we have your answers and assess the results, we will compare them to the study inclusion/ exclusion criteria (see information on 'who can take part in this study?' above), and if we think you are suitable for the trial, we will contact you via email or telephone to let you know. If you are suitable and happy to proceed, we will then arrange your study dates. If you are not eligible to take part, we will explain why this is, and you will be encouraged to contact your GP if you have any concerns.

Dietary intervention: We will ask you to follow a meal plan for 5-days on two different occasions with a four-week break in between. We will provide all your food (we will arrange supermarket delivery to your home) for the two five-day periods and full instructions on how to prepare the food. We will ask you to complete daily checklists (*Appendix 1 and 2*), and we will contact you to find out if you are managing to follow the diet. On days one and six of each of the dietary intervention period, we will ask you to attend on-site appointments at the CRF as detailed below.

Figure 1. The study overview

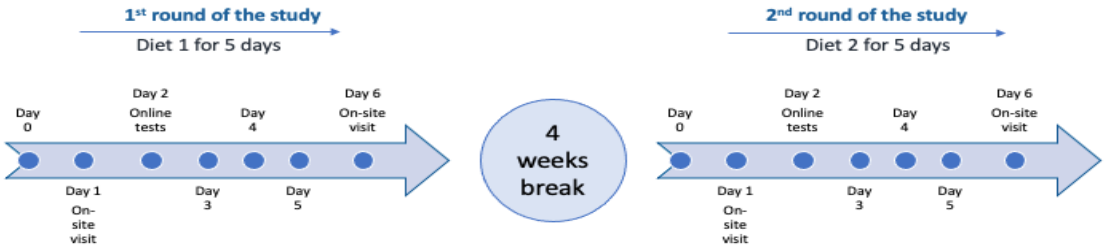
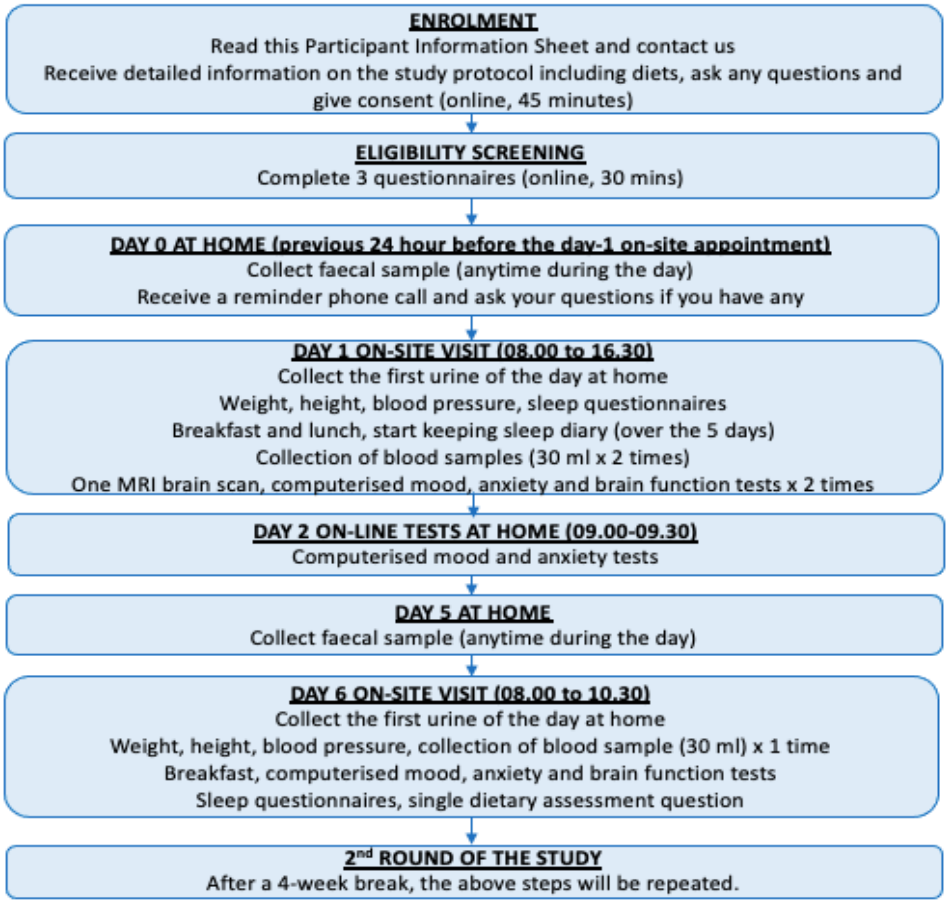


Figure 2. The study steps


ENROLMENT
Read this Participant Information Sheet and contact us
Receive detailed information on the study protocol including diets, ask any questions and give consent (online, 45 minutes)
ELIGIBILITY SCREENING
Complete 3 questionnaires (online, 30 mins)
DAY 0 AT HOME (previous 24 hour before the day-1 on-site appointment)
Collect faecal sample (anytime during the day)
Receive a reminder phone call and ask your questions if you have any
DAY 1 ON-SITE VISIT (08.00 to 16.30)
Collect the first urine of the day at home
Weight, height, blood pressure, sleep questionnaires
Breakfast and lunch, start keeping sleep diary (over the 5 days)
Collection of blood samples (30 ml x 2 times)
One MRI brain scan, computerised mood, anxiety and brain function tests x 2 times
DAY 2 ON-LINE TESTS AT HOME (09.00-09.30)
Computerised mood and anxiety tests
DAY 5 AT HOME
Collect faecal sample (anytime during the day)
DAY 6 ON-SITE VISIT (08.00 to 10.30)
Collect the first urine of the day at home
Weight, height, blood pressure, collection of blood sample (30 ml) x 1 time
Breakfast, computerised mood, anxiety and brain function tests
Sleep questionnaires, single dietary assessment question
2nd ROUND OF THE STUDY
After a 4-week break, the above steps will be repeated.

3. On-site and online measurement appointments

Day 0: In the 24 hours prior to the day-1 visit, you will be asked to collect a faecal sample using the kit and instructions sent to you beforehand. You will be asked not to eat or drink (except water) from 8 pm until you arrive for your on-site appointment the following morning at 8 am.

Day 1 (8 hours): You will be asked to collect the first urine you pass in the morning at home in a container provided. You will be invited to the CRF, UEA, at 8 am in the morning. During your visit, a researcher will take your urine and faecal samples collected at home, measure your weight, height, and blood pressure, and collect a blood sample (30 ml).

You will be then provided with a light breakfast of a cereal bar and water. Following a 10-15 minute break, we will ask you to complete mood-related and cognitive tests with a researcher. These tests will assess different aspects of your mood and overall brain function and will take approximately one hour. We will then ask you to remain in the CRF and rest for 2 hours and complete a short questionnaire assessing your usual sleep habits.

At approximately 12 pm, we will provide you with a lunch and ask you to visit the main UEA campus where you will have a brain scan using MRI which will take approximately 30 minutes and allow us to look at the structure, function, and blood flow of your brain. As the MRI scanner has a strong magnetic field, it is not safe for some people to have an MRI scan. If you have any concerns about the scan e.g., metal pins (used to repair fractures) or other implemented medical devices, please bring this to the attention of the researcher (please see Appendix 3 for MRI specific information later in this document). Subsequently, we will repeat the mood and cognitive tests and take you back to the CRF and where a nurse will take another blood sample (30 ml), at around 4.30 pm.

Day 2 (30 mins): We will ask you to complete online mood and anxiety tests at home. Similar to day one, first we will ask you to have the light breakfast supplied (a cereal bar and water), and then complete (9-9.30 am) the online tests via a link which will be sent to you. After completing the tests, you will follow your assigned meal plan including breakfast.

Day 5: Similar to day 0, we will ask you to collect a faecal sample at home. You will be asked not to eat or drink (except water) from 8 pm until you arrive for your clinical visit the next day.

Day 6 (2.5 hours): You will be asked to collect the first urine sample of the day in a container provided. We will invite you to the CRF for the last time before your 4 weeks rest period. As for Day 1, we will ask you to arrive at the CRF fasted at 8 am. We will measure your weight and blood pressure and a nurse will collect a blood sample (30 ml), along with the already collected urine and faecal samples. We will provide the same light

breakfast and ask you to complete mood and cognitive tests (1 hour), a sleep diary and ask how you found following the meal plan.

Sleep assessment: As sleep plays a significant role on our mood and brain functions and is affected by what we eat. Therefore, we will measure your sleep quality throughout the two 5-day intervention periods.

You will be asked to complete a questionnaire on your day 1 on-site visit for us to establish your sleep quality (5 mins). You will also be required to keep a sleep diary (*Appendix 4*) covering each 5-day intervention period. You will be asked to estimate the duration, timing, and quality of all sleep periods (3 mins).

Figure 3. Image of a MotionWare 8 actiwatch

You will be asked to wear a MotionWare 8 actiwatch (CamNtech Ltd, UK) continuously during the two 5-day intervention periods (24 hours per day) (Figure 3). Actiwatches are compact, unobtrusive, lightweight, water-resistant wrist worn devices measuring sleep rhythms. We will not hold you responsible if watches become broken or lost when they are with you. In case of broken/lost devices, please contact us for a replacement.

We will ask you to not to change your physical activity levels and use of probiotic supplements use over the course of the study, as these could affect your study results. After the completion of your first 5 days period, you will have a 4 week break where you will continue to follow your usual diet. We will then invite you for to start the second diet for five days and attend the same on-site appointments as for the first phase. This time you will allocated to the other diet, for example, if you were on a Mediterranean diet in the 1st round, you will be following a Western diet in the 2nd round.

How many times will I need to come to the clinical research facility?

You will be expected to visit us 4 times in total over the course of two months.

What if any abnormal results emerge?

MediMood is not a clinical examination and we do not run diagnostic tests. It is important to note that elevated scores of mental health screening are not a clinical diagnosis of depression or anxiety.

However, if any of your screening tests (mental health questionnaires), and/or MRI scan are outside of the range considered healthy, we will provide signposting to relevant services where you can access further support (for mental wellbeing support) and contact your GP who may then contact you to discuss your results further. Please note

that a research MRI scan is not a substitute for proper clinical investigation, if you suspect you are suffering from a neurological problem (affecting the brain or nervous system) you should always consult your GP in the first instance.

What will be measured in the samples collected?

The blood samples collected during your assessment visits will be analysed for blood glucose, fats, markers of brain function, vascular health and inflammation, hormones, levels of antioxidants, and select gene variants (from your DNA).

We will analyse your urine and faecal samples for various markers of gut and brain health. In the faecal samples we will also assess your gut bacteria as recent evidence suggests that gut bacteria are important in overall health, including mental wellbeing.

The samples collected will be securely stored in the biorepository, for up to 10 years, which is only accessible by approved personnel with swipe card access. These samples will be de-identified and only have your study ID on them.

Are there any risks or burdens associated with taking part in the study?

Both diets are based on commercially available foods which are already widely consumed by public. There is a small risk that change in your diet may affect your mood/anxiety levels. If you experience a change in your health (including your mood and anxiety) during the study and you are concerned please contact a member of the study team who will immediately signpost you to services that can offer support. If any concerns about the psychological wellbeing of any participant are raised, the Consultant Clinical Psychologist attached to the research team will be contacted for advice. We may also ask you to stop following the diet.

If food and diet are sensitive subjects for you, you may want to consider whether participation in MediMood is right for you.

It is normal that you feel some mild discomfort when giving a blood sample and there is a risk of slight tenderness on your arm and occasional bruising. The nurses involved in our study are specifically trained at taking blood samples.

There is also some risk of becoming tired or frustrated when completing the questionnaires and/or cognitive tests, and of symptoms of cognitive decline being identified due to participating in the research. However, researchers will provide you as many breaks as you need.

With the appropriate safety checks in place MRI is a safe, non-invasive imaging technique, with no known side effects. There are no obvious risks from the scans that you will be asked to undergo. If you become tired or uncomfortable during the MRI scan, please let the MRI operator know and we can take a break or end the session.

Where can I get mental wellbeing support?

If you need support with your wellbeing or mental health, there are many services available which are ready to support you.

Call your GP at first instance. If you are a student or a staff member at UEA, you can also contact the university wellbeing services. There are also several charities available for support including Mind and Samaritans who have volunteers to listen to you through helplines/nightlines. Please find the contact details below:

UEA Medical Centre: 01603 251600

UEA Student Support Service: studentsupport@uea.ac.uk

UEA Counselling Service: csr@uea.ac.uk

Norwich Nightline: Call on 01603 597298, or text on 07794 924366

Wellbeing: Call on 0300 123 1503 or email to admin@wellbeingnandw.co.uk

Mind (Norwich branch): 0300 330 5488 or email: enquiries@norfolkandwaveneymind.org.uk

Samaritans: Free phone 116123 (24-hour service) or email jo@samaritans.org

What are the potential benefits of taking part?

Your efforts with contributing to the study will contribute to a better understanding of how diet affects mental wellbeing in the short term. This will inform policy makers and contribute to future dietary recommendations focussed on improved mental health.

How will we use information about you?

We will need to use information from you for this research project.

This information will include your

- Initials
- Name
- Contact details

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your de-identified research results, i.e., you cannot be identified, will be shared with national and/or international scientific colleagues for further scientific analyses. These colleagues must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.
- If you were to lose capacity to verbally consent to your continued participation in the research you would no longer be able to participate, however we would retain and use any collected data.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- by asking one of the research team
- by sending an email to the University's Data Protection Officer, Ellen Paterson at: dataprotection@uea.ac.uk or
- by ringing the University's Data Protection Officer on 07824 527234.

What will happen to the results of the research study?

The results of this research study will be published in scientific journals and presented at national and international scientific meetings. All results will be in an anonymised format so that no individual can be identified. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. Once the data has been made public, we will send you a letter summarising our findings. Unfortunately, we cannot report on the findings of specific individuals.

Are there any circumstances in which you would divulge my Personally Identifiable Information to anyone outside of the research team?

We have a duty of care to volunteers and the general public. If you give us information that indicates a real risk of harm to yourself or another person, we have a responsibility to share that information with relevant services. You should only consent to taking part if you understand this possibility.

Expense Payments

Participating in this study is on a voluntary basis. Participants will receive a one-off payment of £50 in the form of a gift voucher, to cover costs incurred. This will be provided by a member of the research team upon completion of the 2x5 days study period. You can claim travel expenses to the NNUH CRF. All study food will be provided.

Who has reviewed the study?

The study is sponsored by the UEA and has been reviewed and received a favourable opinion from Health Research Authority and the associated [insert the name of approving ethics committee] Research Ethics Committee who works independently and have a duty to protect research volunteers' safety, rights, wellbeing, and dignity.

Insurance

Insurance for the study is from the NNUH for the clinical activities undertaken in the CRF and from the UEA for all other activities.

What if I want to complain?

If you have any concerns about the study and your participation in it, or wish to make a complaint, please contact Professor Charles ffrench-Constant, pro-vice-chancellor for the Faculty of Medicine and Health Sciences (cffc@uea.ac.uk).

Contact for further information

Thank you for reading this and showing an interest in our study. If you have any questions or would like further information about the study, please contact the study team who are happy to answer your questions.

Phone: +44 (0) 1603591949

Emails: medimood@uea.ac.uk

Appendix: 1 day meal plan with checklist for Diet 1

Meal	Food / drink item	Weight	Consumption status (✓ for yes and × for no)	Any additional comment (Eaten less or more, how much)
Breakfast	Natural yoghurt	120 g		
	Blueberries	75 g		
	Muesli	30 g		
Snack 1	Orange juice	150 g		
Lunch	Chicken and salad sandwich (Malted bread, chicken, lettuce, cucumber, tomato, mayonnaise)	220 g		
Snack 2	Humous	70 g		
	Carrot sticks	100 g		
Dinner	Roast salmon with spinach & tomatoes (Salmon fillet, new potatoes, spinach, roasted cherry tomatoes, olive oil 2 tbsp, garlic, pesto)	445 g		
Snack 3	Fruit salad (supermarket fresh pot)	120 g		
Beverages (please specify)				

Appendix 2: 1 day meal plan with checklist for Diet 2

Meal	Food / drink item	Weight	Consumption status (✓ for yes and × for no)	Any additional comment (Eaten less or more, how much)
Breakfast	Semi skimmed milk	100 g		
	Cereal (Kellogs crunchy not cornflakes)	35 g		
	White toast x 1	27 g		
	Jam	15 g		
	Butter	12 g		
Snack 1	Tunnocks caramel wafer	30 g		
Lunch	Ham and cheese sandwich (2 slices of white bread, ham, mayonnaise, cheddar cheese)	160 g		
Snack 2	Muller chocolate digestive corner yoghurt	130 g		
	A can of coke	330 g		
Dinner	Beef burger with potato wedges (Beef and cheddar burger, brioche bun, potato wedges, sliced half tomato)	370 g		
Snack 3	Triple chocolate muffin	106 g		
Beverages (please specify)				

Appendix 4. MRI scan

MRI stands for “magnetic resonance imaging.” MRI uses a strong magnetic field to give us a 3D picture of your brain and allows us to see changes in the activity of different parts of your brain.

MRI is a non-invasive technique, it does not involve injections or x-rays, and is used routinely in modern medicine. It has no known side effects.

Because of the strong magnetic field, before you can go into the scanner, a qualified MRI operator will ask you to remove all metal belongings (which we will store safely) and check that you have no metal within your body. When you attend for your scan, please try to wear clothing that is comfortable and loose fitting and does not have metal parts (e.g., wear jogging pants instead of jeans with zipper). Occasionally it may be necessary for participants to remove items of clothing e.g., bra (due to the underwire/adjusters), so you may prefer to wear a sports bra for your visit. If the MRI operator does not think it is safe for you to be scanned, we will not continue. They will ask you questions to ensure that you will be comfortable in the scanner. If you are very uncomfortable in small, confined spaces you may not wish to participate. If it is safe and you are happy to proceed, you would be placed on the scanner bed and made comfortable with the use of padding (e.g., under your knees). For brain scans you would then move into the scanner head first and remain inside the long tube whilst the scans are taken. There is normally a mirror placed above your eyes that will allow you to see the screen inside the scanner, so you can watch a movie or complete the tasks. In between scans a two-way intercom will allow you to communicate with the MRI operator. The scanner is very noisy and you will be asked to wear earplugs. You will be provided with a hand-held alarm that you can squeeze if you become uncomfortable or distressed at any time. This will alert the operator who will immediately stop the scan and check you are okay, and if necessary, remove you from the scanner. To collect good quality scans, it is important that you keep your head and body as still as possible when in the scanner. Scans typically last 30 minutes.

Appendix 4. Sleep diary

Instructions:

Please refer to your last overnight sleep episode, i.e., not a daytime nap, when answering the following questions. Please indicate whether the time is am or pm.

What time did you go to bed?		AM/PM
What time did you try starting to sleep at?		AM/PM
How long did it take you to fall asleep? (min)		
How many times did you wake up?		
How long were you awake for? (min) Please estimate the time and duration of each night awakening.		
What time did you wake up?		AM/PM
What time did you get up?		AM/PM
Did your alarm clock wake you up?		
Did you do any strenuous activity during the last 24 hours (if yes, please specify)		

How would you rate your quality of sleep?

Best sleep ever								**Worst sleep ever**
1	2	3	4	5	6	7	8	9

How difficult did you find to wake up/get up?

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

Very easy **Quite hard**

Instructions:

Please indicate your level of sleepiness for the previous 5 minutes using the scale below.

Extremely alert	1
	2
Alert	3
	4
Neither sleepy nor alert	5
	6
Sleepy, but not fighting sleep	7
	8
Extremely sleepy; it is an effort to stay awake	9

Appendix 10. Online informed consent form

MediMood: A randomised controlled trial investigating the immediate effects of a plant based Mediterranean-style dietary pattern (MDP) and Western-style Diet (WD) on mood, anxiety and cognition in adults with mild to moderate mental health complaints

Study IRAS ID: 320471, Date and version: 24/05/2023, V2.3

Principal Investigator: Prof Anne Marie Minihane

Please tick the boxes below to confirm your consent and then click the submit button:

I confirm that I have been provided with a copy of the participant information sheet (dated 24/05/2023 and version 2.3), which I have read and understood. I have had the opportunity to ask any questions and they were answered to my satisfaction.	
I confirm that the possible risks have been explained to my satisfaction.	
I understand that one copy of the signed version of this form will be provided to me and one copy will be kept for the research team's record.	
I understand that my participation is voluntary, and I am free to withdraw from the project at any time without giving a reason.	
I understand that this project is for the purpose of research and not for profit.	
I agree to complete questionnaires about my medical history, sleep, mood, anxiety, and diet.	
I agree to make changes to my diet for 10 days as part of the research and to receive supermarket deliveries of foods.	
During the 10 days intervention period, I also agree to;	
attend four clinical visits to participate in a series of mood, memory and brain function tests and have my height, weight and blood pressure measured	
have an MRI brain scan which is a research scan, not a clinical scan and will not be explicitly screened for medical disorders or diagnostic purposes.	

provide venous blood samples at the four clinical visits (which will be used for research purposes to assess blood glucose, fats, hormones, markers of brain function, genetics, vascular health, inflammation, levels of antioxidants)	
provide urine and faecal samples at home prior to the four clinical visits (which will be used for research purposes to assess markers of gut and brain health and gut bacteria).	
take part in two tests of mood at home	
complete a daily dietary checklist during the two 5-day intervention periods	
wear an actiwatch continuously during the two 5-day interventions periods (for 24 hours per day)	
complete a dietary questionnaire 3 months after the intervention	
I agree for my GP to be contacted if;	
My mental health screening indicates above a low level of anxiety or depression	
A significant abnormality is noticed in my blood results or MRI scan by the University of East Anglia Wellcome-Wolfson Brain Imaging Centre (UWWBIC)	
Please provide your GP details below: GP name: GP address and postcode:	
I agree for my data/samples to be used for future studies for up to 10 years which have been approved by the ethics committee	
I understand that any personal or health information about me which is collected during the study my participation will be treated as highly confidential. My anonymity will be preserved, and I will not be identified in publications or otherwise without my express consent.	
I understand that UEA has a duty of care to volunteers and the general public, therefore, in case of any possibility of harm to myself or others, my personally identifiable information may be divulged.	
I read and understand this document and agree to above statements. Thus, I consent to participate in the MediMood study.	
I agree to be contacted about future studies (Please note that this is optional, only tick if you are happy to be contacted for futures studies).	

Appendix 11. Print version of the consent form

MediMood: A randomised controlled trial investigating the immediate effects of a plant based Mediterranean-style dietary pattern (MDP) and a Western-style diet on mood, anxiety and cognition in adults with mild to moderate mental health complaints

Study IRAS ID: 320471

Principal Investigator: Prof Anne Marie Minihane

I consent to participate in the project named above. I have been provided a copy of the participant information sheet and this consent form (dated 24/05/2023 and version 2.3) and any questions I have asked were answered to my satisfaction.

Please initial to confirm acceptance

I agree to be interviewed by a researcher and complete questionnaires asking about my medical history, sleep, mood and anxiety states, and diet ☐

I agree to make changes to my diet for 10 days as part of the research and receive to supermarket deliveries of foods ☐

During the 10 days intervention period, I also agree to:

attend four clinical visits to participate in a series of mood, and brain function tests and have my height, weight and blood pressure measured ☐

have an MRI brain scan which is a research scan, not a clinical scan and will not be explicitly screened for medical disorders or diagnostic purposes. ☐

provide a venous blood sample at the four clinical visits (which will be used for research purposes to assess blood glucose, fats, hormones, markers of brain function, genetics, vascular health, inflammation, levels of antioxidants) ☐

provide urine and faecal samples at home prior to the four clinical visits (which will be used for research purposes to assess markers of gut and brain health and gut bacteria) ☐

take part in two tests of mood at home ☐

complete a daily dietary checklist ☐

wear an actiwatch continuously during the two 5-day intervention periods (for 24 hours per day) ☐

complete a dietary questionnaire 3 months after the intervention ☐

I agree for my GP to be contacted if

My mental health screening indicates above a low level of anxiety or depression ☐

A significant abnormality is noticed in my blood results or MRI scan by the University of East Anglia Wellcome-Wolfson Brain Imaging Centre (UWWBIC) ☐

Please provide your GP details below:

GP name:

GP address & postcode:

I agree for my data/samples to be used for future studies for up to 10 years which have been approved by the ethics committee ☐

I understand that one copy of the signed version of this form will be provided to me and one copy will be kept for the research team's record. ☐

I acknowledge that:

a) *the possible risks have been explained to me to my satisfaction*

b) *my participation is voluntary and that I am free to withdraw from the project at any time*

c) *this project is for the purpose of research and not for profit*

d) *any personal or health information about me which is gathered in the course of my participation*

will be treated as highly confidential, and retained and analysed solely for the purposes of the study

e) *my anonymity will be preserved, and I will not be identified in publications or otherwise without*

my express written consent.

f) UEA has a duty of care to volunteers and the general public, therefore, in case of any possibility of harm to myself or others, my personally identifiable information may be divulged.

I agree to be contacted about future studies
(Please note that this is optional – only initial if you are happy to be contacted for future studies)

By signing this document, I agree to the above statements and to participate in this project.

Name of Participant:

Signature **Date**

Name of Investigator:

Signature **Date**

Appendix 12. Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

2. Feeling down, depressed, or hopeless?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

3. Trouble falling or staying asleep, or sleeping too much?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

4. Feeling tired or having little energy?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

5. Poor appetite or overeating?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down?
    - Not at all

- Several days
- More than half the days
- Nearly every day

7. Trouble concentrating on things, such as reading the newspaper or watching television?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

9. Thoughts that you would be better off dead, or of hurting yourself in some way?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

Appendix 13. Generalised Anxiety Disorder questionnaire (GAD-7)

1. Feeling nervous, anxious or on edge?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

2. Not being able to stop or control worrying?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

3. Worrying too much about different things?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

4. Trouble relaxing?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

5. Being so restless that it is hard to sit still?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

6. Becoming easily annoyed or irritable?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

7. Feeling afraid as if something awful might happen?
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day

The followings were added for the purposes of the MediMood screening:

- Are you currently on any antidepressant or antianxiety medication?
- If so, did its dosage change in the last 3 months or is it likely to be changed in the next 3 months?

Appendix 14. UWWBIC MRI screening form

MRI Safety Screening Form (v1.1w) VOLUNTEER

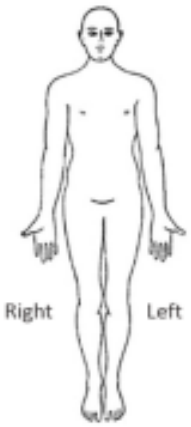
UEA University of East Anglia

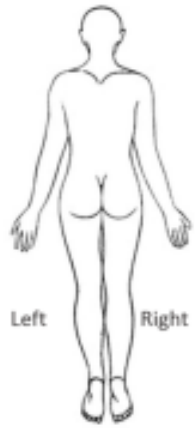
Last Name		**First Name**		**Weight (kg)**	
DOB	/ /	**Email**		**Height (m)**	
Address			**Postcode**		
			Telephone		
GP's Name & Address					

Please answer the following questions as best as you can. Some of the items on the list are contraindications for MRI. If you answered **Yes** to any of the questions, please give more information to the scanner operator/researcher who asked you to complete this form. Please use the diagrams to indicate the location of any surgery/implant/device.

Failure to disclose information could result in serious injury.

	Yes	No
Any surgery or other invasive procedures in the last six weeks		
Any injury to your eye involving metallic fragments		
Any possibility you may be pregnant		
Cardiac pacemaker		
Internal Cardiac Defibrillator		
Pacing wires		
Aneurysm or other type of blood vessel clips		
Cochlear or other type of ear implant		
Deep brain stimulator		
Implanted insulin or other drug delivery pump		
Intraventricular or spinal shunt		
Artificial heart valve/ Annuloplasty Rings/ Sternal Suture Wires		
Venous umbrella/filter		
Vascular stents		
Implanted contraceptive device (intrauterine device/IUD/"coil")		
Embolisation coils		
Vascular access port or catheter		
Loop recorder (event monitor)		
Spinal fusion stimulator		
Harrington rods (spinal rods)		
Eye/orbital prosthesis e.g. intraocular lens, eye buckle		
Artificial limb or joint		
Shrapnel, shot or bullet		
Tattoos (including any semi-permanent makeup)		
Orthopaedic devices (pins, screws, wires or plates)		
Penile/breast or other tissue expanders/implants		
Patches for drug delivery e.g. nicotine, analgesia		
Other implanted device/foreign body not listed above		
Metallic body piercing/jewellery (Remove before entry)		
Hearing aid (Remove before entry)		
Dentures (Remove before entry)		





Now turn over page

Comments/Details

Please remove **all metallic** objects before entering the magnet room including: keys, coins, cards, phones, jewellery, watch, belt etc. Lockers are available to secure your personal belongings. Any clothing containing metallic material might need to be removed. Scrubs will be offered to get changed. **Earplugs are required during the MRI examination.**

I confirm that the above information is correct to the best of my knowledge. I have read and understand the contents of this form and I have had the opportunity to ask questions regarding the information required and regarding the MRI procedure that I am about to undergo.

Your name		Relationship to volunteer. Please circle (self/parent/guardian)	Your Signature	
MR Staff name			MR Staff Signature	
Date	/ /			

For staff use only

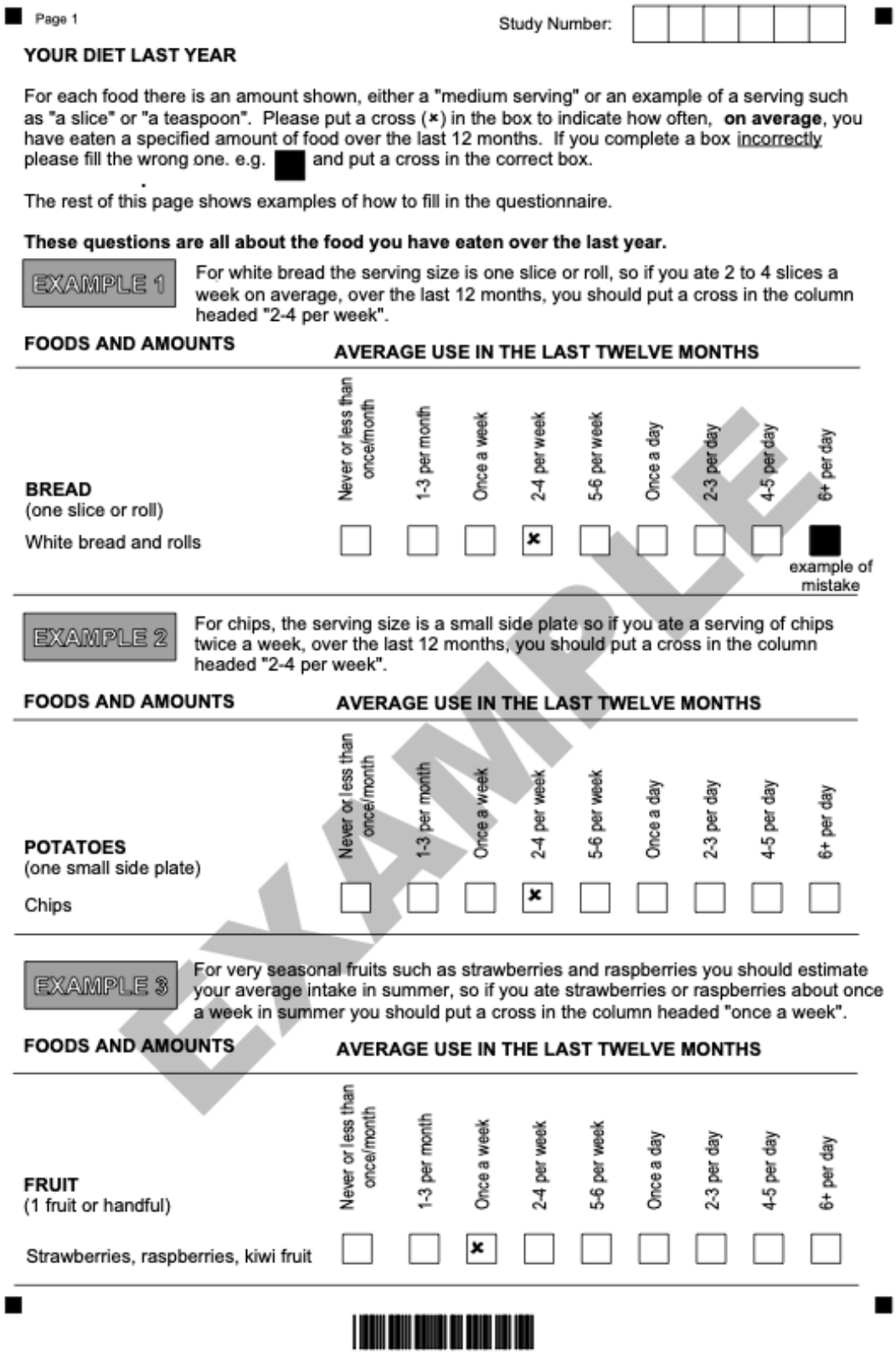
	Yes	No	Comments
Metal detector (wand) used If No, please explain why			
Checked wand is working before use			
Alarmed went off **If yes, please give details**			

- Bra
- Rivets
- Buttons
- Zip
- Hip replacement
- Knee replacement
- Orthopaedic device
- Other (please detail)

Details

Date	/ /	**Principal Investigator/Lab**			
Subject ID		**Scan ID/UBIC No**		**MR No/Study**	

Appendix 15. EPIC Food Frequency Questionnaire



Page 1

Study Number: | | | | | | |

YOUR DIET LAST YEAR

For each food there is an amount shown, either a "medium serving" or an example of a serving such as "a slice" or "a teaspoon". Please put a cross (×) in the box to indicate how often, **on average**, you have eaten a specified amount of food over the last 12 months. If you complete a box incorrectly please fill the wrong one. e.g. ■ and put a cross in the correct box.

The rest of this page shows examples of how to fill in the questionnaire.

These questions are all about the food you have eaten over the last year.

EXAMPLE 1

For white bread the serving size is one slice or roll, so if you ate 2 to 4 slices a week on average, over the last 12 months, you should put a cross in the column headed "2-4 per week".

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
BREAD (one slice or roll)									
White bread and rolls	☐	☐	☐	☒	☐	☐	☐	☐	■ example of mistake

EXAMPLE 2

For chips, the serving size is a small side plate so if you ate a serving of chips twice a week, over the last 12 months, you should put a cross in the column headed "2-4 per week".

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
POTATOES (one small side plate)									
Chips	☐	☐	☐	☒	☐	☐	☐	☐	☐

EXAMPLE 3

For very seasonal fruits such as strawberries and raspberries you should estimate your average intake in summer, so if you ate strawberries or raspberries about once a week in summer you should put a cross in the column headed "once a week".

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
FRUIT (1 fruit or handful)									
Strawberries, raspberries, kiwi fruit	☐	☐	☒	☐	☐	☐	☐	☐	☐

Study Number: | | | | | | |

START OF QUESTIONNAIRE

1a. On average do you think you eat the same, more or less than someone of your own age and sex? **Please put a cross (×) in only one box.** ☐ Same ☐ More ☐ Less

1b. On an average day how many portions of fruit do you eat? ☐

1c. On an average day how many portions of vegetables do you eat? ☐

Please estimate your average food use as best you can, and please answer every question - do not leave ANY lines blank. **PLEASE PUT A CROSS (×) ON EVERY LINE**

FOODS AND AMOUNTS — **AVERAGE USE IN THE LAST TWELVE MONTHS**

DAIRY PRODUCTS AND FATS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Single or sour cream (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Double or clotted cream (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low fat yoghurt, fromage frais (small pot)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Full fat or Greek yoghurt (small pot)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dairy desserts (small pot) e.g. chocolate mousse, cream caramels	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cheese, e.g. cheddar, brie, edam (matchbox size)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low fat cheese e.g. reduced fat cheddar (matchbox size)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cottage cheese, low fat soft cheese (2 tablespoons)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Eggs as boiled, fried, scrambled, etc. (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Quiche (slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low calorie, low fat salad cream (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Full fat salad cream, mayonnaise (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
French dressing (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other salad dressing (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (×) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS **AVERAGE USE IN THE LAST TWELVE MONTHS**

The following list refers to **DAIRY PRODUCTS AND FATS** that you put on bread or cooked vegetables	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Butter (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Reduced fat butter (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Block margarine, e.g. Stork, Krona (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Polyunsaturated margarine, e.g. Flora, sunflower (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Olive oil spread (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other soft margarine, dairy spreads, e.g. Blue Band, Clover (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low fat spread, e.g. Outline, Gold (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Very low fat spread (teaspoon) e.g. Diet Flora	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cholesterol lowering fat spreads e.g. Benecol (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

FRUIT - For seasonal fruits marked*, please estimate your average use in summer

Apples (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pears (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oranges, satsumas, mandarins (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grapefruit (half)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bananas (1fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grapes (handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Melon (1 slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐
* Peaches, plums, apricots (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
* Strawberries, raspberries, other berries, kiwi fruit (one fruit or handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tinned fruit (handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dried fruit, e.g. raisins, prunes (heaped tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number:

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
VEGETABLES Fresh, frozen or tinned (handful)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Carrots	☐	☐	☐	☐	☐	☐	☐	☐	☐
Spinach	☐	☐	☐	☐	☐	☐	☐	☐	☐
Broccoli, spring green, kale	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brussel sprouts	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cabbage	☐	☐	☐	☐	☐	☐	☐	☐	☐
Peas	☐	☐	☐	☐	☐	☐	☐	☐	☐
Green beans, broad beans, runner beans	☐	☐	☐	☐	☐	☐	☐	☐	☐
Baked beans	☐	☐	☐	☐	☐	☐	☐	☐	☐
Marrow, courgettes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cauliflower	☐	☐	☐	☐	☐	☐	☐	☐	☐
Parsnips, turnips, swedes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Leeks	☐	☐	☐	☐	☐	☐	☐	☐	☐
Onions	☐	☐	☐	☐	☐	☐	☐	☐	☐
Garlic (clove)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mushrooms	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sweet peppers	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beansprouts	☐	☐	☐	☐	☐	☐	☐	☐	☐
Green salad, lettuce, cucumber, celery	☐	☐	☐	☐	☐	☐	☐	☐	☐
Watercress	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tomatoes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sweetcorn	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beetroot	☐	☐	☐	☐	☐	☐	☐	☐	☐
Coleslaw	☐	☐	☐	☐	☐	☐	☐	☐	☐
Avocado	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pulses e.g. lentils, beans, peas	☐	☐	☐	☐	☐	☐	☐	☐	☐
Meat substitutes e.g. tofu, soyameat, textured vegetable protein, vegeburger	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS **AVERAGE USE IN THE LAST TWELVE MONTHS**

MEAT AND FISH (half a small side plate)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Beef: roast, steak, mince, stew or casserole	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beefburgers	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pork: roast, chops or stew	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lamb: roast, chops or stew	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chicken or other poultry e.g. turkey	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bacon or gammon	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ham, cured meats & chorizo	☐	☐	☐	☐	☐	☐	☐	☐	☐
Corned Beef, Spam, luncheon meats	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sausages	☐	☐	☐	☐	☐	☐	☐	☐	☐
Savoury pies, e.g. meat pie, pork pie, pasties, steak & kidney pie, sausage rolls	☐	☐	☐	☐	☐	☐	☐	☐	☐
Liver, liver pate, liver sausage	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fried fish in batter, as in fish and chips	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fish fingers, fish cakes & breaded fish	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other white fish, fresh or frozen, e.g. cod, plaice, sole, haddock, halibut	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oily fish, fresh or canned, e.g. tuna, mackerel, kippers, salmon, sardines, herring	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shellfish, e.g. crab, prawns, mussels	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fish roe, taramasalata	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
BREAD AND SAVOURY BISCUITS (one slice, or roll, or biscuit)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread/rolls	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brown bread/rolls	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wholemeal & granary bread/rolls	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cream crackers, savoury biscuits	☐	☐	☐	☐	☐	☐	☐	☐	☐
Crispbread, e.g. Ryvita	☐	☐	☐	☐	☐	☐	☐	☐	☐
Naan, poppadoms, flour tortillas	☐	☐	☐	☐	☐	☐	☐	☐	☐
SOUPS, SAUCES AND SPREADS									
Vegetable soups (bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Meat soups (bowl) (to include meat and vegetable soups)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sauces, e.g. white sauce, cheese sauce, gravy (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tomato ketchup (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pickles, chutney (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Marmite, Bovril (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Jam, marmalade, honey (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Peanut butter (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (✗) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
SWEETS AND SNACKS (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Cakes e.g. fruit, sponge, home baked	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cakes e.g. fruit, sponge, ready made	☐	☐	☐	☐	☐	☐	☐	☐	☐
Buns, pastries e.g. scones, flapjacks, croissants, doughnuts, home baked	☐	☐	☐	☐	☐	☐	☐	☐	☐
Buns, pastries e.g. scones, flapjacks, croissants, doughnuts, ready made	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fruit pies, tarts, crumbles, home baked	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fruit pies, tarts, crumbles, ready made	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sponge puddings, home baked	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sponge puddings, ready made	☐	☐	☐	☐	☐	☐	☐	☐	☐
Milk puddings e.g. rice, custard, trifle	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ice cream, choc ices	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sweet biscuits, chocolate, e.g. digestive (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sweet biscuits, plain, e.g. Nice, ginger (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Reduced fat biscuits e.g. Go Ahead, Highlights (one small packet or one small bar/biscuit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cereal bars (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
White or milk chocolates, single or squares (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dark chocolates, single or squares (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate snack bars e.g. Mars, Crunchie (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sweets, toffees, mints (small packet)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sugar added to tea, coffee, cereal (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS	AVERAGE USE IN THE LAST TWELVE MONTHS								
SWEETS AND SNACKS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Crisps or other packet snacks, e.g. Wotsits (one packet)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salted nuts e.g. peanuts, cashews (handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Unsalted nuts, e.g. brazil, walnuts (handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Seeds e.g. Sunflower, pumpkin (tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
CEREAL (one bowl)									
Porridge, Readybreak, oats	☐	☐	☐	☐	☐	☐	☐	☐	☐
Breakfast cereal e.g. Cornflakes, Rice Krispies	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sugar topped cereals e.g. Frosties	☐	☐	☐	☐	☐	☐	☐	☐	☐
Muesli	☐	☐	☐	☐	☐	☐	☐	☐	☐
High Fibre cereals e.g. Branflakes, All Bran, Fruit and Fibre	☐	☐	☐	☐	☐	☐	☐	☐	☐
POTATOES, RICE AND PASTA (one small side plate)									
Boiled, mashed, instant or one jacket potato	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chips, roast potatoes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Potato salad	☐	☐	☐	☐	☐	☐	☐	☐	☐
White rice	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brown rice	☐	☐	☐	☐	☐	☐	☐	☐	☐
White or green pasta, e.g. spaghetti, macaroni, noodles	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wholemeal pasta	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lasagne, moussaka	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pizza (one slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number: | | | | | | |

FOODS AND AMOUNTS — **AVERAGE USE IN THE LAST TWELVE MONTHS**

DRINKS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Tea (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Green tea (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fruit tea (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Coffee, instant or ground (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Coffee, decaffeinated (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Coffee whitener, e.g. Coffee-mate (teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cocoa, hot chocolate (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low fat hot chocolate (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Horlicks, Ovaltine (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
White wine (small glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Red wine (small glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beer, lager or cider (half pint)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Port, sherry, vermouth, liqueurs (pub measure)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Spirits, e.g. gin, brandy, whisky, vodka (pub measure)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Low calorie or diet fizzy soft drinks (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fizzy soft drinks, e.g. Coca Cola, lemonade (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pure fruit juice (100%) e.g. orange, apple juice (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fruit squash or cordial (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Smoothies (cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Please check that you have a cross (x) on EVERY line

Study Number: | | | | | | |

YOUR DIET LAST YEAR, continued

2. Are there any **OTHER** foods which you ate more than once a week over the last year?

No ☐ ⇨ **GO TO** question 3 Yes ☐ **If yes**, please list below

Food	Usual serving size	Number of times eaten each week

3. Have you drunk milk or a milk substitute over the past year? (including in hot drinks)

No ☐ ⇨ **GO TO** question 6 Yes ☐ ⇨ **GO TO** question 4

4. What type of milk or milk substitute did you most often use over the last year?

Select one only

Full cream ☐ Semi-skimmed ☐

Skimmed ☐ Channel Islands ☐

Dried milk ☐ Soya ☐

Other (please specify) _____

5. About how much milk did you drink each day, including milk with tea, coffee, cereals etc?

Less than a quarter of a pint ☐ One Pint ☐

Half a pint ☐ More than one pint ☐

Three quarters of a pint ☐

6. Did you usually eat breakfast cereal in the last year (excluding Porridge and Ready Brek mentioned earlier)?

No ☐ ⇨ **GO TO** question 7 Yes ☐ **If yes,** which brand and type of breakfast cereal, including muesli, did you usually eat?

List the one or two types most often used

Brand e.g. Kellogg's	Type e.g. cornflakes

7. Do you use oil or fat for frying, roasting, grilling etc?

No ☐ ⇨ **GO TO** question 9 Yes ☐ ⇨ **GO TO** question 8

Study Number: | | | | | | |

8. What kind of fat did you most often use for frying, roasting, grilling etc? **Select one only**

Butter ☐	Olive oil ☐	Margarine ☐	Vegetable oil ☐
Lard/dripping ☐	Solid vegetable fat ☐	Low fat spray ☐	Other ☐

If you used vegetable oil or other oil
please give type e.g. corn, sunflower, sesame _____

9. What kind of fat did you most often use for baking cakes etc? **Select one only**

I don't bake ☐	Lard/dripping ☐	Solid vegetable fat ☐	None ☐
Butter ☐	Vegetable oil ☐	Margarine ☐	

If you used margarine, please give name or type e.g. Flora, Stork _____

10. How often did you eat food that was fried at home?

Never ☐	Less than once a week ☐	1-3 times a week ☐
4-6 times a week ☐	Daily ☐	

11. How often did you eat fried food away from home?

Never ☐	Less than once a week ☐	1-3 times a week ☐
4-6 times a week ☐	Daily ☐	

12. Have you eaten meat in the last year?

No ☐ ⇨ **GO TO** question 17 Yes ☐ ⇨ **GO TO** question 13

13. What did you do with the visible fat on your meat?

Did not eat meat with visible fat ☐	Ate some of the fat ☐
Ate as little as possible ☐	Ate most of the fat ☐

14. Did you eat roast/grilled meat over the past year?

No ☐ ⇨ **GO TO** question 17 Yes ☐ ⇨ **GO TO** question 15

15. How often did you eat grilled or roast meat?

Daily ☐	1-3 times a week ☐
4-6 times a week ☐	Less that once a week ☐

Study Number: | | | | | | |

16. How well cooked did you usually have grilled or roast meat?

Well done / dark brown ☐ Lightly cooked / rare ☐

Medium ☐

17. How often did you add salt to food while cooking?

Never ☐ Sometimes ☐ Always ☐

Rarely ☐ Usually ☐

18. How often did you add salt to any food at the table?

Never ☐ Sometimes ☐ Always ☐

Rarely ☐ Usually ☐

19. Do you regularly use a salt substitute (e.g. LoSalt)?

No ☐ Yes ☐ **If yes,** which brand? _____

20. We would like to summarise what you have told us. During the course of last year, on average, how many times a week did you eat the following foods?

Food Type	**Times/week**	**Portion size**
Vegetables (excluding potatoes but including baked beans)	☐☐	medium serving
Salads	☐☐	medium serving
Fruit and fruit products (not including fruit juice)	☐☐	medium serving or 1 fruit
Oily fish and fish products	☐☐	medium serving
Non oily fish and fish products	☐☐	medium serving
Meat, meat products and meat dishes (including bacon, ham and chicken)	☐☐	medium serving

21. Have you taken any vitamins, minerals, fish oils, fibre or other food supplements during the past year?

No ☐ Yes ☐ ⇨ **GO TO** question 22

Study Number: ☐☐☐☐☐☐

22. Please list any vitamins, minerals, fish oils, fibre or other food supplements taken during the past year. If you have taken more than 6 types of supplement please list the 6 most frequently consumed brands first.

Vitamin supplements

Average frequency
Cross **one** box per line to show how often on average you consumed supplements

Name and brand Please list full name and brand	**Number** Please state number of pills, capsules or teaspoons consumed	Never or less than once a month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per say	4-5 per day	6+ per day
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 - 9	☐	☐	☐	☐	☐	☐	☐	☐	☐

Study Number:

Please return the completed questionnaire, using the pre-paid envelope provided.

Appendix 16. Recruitment poster

Version 1.0
25/02/2022

MediMood

Are you interested in taking part in a study about improving mood and anxiety?

Do you consider your current mood and anxiety levels to be less than optimal?

If you are over 18 years and fluent in English, this could be the research study for you!

Researchers at University of East Anglia want to find out whether eating a plant based Mediterranean style diet improves mood and anxiety in people who are currently concerned about their mental wellbeing.

Participants will be provided with food and a £50 one-off payment.

If you think you might like to take part in the study, simply follow this web link:
[INSERT LINK]

You can contact the study team on:
Tel: Email: medimood@uea.ac.uk

Expressing an interest does not commit you taking part in the study.

Please tear me off and take me away! Please tear me off and take me away! Please tear me off and take me away!

LINK	LINK	LINK	LINK	LINK	LINK	LINK	LINK	LINK	LINK	LINK	LINK

Appendix 17. Recruitment invitation email

Dear [Participant's name]

We are writing to invite you to take part in a research study run by scientists at Norwich Medical School at the University of East Anglia (UEA). The study will be conducted in the Norfolk and Norwich University Hospital's Clinical Research Facility (CRF) based at the Quadram Institute.

We will recruit 25 healthy individuals aged 18 years or over. The purpose of the study is to compare the effect of a Mediterranean-style diet versus a Western-style diet on mood, anxiety and brain function (cognition) over 5 days. Please find attached a copy of the information sheet.

If you think you would like to take part in the study, please reply to this email.

Please note that there is no obligation to take part in the study, and if you are suitable and take part, you can withdraw your interest at any time.

You have received this email as you are registered with the University of East Anglia's Sleep research recruitment database. If you no longer wish to be on the database, please reply to this email to let us know.

Thank you.

Kind regards,
[Researcher's name)
The MediMood Research Team

Appendix 18. GP letter to inform eligibility/participation

[GP name]

[GP Practice address]

[Date]

Dear Doctor

Re: [Patient name], DOB: [insert patient date of birth]

We are writing to inform you that your patient has consented to take part in the nutrition research study entitled: 'MediMood: The effect of a Mediterranean diet on mood, anxiety and cognition in UK adults'. The study is being run within the Norfolk and Norwich University Hospital's Clinical Research Facility (CRF) based at the Quadram Institute on Norwich Research Park, by a team at the Norwich Medical School, University of East Anglia (UEA). The study has full HRA approval.

We anticipate your patient will complete this study within two months. In addition to following the diets provided for two x five-day periods, they will be asked to visit the CRF for baseline and end-point measurements of mental wellbeing and cognitive health and provide blood, urine and faecal samples. The study will also include an MRI brain scan. We will forward you a copy of the MRI results if any incidental findings are detected which are outside the normal range for this age-group.

Our study recruits participants with mild to moderate levels of anxiety and/or depression according to the Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder questionnaire (GAD-7). Your patient had the following scores: XX/27 on PHQ-9 and YY/21 on GAD-7.

We would like to inform you that [Patient name] is now a participant on the study as they were deemed eligible with mild/moderate level anxiety and mild/moderate level depression.

They have been advised this might be something they wish to peruse further and we have signposted them to the Norfolk and Suffolk NHS Wellbeing Service which is the comissioned provider for patiens with anxiety and depression, as well as the following organisations: university

(UEA) counselling services, Minds, Samaritans. However, we understand as their GP that you might wish to contact [him/her] to arrange further follow up and investigation.

Yours sincerely,

[Researcher Name]
Department of Nutrition and Preventive Medicine
Norwich Medical School
University of East Anglia
Norwich NR4 7UQ
+44 (0) 1603 591949
IRAS number: 320471

Appendix 19. GP letter to inform ineligibility because of higher depression

[GP name]

[GP Practice address]

[Date]

Dear Doctor

Re: [Patient name], DOB: [insert patient date of birth]

We are writing to you to inform that your patient has consented to take part in the nutrition research study entitled: 'MediMood: The effect of a Mediterranean diet on mood, anxiety and cognition in UK adults'. The study is being run within the Norfolk and Norwich University Hospital's Clinical Research Facility (CRF) based at the Quadram Institute on Norwich Research Park, by a team at the Norwich Medical School, University of East Anglia (UEA). The study has full HRA approval.

Our study recruits participants with mild to moderate levels of anxiety and/or depression according to the Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder questionnaire (GAD-7). Your patient had the following scores: XX/27 on PHQ-9 and YY/21 on GAD-7.

We would like to inform you that [Patient name] was deemed ineligible to take part in the study due to scoring either in the moderately severe/severe depression range and/or the severe level anxiety range on the PHQ-9 and GAD-7. Whilst this indicates an elevated self-reported level of depression and/or anxiety symptoms this should not be considered a clinical diagnosis. This has been explained to (Patient name).

They have been advised this might be something they wish to puruse further and we have signposted them to the Norfolk and Suffolk NHS Wellbeing Service which is the comissioned provider for patiens with anxiety and depression, as well as the following organisations: university (UEA) counselling services, Minds, Samaritans. However, we understand as their GP that you might wish to contact [him/her] to arrange further follow up and investigation.

Yours sincerely,

[Researcher Name)

Department of Nutrition and Preventive Medicine
Norwich Medical School
University of East Anglia
Norwich NR4 7UQ
+44 (0) 1603 591949
IRAS number: 320471

Appendix 20. MediMood booklets

Mediterranean Diet Meal Plan

PARTICIPANT ID:

This booklet outlines your meal plans for five days, and questions about your sleep which we would like you to complete before your breakfast each day.

Please try your best to stick to the meal plans and weigh and measure foods where possible to ensure accuracy. Do not add any oils/fats to foods or when cooking other than those stated, and use the suggested cooking instructions/methods. You may add additional seasoning to meals using pepper, herbs, spices or garlic, but not salt or sugar. Please note any additions in the comments box.

We would like you to eat the meals on the days stated, however, if for your convenience you wish to swap the order of the lunch and evening meal, you can.

We have provided enough in your food delivery to allow you to eat your evening meal with a companion. If you are eating alone, please do not consume the extra food during the five days. If you choose to swap the order of the meals on any given day, please keep in mind that only ingredients for the evening meal were provided in duplicate.

If you feel unable to eat the full meal, please prioritise the ingredients that are preceded by an asterisk, these are the most important components of the meal/snack for our research.

If you are still hungry after consuming your meals and snacks, you can eat an 'additional' snack from the list of suitable snacks.

Please only drink water, no added sugar/sugar free drinks, tea or coffee in addition to the drinks listed in the meal plans. If you usually drink alcohol, you can continue to do so, but please **only** drink wine.

SHOPPING DELIVERY

Your shopping delivery should consist of the items listed on the following page. As you unpack, please tick off the items and store them according to the instructions on the packaging. Please inform the research team immediately if anything is missing or incorrect e.g., a food swap has been made by the supermarket.

	Item	Storage
☐	Hovis Wholemeal Bread - 800g	*Cool, dry place/freezer*
☐	Free Range Eggs - 6 pack	*Fridge*
☐	Wholewheat Pasta - 500g	*Cool, dry place*
☐	Wholewheat couscous - 500g	*Cool, dry place*
☐	Balsamic Vinegar	*Cool, dry place*
☐	Extra Virgin Olive Oil - 1L	*Cool, dry place*
☐	Green Pesto	*Fridge*
☐	Tomato Puree	*Fridge*
☐	Tesco Soft Figs - 250g	*Cool, dry place*
☐	Tinned prunes in Fruit Juice - 410g	*Cool, dry place*
☐	Tinned Chopped Tomatoes - 3 x 400g	*Cool, dry place*
☐	Chickpeas in Water - 400g x 1	*Cool, dry place*
☐	Tinned Black Beans in Water - 400g	*Cool, dry place*
☐	Tuna Chunks in Spring Water - 145g	*Cool, dry place*
☐	Yeo Valley Greek Yogurt - 4 x 110g	*Fridge*
☐	Blueberries - 125g x 2 packs	*Fridge*
☐	Fruit Salad - 400g	*Fridge*
☐	Pears x 5	*Cool, dry place*

☐	Apples x 2	*Cool, dry place*
☐	Orange Juice - 900ml	*Fridge*
☐	Cherry Tomatoes - 2 x 250g packs	*Fridge*
☐	Tesco Mixed Leaf Salad - 120g	*Fridge*
☐	Large Cucumber x 1	*Fridge*
☐	Red Peppers x 3	*Fridge*
☐	Carrot x 1	*Fridge*
☐	Mixed Chilli peppers - 65g pack	*Fridge*
☐	Coriander - 30g	*Fridge*
☐	Frozen Sliced Mixed Peppers - 500g	*Freezer*
☐	Frozen Butternut Squash - 500g	*Freezer*
☐	Frozen Spinach - 900g	*Freezer*
☐	Baking potato x 1	*Cool, dry place*
☐	Norfolk potatoes - 750g	*Cool, dry place*
☐	Red Onions x 4	*Cool, dry place*
☐	Garlic 4 pack	*Cool, dry place*
☐	Tesco Three Bean Chilli Soup - 600g	*Fridge*
☐	Foodologie Lentil & Turmeric Daal	*Fridge/Freezer*
☐	Gosh Original Falafel - 300g	*Fridge/Freezer*
☐	Houmous - 3 x 60g	*Fridge*
☐	Salmon Fillets - 240g	*Fridge/Freezer*
☐	Chicken Breast Fillets - 300g x 2 packs	*Fridge/Freezer*
☐	Walnut Halves - 100g	*Cool, dry place*
☐	Mixed Nuts - 25g x 4 packs	*Cool, dry place*
☐	Rice cakes	*Cool, dry place*

IMPORTANT NOTE: Please wash fresh fruit, vegetables, and salad items before consuming.

ADDITIONAL SNACK OPTIONS:

Do not consume more than the quantities stated at mealtimes. If you are still hungry after consuming your meals and snacks, you can eat 'additional' snacks from the list of suitable snacks below. Please only eat snacks from this list.

- Rice cakes/oat cakes/wholemeal bread/toast
- Cottage cheese or low fat cream cheese spread e.g. Philadelphia
- Low sugar breakfast cereal e.g. Rice Krispies, Cornflakes (not Crunchy Nut) with milk.

If you are unsure if a snack is suitable, please contact the MediMood Research Team.

Please consume the drinks that are specified in the meal plan. In addition, you can drink any of the following to make up your daily fluid intake:

- Water
- Tea/coffee (without sugar) (caffeinated or decaf)
- Sugar free drinks

If you usually drink alcohol, you can continue to do so, but please **only** drink wine and consume no more than 5 small (125ml) glasses over the five days.

Remember to note any additional snacks and drinks in the comments box.

Please contact the MediMood research team if you have any queries:

medimood@uea.ac.uk

DAY 1

DINNER – Soup		
Item	**Quantity**	**Amount Eaten**
• Extra virgin olive oil	2tbsp/25ml	
• Three bean chilli soup	½ pack/300g	
Wholemeal bread	2 slices/80g	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See soup packaging for heating instructions. Extra virgin olive oil can be stirred into the soup or used for dipping the bread.		

SNACK		
Item	**Quantity**	**Amount Eaten**
• Fruit salad	½ pack/200g	

DAY 1 CONTINUED

DAY 1 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

On the morning of day 2 do **NOT** drink any **caffeinated drinks** prior to your online test

DAY 2

SNACK - To be eaten before MediMood online tests		
Item	**Quantity**	**Amount Eaten**
*Nature Valley Honey and Oat Bar	1 pack/42g	

BREAKFAST		
Item	**Quantity**	**Amount Eaten**
• Blueberries	80g	
Yeo Valley Greek Style Yogurt	1 pot/110g	

SNACK		
Item	**Quantity**	**Amount Eaten**
• Orange Juice	150ml	

DAY 2 CONTINUED

LUNCH – Falafel salad		
Item	**Quantity**	**Amount Eaten**
*Falafel balls	6 balls/150g	
*Houmous	½ pot/30g	
• Cucumber	1 inch/60g	
• Mixed salad leaves	⅓ packet/40g	
• Cherry Tomatoes	6 tomatoes/90g	
• Extra Virgin Olive Oil	2tbsp/25ml	
Balsamic vinegar	To taste	
PREPARATION GUIDELINES		
▪ Olive oil and balsamic vinegar can be combined to make a salad dressing. A recommended ratio of oil to vinegar is 3 parts oil: 1 part balsamic		

NOTE: The remaining falafel can be frozen and saved for consumption following the 5 day meal plan, if required. See packaging.

DAY 2 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
• Cucumber	1.5 inch/90g	
• Houmous	½ pot/30g	

DAY 2 CONTINUED

DINNER - Black bean and butternut squash chilli – DOUBLE the ingredient amounts if making for 2 people		
Item	**Quantity**	**Amount Eaten**
• Frozen spinach blocks	2 blocks/80g	
*Frozen butternut squash cubes	125g	
*Red Onion	½ onion/75g	
*Tinned tomatoes	½ can/200g	
• Extra Virgin Olive Oil	2tbsp/25ml	
• Black beans, canned	½ can/120g	
• chilli pepper	10g	
• Tomato Puree	10g	
• Garlic	1 clove/3g	
• Coriander	15g	

Please turn over for preparation guidelines

DAY 2 CONTINUED

PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people
▪ Peel and slice the onion and garlic. Chop the chilli pepper. Drain and rinse the beans. ▪ Heat 2 tbsp of olive oil in a large pan or casserole dish. ▪ Gently sauté the onion for 5 minutes, stirring occasionally. Add the chopped garlic and chilli pepper and fry for a further 1 minute. ▪ Add the butternut squash cubes and sauté for 5 minutes. ▪ Add the tomato purée and stir to coat. ▪ Add the tomatoes, and a little water if needed, to cover the squash. Bring to the boil. ▪ Add the frozen spinach blocks. ▪ Simmer, under cover for 20-25 minutes until tender. Add the black beans and cook for another 5 minutes. ▪ Stir through the coriander leaves and serve.

SNACK		
Item	**Quantity**	**Amount Eaten**
• Walnuts	3 halves/10g	
• Figs	30g	

DAY 2 CONTINUED

DAY 2 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the **Daal** or ***salmon fillets***, please defrost the required quantity according ahead of your day 3 lunch and evening meal. See defrosting instructions on the packaging.

DAY 3

BREAKFAST		
Item	**Quantity**	**Amount Eaten**
Wholemeal Bread	1 slice/40g	
Boiled eggs	2 eggs	
PREPARATION GUIDELINES		
▪ Lower room temperature eggs into boiling water for the desired amount of time. **5 minutes:** set white and runny yolk **6 minutes:** liquid yolk **7 minutes:** almost set **8 minutes:** softly set **10 minutes:** the classic hard-boiled egg ▪ When cooked, scoop the eggs out of the pan with a suitable spoon.		

SNACK		
Item	**Quantity**	**Amount Eaten**
• Orange Juice	150ml	

DAY 3 CONTINUED

LUNCH – Daal		
Item	**Quantity**	**Amount Eaten**
*Foodologie lentil and turmeric Daal	1 pot/400g	
*Olive oil	2tbsp/25ml	
PREPARATION GUIDELINES		
See Daal packaging for heating instructions. Before serving, add olive oil to the daal and stir.		

SNACK		
Item	**Quantity**	**Amount Eaten**
• Pear	1 fruit	
• Walnuts	3 halves/10g	

DAY 3 CONTINUED

DINNER – Salmon, New Potatoes and Salad		
Item	**Quantity**	**Amount Eaten**
• Salmon	1 fillet	
Pesto	1tbsp/24g	
New Potatoes, boiled	2 pot/85g	
• Mixed salad leaves	⅓ packet/40g	
• Cherry Tomatoes	6 tom/90g	
• Extra Virgin Olive Oil	2tbsp/25ml	
• Garlic	1 clove/3g	

PREPARATION GUIDELINES – DOUBLE the ingredient amounts if making for 2 people

- Spread a tablespoon of pesto over the top of the salmon fillet and oven bake according to instructions on salmon packaging.
- Wash the baby potatoes. Bring a pan of water to the boil. Gently simmer potatoes for approximately 15-20 minutes, until just tender.
- Serve salmon and potatoes with the fresh salad leaves and chopped cherry tomatoes.
- Drizzle with the olive oil. Add crushed garlic if desired.

DAY 3 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
• Mixed Nuts	1 pack/25g	
• Prunes in Juice	½ can/205g	

DAY 3 CONTINUED

DAY 3 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***chicken fillets***, please defrost the required quantity according ahead of your day 4 evening meal. See defrosting instructions on the packaging.

DAY 4

BREAKFAST		
Item	**Quantity**	**Amount Eaten**
*walnuts	9 halves/30g	
• Blueberries	80g	
Yeo Valley Greek Style Yogurt	1 pot/110g	

SNACK		
Item	**Quantity**	**Amount Eaten**
• Orange Juice	150ml	

DAY 4 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
• Figs	30g	

DAY 4 CONTINUED

LUNCH – Baked Potato with Tuna and Salad		
Item	**Quantity**	**Amount Eaten**
Baked Potato	1 potato	
• Canned Tuna, drained	1 can/105g	
• Extra Virgin Olive Oil	2tbsp/25ml	
Balsamic Vinegar	Add to taste	
• Cucumber	1.5 inches/90g	
• Cherry Tomatoes	7 toms/105g	

PREPARATION GUIDELINES

- Heat the oven to 220C/200C fan/gas 7. Put the potato on the top shelf of the oven. Bake for 20 mins, then turn down the oven to 190C/170C fan/ gas 5 and bake for 45 mins-1 hr more until the skin is crisp and the inside soft.
- Make a cross in the centre of the potato and add the tuna and drizzle with the olive oil.
- Serve with a side of cucumber and cherry tomatoes

DAY 4 CONTINUED

DINNER – Grilled Chicken with Mediterranean Vegetables and Couscous		
Item	**Quantity**	**Amount Eaten**
*Grilled Chicken Breast	1 fillet	
*Butternut squash chunks	125g	
*Frozen sliced mixed peppers	125g	
Wholewheat Couscous	50g (dry weight)	
* Extra Virgin Olive Oil	2tbsp/25ml	

PREPARATION GUIDELINES – DOUBLE the ingredient amounts if making for 2 people

- Roast butternut squash according to instructions on packaging, using ½ tbsp of olive oil. Add the frozen peppers to the roasting tray for the final 5-10 minutes or until thoroughly heated through.
- Grill chicken breast according to instructions on packaging.
- Place 50g wholewheat couscous to a heatproof bowl or jug. Add 100ml boiling water, cover and stand for 5-10 minutes. Add the remaining olive oil to the couscous and stir through with a fork before serving.

DAY 4 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
• Pears	1 fruit	
• Mixed Nuts	1 pack/25g	

DAY 4 CONTINUED

DAY 4 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***chicken fillets***, please defrost the required quantity according ahead of your day 4 evening meal. See defrosting instructions on the packaging.

DAY 5

BREAKFAST		
Item	**Quantity**	**Amount Eaten**
• Blueberries	80g	
• Walnuts	9 halves/30g	
Yeo Valley Greek Style Yogurt	1 pot/110g	

SNACK		
Item	**Quantity**	**Amount Eaten**
• Orange Juice	150ml	

DAY 5 CONTINUED

LUNCH – Pasta and Tomato Sauce		
Item	**Quantity**	**Amount Eaten**
Wholemeal Pasta	75g (dry weight)	
• Extra Virgin Olive Oil	2tbsp/25ml	
• Red Onion	½ onion/75g	
• Garlic	2 cloves/6g	
• Canned tomatoes	½ can/200g	
• Red Pepper	½ pepper/80g	

PREPARATION GUIDELINES

- Peel and slice the onion and garlic. Dice the red pepper.
- Heat 2 tbsp of olive oil in a large pan or casserole dish.
- Gently sauté the onion for 5 minutes, stirring occasionally. Add the chopped garlic and fry for a further 1 minute. Add the diced red pepper and stir for 2-3 minutes.
- Tip in the canned tomatoes, then bring to the boil. Reduce the heat, then simmer uncovered for 5 mins, stirring occasionally.
- Cook pasta according to instructions on the packaging.
- Mix the cooked pasta and sauce together and serve.

DAY 5 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
• Carrot sticks	80g	
• Cucumber	90g	
• Houmous	1 pot/60g	

DAY 5 CONTINUED

DINNER – Chicken with Chickpeas in Tomato Sauce		
Item	**Quantity**	**Amount Eaten**
• Chicken	1 fillet	
• Extra Virgin Olive Oil	2tbsp/25ml	
• Red onion	½ onion/75g	
• Red pepper	160g	
• Garlic	2 cloves/6g	
• Canned Tomatoes	½ can/200g	
• Canned Chickpeas	½ can/120g	
• Spinach	2 cubes/80g	

Please turn over for preparation guidelines

PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people
▪ Peel and slice the onion and garlic. Dice the red pepper. Drain and rinse the chickpeas. ▪ Heat 2 tbsp of olive oil in a large pan or casserole dish. ▪ Gently sauté the onion for 5 minutes, stirring occasionally. Add the chopped garlic and fry for a further 1 minute. Add the diced red pepper and stir for 2-3 minutes. ▪ Tip in the chopped tomatoes and add the frozen blocks of spinach. Bring to the boil. Reduce the heat, then simmer uncovered until the spinach has heated through, stirring occasionally. ▪ Add the Chickpeas and heat for a further 5 minutes. ▪ Meanwhile, grill the chicken breast according to instructions on packaging. ▪ Once cooked, poor the sauce over the chicken and serve.

SNACK		
Item	**Quantity**	**Amount Eaten**
*Apple	1 fruit	
*Pear	1 fruit	

DAY 5 CONTINUED

DAY 5 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

Please bring your booklet with you when you attend your next appointment

medimood@uea.ac.uk

Tel: 01603 591949

Western Diet Meal Plan

PARTICIPANT ID:

SHOPPING DELIVERY

Your shopping delivery should consist of the items listed on the following page. As you unpack, please tick off the items and store them according to the instructions on the packaging. Please inform the research team immediately if anything is missing or incorrect e.g., a food swap has been made by the supermarket.

	Item	Storage
☐	Raspberry Jam - 454g jar	*Fridge*
☐	Semi Skimmed Milk - 2 pints	*Fridge*
☐	Kellogg's Frosties cereal - 470g	*Cool, dry place*
☐	Free Range Eggs - 6 pack	*Fridge*
☐	Hovis White Bread Medium - 800g	*Cool, dry place/freezer*
☐	Tesco Brioche Buns - 4 pack	*Cool, dry place/freezer*
☐	Tesco Potato Salad - 300g	*Fridge*
☐	Tesco Quiche Lorraine - 160g x 2	*Fridge/Freezer*
☐	Unsmoked Back Bacon – 300g	*Fridge/Freezer*
☐	Tesco Pork Sausages- 8 pack	*Fridge/Freezer*
☐	Tesco Beef Quarter Pounder - 4 pack	*Freezer*
☐	Tesco straight cut oven chips - 950g	*Freezer*
☐	Chicago Town Meaty Pizza - 2 pack	*Freezer*
☐	Tesco Spaghetti Carbonara 2 x 400g	*Fridge/Freezer*
☐	Lurpak butter - 250g	*Fridge*
☐	Tesco Cream of Chicken Soup - 3 x 400g	*Cool, dry place*
☐	Aero Chocolate Mousse - 4 pack	*fridge*
☐	Vanilla & Choc Cheesecake - 2 slices	*Fridge*
☐	Cadbury Caramel cake bars - 5 pack	*Cool, dry place*
☐	Mr Kipling Bakewell Tarts - 6 pack	*Cool, dry place*
☐	KitKat 2 Finger - 9 pack	*Cool, dry place*
☐	Walkers Baked Sea Salt snacks - 6 pack	*Cool, dry place*
☐	Coca-Cola original 150ml - 6 cans	*Fridge*
☐	Tomato Ketchup	*Fridge*

SUITABLE SNACK AND DRINK OPTIONS:

Do not consume more than the quantities stated at mealtimes. If you are still hungry after consuming your meals and snacks, you can eat 'additional' snacks from the list of suitable snacks below. Please only eat snacks from this list.

- White bread/Toast with jam/marmalade (no butter)
- High sugar breakfast cereal e.g. Frosties, Crunchy Nut Cornflakes, Coco-Pops with milk
- Chips
- Crisps

If you are unsure if a snack is suitable, please contact the MediMood Research Team.

Please consume the drinks that are specified in the meal plan. In addition, you can drink any of the following to make up your daily fluid intake:

- Water
- Tea/coffee/milk (without sugar) (caffeinated or decaf)
- No added sugar/sugar free drinks (NOT fruit/vegetable juice)

If you usually drink alcohol, you can continue to do so, but please do NOT drink wine.

Remember to note any additional snacks and drinks in the comments box

Please contact the MediMood Research Team if you have any queries:

medimood@uea.ac.uk

DAY 1

EVENING MEAL – Soup and Bread		
Item	**Quantity**	**Amount Eaten**
Cream of chicken soup	1 can/400g	
White bread/toast	1 slice/40g	
*Butter for toast	½ tbsp/6g	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See soup packaging for heating instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Bakewell tart	1 tart/46g	

DAY 1 CONTINUED

DAY 1 COMMENTS	
Please list any additional foods and drinks that you have consumed today, since leaving your appointment. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***sausages*** or ***quiche***, please defrost the required quantity ahead of your day 2 meals following the instructions on the packaging.

On the morning of day 2 do **NOT** drink any **caffeinated drinks** prior to your online tests.

DAY 2

SNACK – To be eaten before MediMood online tests		
Item	**Quantity**	**Amount Eaten**
*Nature Valley Honey and Oat Bar	1 pack/42g	

BREAKFAST - Toast		
Item	**Quantity**	**Amount Eaten**
White bread/toast	1 slice/40g	
Jam	Heaped tsp/18g	
*Butter for toast	1 tbsp/12g	

DAY 2 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
*KitKat (2 finger)	1 KitKat	

LUNCH – Quiche and Potato Salad		
Item	**Quantity**	**Amount Eaten**
*Quiche Lorraine	1 quiche/160g	
Potato salad	⅓ pot/100g	
PREPARATION GUIDELINES		
Quiche can be eaten hot or cold. See packaging for heating instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Coca-Cola original	150ml can	

DAY 2 CONTINUED

EVENING MEAL – Sausage and Chips		
Item	**Quantity**	**Amount Eaten**
*Sausages, grilled/oven baked	2 sausages	
Chips	165g	
Ketchup	1 tbsp/24g	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See sausage packaging for cooking instructions. See oven chip packaging for cooking instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*KitKat (2 finger)	1 KitKat	

DAY 2 CONTINUED

DAY 2 COMMENTS	
Please list any additional foods and drinks that you have consumed today. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***bacon*** or ***brioche buns,*** please defrost the required quantity ahead of your day 3 lunch. See defrosting instructions on the packaging.

DAY 3

BREAKFAST - Cereal		
Item	**Quantity**	**Amount Eaten**
Frosties cereal	50g	
Semi Skimmed Milk	135ml	

SNACK		
Item	**Quantity**	**Amount Eaten**
*KitKat (2 finger)	1 KitKat	

DAY 3 CONTINUED

LUNCH – Bacon Roll		
Item	**Quantity**	**Amount Eaten**
*Bacon, grilled	5 rashers/150g	
Brioche bun	1 roll/63g	
*Butter for bun	1 tbsp/12g	
Ketchup	1 tbsp/24g	
PREPARATION GUIDELINES		
See bacon packaging for grilling instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Bakewell tart	1 tart/46g	

DAY 3 CONTINUED

DINNER – Pizza and Potato Salad		
Item	**Quantity**	**Amount Eaten**
*Mega meaty Chicago Town pizza	1 pizza/157g	
Potato salad	⅓ pot/100g	
*Coca-Cola original	150ml can	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See pizza packaging for cooking instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Vanilla and chocolate cheesecake	1 slice/90g	

DAY 3 CONTINUED

DAY 3 COMMENTS	
Please list any additional foods and drinks that you have consumed today. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***sausages***, please defrost the required quantity ahead of your day 4 breakfast. See defrosting instructions on the packaging.

DAY 4

BREAKFAST – Sausages and Eggs		
Item	**Quantity**	**Amount Eaten**
White bread/toast	1 slice/40g	
*Sausages, grilled/oven cooked	2 sausages	
Eggs, fried	2 eggs	
*Butter for frying	1 tbsp/12g	

PREPARATION GUIDELINES

See sausage packaging for grilling or oven cooking guidelines.

Fried eggs:

- Heat the butter in a frying pan until melted, but not hot enough to brown.
- Crack the eggs into the pan.
- Cover with a lid and leave for 3 minutes over a low heat. Check the white is set, if not, leave it for another 30 seconds and check again.

DAY 4 CONTINUED

SNACK		
Item	**Quantity**	**Amount Eaten**
*KitKat (2 finger)	1 KitKat	

LUNCH – Soup and Bread		
Item	**Quantity**	**Amount Eaten**
Cream of chicken soup	1 can/400g	
White bread/toast	2 slices/80g	
PREPARATION GUIDELINES		
See soup packaging for heating instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Aero chocolate mousse	1 pot/59g	

DAY 4 CONTINUED

EVENING MEAL – Spaghetti Carbonara		
Item	**Quantity**	**Amount Eaten**
*Spaghetti carbonara	1 meal/400g	
* Coca-Cola original	150ml can	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See spaghetti carbonara packaging for heating instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Cadbury caramel cake bar	2 bars/2 x 25g	

DAY 4 CONTINUED

DAY 4 COMMENTS	
Please list any additional foods and drinks that you have consumed today. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

IMPORTANT: If you have frozen the ***quiche*** or ***brioche buns,*** please defrost the required quantity ahead of your day 5 meals. See defrosting instructions on the packaging.

DAY 5

BREAKFAST - Cereal		
Item	**Quantity**	**Amount Eaten**
Frosties cereal	50g	
Semi Skimmed Milk	135ml	

SNACK		
Item	**Quantity**	**Amount Eaten**
*KitKat (2 finger)	1 KitKat	

DAY 5 CONTINUED

LUNCH – Quiche		
Item	**Quantity**	**Amount Eaten**
*Quiche Lorraine	1 quiche/160g	
Walkers	1 packet/22g	
*Coca-Cola original	150ml can	
PREPARATION GUIDELINES		
Quiche can be eaten hot or cold. See packaging for heating instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Bakewell tart	1 tart/46g	

DAY 5 CONTINUED

DINNER – Burger and Chips		
Item	**Quantity**	**Amount Eaten**
*Quarter pound beef burger	1 burger/114g	
Brioche bun	1 roll/63g	
*Butter for bun	1 tbsp/12g	
Chips, oven cooked	135g	
Ketchup	1 tbsp/24g	
PREPARATION GUIDELINES - DOUBLE the ingredient amounts if making for 2 people		
See burger packaging for grilling instructions. See chip packing for oven cooking instructions.		

SNACK		
Item	**Quantity**	**Amount Eaten**
*Aero chocolate mousse	1 pot/59g	

DAY 5 CONTINUED

DAY 5 COMMENTS	
Please list any additional foods and drinks that you have consumed today. Include quantities, brand names and any additional details e.g. 'sugar free'.	
Foods:	**Drinks:**

Please bring your booklet with you when you attend your next appointment

medimood@uea.ac.uk

Tel: 01603 591949

Appendix 21. Daily reminder email

Good morning [Participant name]

We hope you are doing well with your diet. Please do not forget wearing your watch, and completing the questionnaires on the booklet.

If you have any question, please do not hesitate to contact us by either replying to this email.

This study would not have been possible without you. Many thanks for your participation.

See you soon on your next study visit!

Kind regards,
The MediMood Research Team

Appendix 22. 3-months follow-up invitation email

Dear [Participant's name]

Thank you for your participation in the MediMood study.

For the final stage of the study, we would like you to complete a short questionnaire about your current diet. The questionnaire contains 14 questions and will take approximately 10 minutes to complete.

[link to the study website]

Please let the research team know if you have any questions.

Many thanks,

The MediMood Team

Appendix 23. Profile of Mood States (POMS)

Below is a list of words that describe feelings people have. Please read each one carefully, the circle the one that best describes HOW YOU HAVE BEEN FEELING IN THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phases: 0 – Not at all 1 – A little 2 – Moderately 3 – Quite a bit 4 – Extremely		43. Good natured. 0 1 2 3 4 44. Gloomy 0 1 2 3 4
	21. Hopeless 0 1 2 3 4 22. Relaxed 0 1 2 3 4	45. Desperate 0 1 2 3 4 46. Sluggish 0 1 2 3 4
1. Friendly 0 1 2 3 4 2. Tense 0 1 2 3 4	23. Unworthy. 0 1 2 3 4 24. Spiteful 0 1 2 3 4	47. Rebellious 0 1 2 3 4 48. Helpless 0 1 2 3 4
3. Angry 0 1 2 3 4 4. Worn out 0 1 2 3 4	25. Sympathetic 0 1 2 3 4 26. Uneasy 0 1 2 3 4	49. Weary 0 1 2 3 4 50. Bewildered 0 1 2 3 4
5. Unhappy 0 1 2 3 4 6. Clear headed 0 1 2 3 4	27. Restless 0 1 2 3 4 28. Unable to concentrate 0 1 2 3 4	51. Alert 0 1 2 3 4 52. Deceived 0 1 2 3 4
7. Lively 0 1 2 3 4 8. Confused 0 1 2 3 4	29. Fatigued 0 1 2 3 4 30. Helpful 0 1 2 3 4	53. Furious 0 1 2 3 4 54. Efficient 0 1 2 3 4
9. Sorry for things done 0 1 2 3 4 10. Shaky 0 1 2 3 4	31. Annoyed 0 1 2 3 4 32. Discouraged 0 1 2 3 4	55. Trusting 0 1 2 3 4 56. Full of pep 0 1 2 3 4
11. Listless 0 1 2 3 4 12. Peeved 0 1 2 3 4	33. Resentful 0 1 2 3 4 34. Nervous 0 1 2 3 4	57. Bad tempered 0 1 2 3 4 58. Worthless 0 1 2 3 4
13. Considerate 0 1 2 3 4 14. Sad 0 1 2 3 4	35. Lonely 0 1 2 3 4 36. Miserable 0 1 2 3 4	59. Forgetful 0 1 2 3 4 60. Carefree 0 1 2 3 4
15. Active. 0 1 2 3 4 16. On edge 0 1 2 3 4	37. Muddled 0 1 2 3 4 38. Cheerful 0 1 2 3 4	61. Terrified 0 1 2 3 4 62. Guilty 0 1 2 3 4
17. Grouchy 0 1 2 3 4 18. Blue 0 1 2 3 4	39. Bitter 0 1 2 3 4 40. Exhausted 0 1 2 3 4	63. Vigorous 0 1 2 3 4 64. Uncertain about things 0 1 2 3 4
19. Energetic 0 1 2 3 4 20. Panicky 0 1 2 3 4	41. Anxious 0 1 2 3 4 42. Ready to fight 0 1 2 3 4	65. Bushed 0 1 2 3 4

Appendix 24. Bond-Lader Visual Analogue Scale

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing in the full range of each dimensions.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert		Drowsy
Calm		Excited
Strong		Feeble
Muzzy		Clear-headed
Well-coordinated		Clumsy
Lethargic		Energetic
Contented		Discontented
Troubled		Tranquil
Mentally slow		Quick-witted
Tense		Relaxed
Attentive		Dreamy
Incompetent		Proficient
Happy		Sad
Antagonistic		Amicable
Interested		Bored
Withdrawn		Gregarious

Appendix 25. Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month:

1. When have you usually gone to bed at night?
2. How long (in minutes) has it usually taken you to fall asleep each night?
3. When you usually gotten up in the morning?
4. How many hours of actual sleep did you get at night? (This may be different than the hours you spend in bed)

For the remaining questions, choose the best response.

During the past month, how often have you had trouble sleeping because you:

5. Cannot get to sleep within 30 minutes
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

6. Wake up in the middle of the night or in the night or early morning
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

7. Have to get up to use the bathroom
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

8. Cannot breath comfortably
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

9. Cough or snore loudly
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

10. Feel too cold
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

11. Feel too hot
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

12. Had bad dreams
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

13. Have pain
    - Not during the past month
    - Less than once a week
    - Once or twice a week
    - Three or more times a week

Appendix 26. Karolinska Sleep Diary (KSD)

Instructions:

Please refer to your last overnight sleep episode, i.e. not a daytime nap, when answering the following questions. Please indicate whether the time is am or pm.

What time did you go to bed?		AM/PM
What time did you try starting to sleep at?		AM/PM
How long did it take you to fall asleep? (min)		
How many times did you wake up?		
How long were you awake for? (min) Please estimate the time and duration of each night awakening.		
What time did you wake up?		AM/PM
What time did you get up?		AM/PM
Did your alarm clock wake you up?		
Did you do any strenuous activity during the last 24 hours (if yes, please specify)		

How would you rate your quality of sleep?

Best sleep ever								**Worst sleep ever**
1	2	3	4	5	6	7	8	9

How difficult did you find to wake up/get up?

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Very easy										**Quite hard**

Appendix 27. Karolinska Sleepiness Scale (KSS)

Instructions:

Please indicate your level of sleepiness for the previous 5 minutes using the scale below.

Extremely alert	1
	2
Alert	3
	4
Neither sleepy nor alert	5
	6
Sleepy, but not fighting sleep	7
	8
Extremely sleepy; it is an effort to stay awake	9

Appendix 28. Statement of the Assessment of MediMood protocol

To explain my learning curve in a structured way, I use Gibbs' Reflective Cycle which is an academic reflective tool and includes the followings; "description of the experience, feelings and thoughts about the experience, evaluation of the experience, both good and bad, analysis to make sense of the situation, conclusion about what you learned and what you could have done differently and action plan for how you would deal with similar situations in the future, or general changes you might find appropriate" (463).

Funding

When we began designing the study, the budget was not confirmed. Therefore, we decided to chase relevant grant calls alongside producing the protocol. We applied for Rank Prize (£1500, Return to Research Grant) and Cure Alzheimer's. We had received the former but were not successful with the latter. I looked for further grants for the next few months but there was none available at the time, which taught me the difficulties with getting a grant, such as the amount of the funding, the discrepancies between grants' timelines and the ideal study timeline, and the effort required. Later, my primary supervisor secured a pump priming grant.

Another small but troublesome issue was the gift vouchers to be used for reimbursement purposes that were misdelivered by Amazon. Amazon initially neither took any responsibility for the loss nor offered any solution. It was a purchase worth £950 for which I used the Rank Prize grant. Although my supervisors comforted me saying that "it was not my mistake, even if they do not refund, it is not the end of the world. It is not worth as it consumes some much of my time and energy." It was relieving but I felt responsible for the research grant. I took all the screenshots of numerous live chats with Amazon customer services, and I requested my primary supervisor to email them, which she did. Thus, I was able to prove their mistake at the end of two months. Finally, they refunded us the money and provided me with a £100 gift voucher to apologise, which I used for the study expenses. Although it seems quite a small detail, it was a very frustrating experience, teaching me the least expected incidents can turn into a real struggle.

Ethics and internal approvals

The main issue we encountered with the MediMood was the attainment of the NHS ethics approval which was a lengthy process taking 11 months in total. I put the first IRAS application in March 2022 and a UEA FMH Ethics monitor application in April 2022, both required to be withdrawn. I submitted next IRAS application in June 2022, and we attended the meeting in July 2022. Two weeks later we were given an unfavourable opinion. The main reason was the committee thought we were not prepared adequately for the possibility that a Western diet could exacerbate the mild to moderate mental health symptoms of participants. They signified the necessity of a 'safety net'. To respond, we invited a clinical psychologist to our team. We also highlighted that the duration was going to be only five days and equated to the current dietary practices of the bottom decile of the UK population and thus was very unlikely to cause any permanent negative health effects. There were a few other minor issues raised, mainly around Participant Information Sheet such as the language we used could cause bias in favour of a MDP, and the study could be sensitive for some people with eating disorders. I submitted the fourth ethics application with revised documents in October 2022, and we attended the meeting in November 2022. The committee provided us with a provisional outcome and requested further information, which we submitted in mid-December 2022. We hoped to hear in the beginning of January 2023, but we did not. Then I tried contacting the ethics secretary several times but did not hear from them. I found the institutional email address of the chair and requested my supervisors to reach them out thinking they would be more efficient than myself. My primary supervisor emailed them on 6th February 2023. Consequently, we received the favourable ethical opinion on 8th February 2023.

Next, we needed R&D study approval from the NNUH as the trial involved the CRF facilities. During the next few months, I was heavily in contact with CRF personnel, prepared Standard Operating Procedures for kitchen use and food storage, and conducted Site Initiation Visits. We were provided with the green light in May 2023, and had the first participant in June 2023. The recruitment and data collection were concluded in December 2023.

Study design

Conducting an acute randomised controlled trial (RCT) as the main project of my PhD was determined when I applied. To begin with, I conducted a systematic review (Chapter 2) to identify the research gaps to justify and inform the study design. After publishing the systematic review in June 2021, the plan was to continue with the COVID-19 data analysis first (Chapter 5) and then to start producing the RCT protocol. In my second-year annual review meeting in August 2021, I proposed generating the protocol first, and then analysing the COVID-19 data whilst waiting for the study ethics approval with the interest of time. Thus, we started designing the study in September 2021.

The key objective of the study was going to be the short-term effects of a Mediterranean diet on brain health. My research interests included the ketone use by the brain in neurodegenerative diseases. My primary supervisor informed me about the likelihood of a new PhD student joining the project who was interested in the fibre and the gut-brain axis, which forwarded me to think of a three-arm study with two test arms (one enriched with unsaturated fat and one enriched with fibre) and one common control arm. Then, my primary supervisor highlighted the impracticalities of running a three-arm study such as a big sample size required. We also discussed the design (parallel or cross-over arms) and a few possible scenarios with the arms, the selection of primary outcomes and their measures. This early brainstorming enabled me to notice the number of critical decisions that need to be made at early stages in order to build a study from scratch.

My supervisors and I held regular weekly discussions to set up the study, where I initially thought that I should listen to them and follow their ideas only as they are well established and experienced academics whilst I was only a second year PhD student, and the idea of making mistakes was risky. Within a few weeks, I felt confident enough to propose my own ideas to contribute to the study owing to the atmosphere my supervisors' approach brought, that was safe to make mistakes and to learn from them. In November 2021, we finalized the main elements of the study, i.e. participants' characteristics, study type and duration, and outcomes.

The primary outcomes were going to be associated with mental health. To decide the domains to measure and the tools to use, we took our systematic review findings as reference alongside the further literature search conducted. My primary supervisor consulted the experts in mood and cognition in November 2021. Then we had a meeting

with Michael Hornberger (UEA) in January 2022 to discuss the cognitive side further. I also offered adding sleep component as both a confounding factor and a secondary outcome as I thought that the dietary intake and mental wellbeing status affect sleep quality and quantity, which in turn affect mood and cognition. As a result, we requested Alpar Lazar's (UEA) expertise on this in February 2022.

Brain perfusion was one of the things my primary supervisor mentioned about the mechanisms that is likely to be rapidly responsive to the intervention and to affect the outcomes. As the study budget was uncertain at the time, my second supervisor suggested creating two different versions of the study documents (protocol, participant information sheet and consent form), one implementing MRI and one without MRI to be prepared for each scenario, which I did. Then as I read the literature, I realised it has a likelihood to be the most impactful outcome, therefore, it seemed an essential component to have to me rather than keeping it optional. Furthermore, the gold standard to measure CBF was Arterial Spin Labelling (ASL) assessed by MRI (279) which was a very expensive method (in our MRI centre, the costing was £510 p/h for external funders that provide full economic costing e.g. UKRI). In February 2022, I attempted to highlight the importance of the MRI and the value it will add. As I was aware of the limited budget, I offered to conduct two scans instead of three. My primary supervisor agreed with me, and we later reduced the number of scans to one per arm per participant. We requested advice from cognitive and neuroimaging experts on MRI sequences, and we had a meeting with colleagues from UWWBIC in April 2022, which was amazing as it was one of the first in-person meetings I had the chance to attend after the pandemic.

To decide the duration of the washout period, I proposed four weeks considering the menstrual cycle as it can cause significant fluctuations in our primary outcomes. I initially questioned myself whether it was professional to bring up ideas from subjective experiences to a professional meeting. I looked in the literature and saw that those ideas were well aligned with the evidence, that premenstrual syndrome (PMS) is common and causes significant mood swings occurring on day to day basis (464). Besides, ignoring menstrual cycle in study designs is unfortunately not uncommon although it is a very natural part of women health, and causes 'sex bias' and heterogeneity in findings (465). Later my teammates noticed that the washout duration should be 23 days to achieve that aim of 28 days between the start of each dietary arm (with each arm itself being 5 days),

which was one of the points I appreciated working with a team can mean you have well considered decisions which minimise any errors in the protocol.

Following participants up with the MEDAS questionnaire at three months, to see how MediMood could influence longer term eating behaviour was my idea. Although I was aware that it might have slightly seemed out of main scope, I wanted to take the opportunity to evaluate whether individuals would voluntarily make any long-term change to their dietary behaviours as feasibility of adopting a MDP in non-Mediterranean populations is also interest of MDP research.

Dietary design

The research assistant of our group created the first meal plans in October 2021. Later, as a result of our rigorous debates, we decided to go for the extreme ends of both diets and took several resources as reference points as explained in detail in the protocol. I recommended to keep the wine consumption not mandatory for two reasons. First, because of the characteristics of our target population, I thought there might be people trying to better control their alcohol consumption behaviours. I also wanted to be as inclusive as possible. I am a member of a minority group and wanted people from different religious backgrounds to be able to participate when alcohol was not mandatory. For the same reason, I also offered to keep flexible on meat provision not to exclude anyone because of their lifestyle. I think it is important to have a diverse team to be more aware of the lifestyles of others in designation of studies to get those individuals into research and thus increase the generalisability of study findings, as recently proposed by NHS to implement Patient and Public Involvement (PPI) strategies (466).

I recommended purchasing the Nutritics software to automatically calculate and monitor meal compositions in terms of macro- and micronutrients, fibre and sugar in order to be more precise. My supervisors approved and I purchased an annual membership using the Rank Prize grant I held. I made adoptions to finalise the diets in June 2022. I was more confident with designing the Mediterranean meals as I am from a Mediterranean country but was hesitant about Western eating habits as I knew them only by theory with no real-life experience. After obtaining the ethics approval, my native teammates checked the plans and made further adoptions in February-March 2023 to

make them more practical/edible/realistic for a UK population. Then I was suggested to do a mock run-through on a friend, which was a great idea to see how everything goes. My friend's feedback helped us to realise we needed to provide participants with snack options in case they were not full. Thus, we chose snack options that do not affect the MEDAS score.

With the changes I made to the diets in June 2022, the daily caloric content ranged between 1990-2010 as I allowed myself a flexibility for ±10 kcal/day. When we started reviewing them as a team, I asked my primary supervisor what range we should keep the total daily energy intake as it is almost impossible to keep them exactly at 2000 kcal/day every day. She responded that as long as the total 5-day diet added up to 10,000 kcal, that up to 10% variability per day (±200 kcal/day) was acceptable, which was 20-fold higher flexibility than I allowed myself. I, thus, realised sometimes I may be too much of perfectionist and for my future projects I need to be more realistic and easier on myself and my teammates.

There were also a number of practical considerations for serving the lunch in our Clinical Research facility (CRF). Due to allergen status of nuts, we were not allowed to store any opened package there and it had suggested us to find single use pack options. We had planned to serve 30 grams. Due to practical considerations, my colleagues suggested to go for a 25 grams mixed nuts (almonds, hazelnuts, cashews and pecans) to make things more practical. However, I was not convinced by this as I intuitively thought that walnuts would be a more powerful option for our trial purposes, with evidence that walnuts are likely to support brain health and circulation (467, 468) due to their superior PUFA composition compared to hazelnuts and almonds (469). I spoke to my primary supervisor if it would be okay from the financial perspective to use a large packet of walnuts each time as we were going to need to discard the remaining amount of the package after every use and she confirmed we could afford that as it was a small sample size.

Pros, cons and lessons learnt

Running this type of a study as a PhD student was subject to its own pros and cons. The main advantage was the incredible learning curve; how to create a new study

from the scratch and how to handle the ethics process, which I feel very lucky about as not all PhD students build their own studies and are involved in every step undertaken. I now have an in-depth understanding on constructing and conducting a project. I feel confident that I can manage this on my own in my future career as I am now experienced with every possible scenario, particularly with the ethics process. The skills I gained have significantly elevated my ability to oversee and execute complex research activities with precision. The main disadvantage was the pressure brought by the undeniable nature of a PhD as it must be completed within a limited timeframe with limited resources. In that sense, my year three and four was extra stressful due to the impacts of the delays on the timescale of my PhD as I had to start my data collection in my year four.

I believe, my main strength was being good at coordination and organisation. I also displayed some leadership skills as I contributed to the study design. It felt amazing and boosted my confidence when my opinions were listened and appreciated by well-established academics. Furthermore, I served as the study coordinator for a detailed RCT created and run by a wide range of academic professionals (undergraduate students, another PhD student alongside myself, a research associate, doctors and professors), together with several departments i.e. Clinical Research Facility, UEA Research and Innovation Services, ethics committees and some IT support. I maintained the study documentation throughout, i.e. IRAS, Trial Master File. My weaknesses were I sometimes struggled with staying calm because of some internal and external factors. If I were to redo everything, I would have more open communication with relevant people when I needed to. However, it is essential to be aware of the fact that this study was developed under partly pandemic circumstances, therefore I did my best.

Overall, I learnt

- the value of having experienced advisors and a skilled professional network
- the importance of knowing the limits of your knowledge, and consulting the experts where it is not your primary expertise area
- the invaluable sense of being a part of a team involving people from different backgrounds at different stages in their careers
- the importance of creating a safe space for junior colleagues to help them grow
- the value of maintaining good relationships with colleagues

- that it is good to follow your intuitions as long as they can be justified by scientific evidence.

Implementing an RCT is an arduous task which requires a good amount of resilience and flexibility. For example, the paperwork side or the practical side may not proceed as planned. Having encountered several obstacles and gained insights, I will be more prepared for the challenges in my future actions, especially in terms of time management as it is not uncommon to have delays in research. It is important to be ready to deal with unpredicted challenges. In my opinion, getting benefits from past experiences, considering different perspectives and having open communications are key to mitigate risks and to overcome those challenges.

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Appendix 29. Impacts of MDP and WD interventions on mood and anxiety after one and five days

	Scale		N	D1 morning (mean ± SD)	N	D2 morning (mean ± SD)	N1	D6 morning (mean ± SD)	Treatment Effect size β (95% CI) *p* value	Time Effect size β (95% CI) *p* value	Treatment * time Effect size β (95% CI) *p* value
POMS	Anxiety (9-36)	MDP	25	15.7 ± 6.0	25	15.5 ± 5.8	23	11.7 ± 4.9	**-2.2 (-4.0, -0.4) 0.018**	**-1.9 (-3.6, -0.1) 0.039**	**-4.3 (-7.7, -0.9) 0.014**
		WD	23	16.0 ± 5.4	23	15.9 ± 5.1	22	16.0 ± 6.6			
	Depression (15-60)	MDP	25	14.9 ± 7.2	25	14.9 ± 10.2	23	9.0 ± 7.3	**-2.3 (-5.8, -0.2) 0.033**	-2.1 (-4.8, 0.6) 0.130	**-7.3 (-12.5, -2.1) 0.007**
		WD	23	15.3 ± 9.0	23	14.8 ± 8.8	21	16.4 ± 11.0			
	Anger (12-48)	MDP	25	8.4 ± 4.9	25	9.3 ± 6.7	23	7.0 ± 5.3	0.1 (-1.7, 2.0) 0.885	-0.7 (-2.5, 1.2) 0.465	-2.4 (-6.0, 1.2) 0.194
		WD	23	10.3 ± 7.3	23	10.0 ± 8.0	21	9.6 ± 6.4			
	Vigour (8-32)	MDP	25	11.4 ± 5.5	25	11.2 ± 5.5	23	13.5 ± 5.4	**2.3 (0.5, 4.1) 0.013**	0.8 (-1.0, 2.6) 0.397	**4.4 (0.9, 7.9) 0.014**
		WD	23	11.7 ± 3.2	23	11.3 ± 4.8	22	10.0 ± 4.3			
	Fatigue (7-28)	MDP	25	13.8 ± 5.6	25	12.8 ± 6.4	23	9.9 ± 4.2	**-3.2 (-5.1, -1.4) 0.001**	0.356 -0.9 (-2.7, 1.0)	**-3.8 (-7.4, -0.1) 0.044**
		WD	23	11.8 ± 5.1	23	12.4 ± 5.1	22	12.9 ± 5.6			
	Confusion (7-28)	MDP	25	11.1 ± 3.6	25	9.9 ± 4.2	23	7.4 ± 3.4	**-3.2 (-4.6, -1.7) < 0.001**	0.115 -1.1 (-2.5, 0.3)	-2.4 (-5.2, 0.4) 0.097
		WD	23	10.2 ± 4.2	23	11.0 ± 3.8	22	10.6 ± 4.5			
	TMD	MDP	25	52.4 ± 22.3	25	51.2 ± 27.1	23	31.5 ± 19.8	**-14.1 (-23.0, -5.2)**	-7.3 (16.2, 1.5)	**-25.2 (-41.9, -8.4)**

	(-32-200)	WD	23	51.9 ± 26.9	23	52.8 ± 22.7	22	55.5 ± 30.8	**0.002**	0.101	**0.004**
Bond-Lader	Contentment	MDP	25	60.2 ± 13.5	25	59.1 ± 15.9	23	64.6 ± 15.4	5.2 (-1.7, 12.0)	3.4 (-3.5, 10.3)	4.4 (-9.4, 18.3)
	(0-100)	WD	23	58.5 ± 13.2	23	54.3 ± 12.4	22	56.7 ± 13.7	0.140	0.333	0.524
	Alertness	MDP	25	49.0 ± 13.1	25	54.9 ± 13.7	22	61.1 ± 14.0	**7.9 (0.9, 14.9)**	5 (-2.0, 12.0)	6.2 (-7.8, 20.1)
	(0-100)	WD	23	48.6 ± 10.5	23	49.7 ± 14.7	22	51.7 ± 13.7	**0.028**	0.157	0.381
	Calmness	MDP	25	60.3 ± 15.4	25	59.4 ± 13.8	23	60.9 ± 16.5	-1.2 (-9.0, 6.6) *	0.6 (-7.3, 8.4) *	4.8 (-11.3, 20.2) *
	(0-100)	WD	23	52.9 ± 16.7	23	55.6 ± 14.6	22	54.3 ± 16.4	0.755	0.888	0.572

MDP: Mediterranean-style dietary pattern. WD: Western-style diet. N: number of observations with maximum possible N being 25, however N varies due to dropouts, missing data and extreme outliers. SD: Standard deviation. β: Coefficient. CI: Confidence Interval. D1: Day 1 (baseline), D2: Day 2 (24h), D6: Day 6 (end of 5-day intervention). POMS: Profile of Mood States questionnaire (65 items, 0-4 scale). TMD: Total Mood Disturbance is an overall score generated using tension, depression, anger, vigour, fatigue and confusion scores. Bond-Lader is a visual analogue scale with each item has 0-100 mm scales. A linear mixed model was run for the statistical analyses, adjusted for treatment, sequence and period effects. All significant effects were highlighted in bold. * Significant period effect.

Appendix 30. C-19 Baseline questionnaire

Survey Flow

Block: Participant info (2 Questions)
Standard: Screening questions and contact info (10 Questions)
Standard: C19 health questions (6 Questions)
Standard: Demographics (8 Questions)
Standard: Employment (16 Questions)
Standard: Nutrition and exercise (13 Questions)
Standard: Smoking and Cessation (12 Questions)
Standard: Drugs and alcohol (10 Questions)
Standard: Debrief block (1 Question)

Page Break

Start of Block: Participant info

Q1

COVID-19 WELLBEING STUDY

We have had a fantastic response to the survey, especially from women, and are therefore no longer recruiting women to take part.

We would like more men to take part in the study and the survey is still open to people who identify as male or non-binary.

Help us track how health behaviours and wellbeing are affected by the COVID-19 pandemic and social distancing.

We would like to know how this is affecting you on a daily basis. Take 3 minutes to fill in a brief daily survey for the next 12 weeks about your mood, nutrition, physical activity, sleep, alcohol and drug use.

The findings will help researchers, policy makers, and government to understand how best to plan for health and wellbeing support.

To take part in this research study, you will complete an initial 15 minute survey clicking on the link below. Following this, the 3 minute daily survey link will be texted to your phone every day for 12 weeks starting from tomorrow (or as soon as possible after tomorrow if we are experiencing a high number of responses).

If you fill in most of the daily surveys over the 12 week period you will be given the opportunity to have a personalised report at the end of the study. The report will summarise how your behaviour and wellbeing changes over time.

All data will be stored confidentially and will be anonymised.

Thank you for your interest.

- ○ Take me straight to the survey - I agree to participate (1)
- ○ I would like further information about the study (2)

Display This Question:

If COVID-19 WELLBEING STUDYWe have had a fantastic response to the survey, especially from women,... = I would like further information about the study

Q2 Further Study Information Who is organising and funding this study?
The study is being led by a team of researchers at the Faculty of Medicine and Health Sciences based at the University of East Anglia (UEA) and is funded by a UEA impact fund.

Why is this study important?
The COVID-19 pandemic has affected all our lives in a very short space of time. It is essential that we understand more about how our health behaviours and wellbeing are affected. This is to make sure that future support strategies are based on real data and will help the people who need it most.

Who can take part in this study?
Anyone who lives in the UK who is aged 18 years or over and has access to a smartphone.
What will taking part involve?
Clicking on the link below will take you to an initial 15 minute 'baseline' survey which asks you to tell us about yourself and about your past and current health behaviours and wellbeing. Starting from tomorrow (or as soon as possible after tomorrow), you will receive a daily text message every evening with a web-link to a brief online survey. You can choose whether to receive the text at 8pm, 9pm, or 10pm. The survey should take less than three minutes to complete a day. The survey will ask about COVID-19 symptoms and your mood, wellbeing, nutrition, physical activity, sleep, alcohol and drug use. There may also be opportunities to be involved in further research about the COVID-19 pandemic and health behaviours and wellbeing.

What are the possible benefits of taking part?
We plan to give you the opportunity to receive a personalised summary report of your survey results if you complete the daily questionnaire for most of the 12 weeks (84 days).

Your contribution will be very important in helping us understand and best support changes to people’s health behaviours and wellbeing as a result of the COVID-19 or similar future pandemic.

What are the disadvantages of taking part?
There are no direct risks to you from taking part in this research. The daily survey has been designed to be brief and easy to complete. You are free to withdraw from the study at any point during the 12 week (84 day) period.
Will my information be kept confidential?
We will securely store surveys and any personal details that you provide for 36 months after the end of the study. We will use them only for contacting you in relation to this research study. We will not identify your participation to anyone outside of the research team and all data will be reported anonymously. Your mobile phone number will need to be passed to TextAnywhere so we can send you study-related text messages (e.g. daily survey links). This data will not be shared with any other third parties and will only be used for this study. For further information, see

https://www.textanywhere.com/policy-documents/terms-and-conditions/ All data will be handled in accordance with GDPR. Please see the following link for how we use personal information: https://portal.uea.ac.uk/information-services/strategy-planning-and-compliance/regulations-and-policies/information-regulations-and-policies/data-protection Fully anonymised data may be shared on academic open access platforms to ensure transparency, aid peer review and allow others to make use of important data for re-analysis.
What will happen to the results of the study?
We will feedback our findings to healthcare professionals and Public Health Commissioners. We may also publish our findings in academic journals and present at conferences to relevant user and professional groups.
Who has reviewed the study?
The study has been approved by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia (30th March 2020 Ref: 2019-20 089).
Further information and contact details
If you have any questions please feel free to contact Dr Caitlin Notley c.notley@uea.ac.uk Alternatively, if you would prefer to speak to someone independent about this research, please contact: Professor Lee Shepstone, Associate Dean for Research, Norwich Medical School at l.shepstone@uea.ac.uk

○ I agree to participate (1)

End of Block: Participant info

Start of Block: Screening questions and contact info

Q17 What is your gender?

○ Male (1)

○ Female (2)

○ Non-binary/third gender (3)

Display This Question:

If What is your gender? = Female

Q80 Thank you for your interest. We have had a fantastic response to the survey, especially from women, and are therefore no longer recruiting women to take part.

If you are not female, please hit the back button and choose another option.

Skip To: End of Survey If Thank you for your interest. We have had a fantastic response to the survey, especially from wome... Is Displayed

Q3 Are you aged 18 years or over?

- Yes (1)
- No (2)

Display This Question:

If Are you aged 18 years or over? = No

Q4 Thank you for your interest. This study is aimed at adults aged 18 years or over.

If you are aged 18 or over, please hit the back button and select 'yes' to the previous question.

Skip To: End of Survey If Thank you for your interest. This study is aimed at adults aged 18 years or over. If you are aged... Is Displayed

Q5 Do you live in the UK?

- Yes (1)
- No (2)

Display This Question:

If Do you live in the UK? = No

Q6 Thank you for your interest. This study is aimed at adults who are resident in the UK.

If you are resident in the UK, please hit the back button and select 'yes' to the previous question.

Skip To: End of Survey If Thank you for your interest. This study is aimed at adults who are resident in the UK. If you are... Is Displayed

*

Q7 What is your mobile phone number? Please give the number that you would like the survey link texted to on a daily basis.

Please enter your mobile number without any spaces (including at the end of the number).

_____

*

Q8 What is your email address? We will only use your email if we need to contact you about this study.

Please enter your email address without any spaces (including at the end of the address).

_____

Q9 What time would you like to receive the daily text with the three minute survey link? Please pick the time closest to your normal bedtime.

- ○ 8pm (1)
- ○ 9pm (2)
- ○ 10pm (3)

Q10 Please write your preferred name that you would like to be referred to in the text.

_____

End of Block: Screening questions and contact info

Start of Block: C19 health questions

Q11 We need to ask you some questions about you to best understand how you are affected by the COVID-19 pandemic. These questions take around 15 minutes to complete and you will only be asked to fill them in once.

Q12 Have you been tested and diagnosed as having a COVID-19 infection?

- Yes (1)
- No (2)

Q13 Have you experienced any possible COVID-19 symptoms since the pandemic began in the UK in February 2020? e.g. a high temperature and/or new and continuous cough?

- Yes (1)
- No (2)

Q14 Have you been informed by the NHS that you are at very high risk of severe illness if you catch coronavirus, and advised to remain at home for a minimum of 12 weeks? (e.g. transplant recipients, cancer patients, people with severe respiratory conditions such as severe asthma/COPD, people on immunosuppression therapies, pregnant women)

- Yes (1)
- No (2)

Display This Question:

If Have you been informed by the NHS that you are at very high risk of severe illness if you catch c... = No

Q15 Are you in a group at increased risk of severe illness from coronavirus and so advised to follow particularly stringent social distancing measures [but have not been contacted by the NHS and advised to remain at home for 12 weeks]? (e.g. aged over 70 years, suffering from asthma, COPD, bronchitis, high blood pressure, liver disease, chronic neurological conditions, spleen removal, sickle cell, HIV or AIDS, weakened

immune system, BMI of 40 (kg/m2) or above), or anyone instructed to get a flu jab as an adult each year on medical grounds):

- ○ Yes (1)
- ○ No (2)

Q16
Please state any health condition(s) in the box below:

_____

End of Block: C19 health questions

Start of Block: Demographics

*

Q18 What is your date of birth? (e.g. 30/01/1995)

_____

*

Q19 What is your postcode? (e.g. NR4 7TJ)

Please make sure you use capital letters.

_____

Q20 What is your ethnic group?

- White (1)
- Mixed/multiple ethic backgrounds (2)
- Asian/Asian British (3)
- Black/African/Caribbean/Black British (4)
- Arab (5)
- Any other ethnic group, please describe: (6)

_____

Q21 Please state your marital status:

- Single (1)
- Co-habiting (2)
- Civil partnership (3)
- Married (4)
- Divorced (5)
- Widowed (6)

Q22 Please state the number of adults (18 years or over) that currently live in your household including yourself:

_____

Q23 Do you have children (under age 18) currently living in your household?
If you are a blended/step family please include children who currently live with you regularly even if it is not all of the time.

- Yes (1)
- No (2)

Display This Question:

If Do you have children (under age 18) currently living in your household? If you are a blended/ste... = Yes

Q24 Please state the number of children in each age group that live in your household:

- 0-4 years (1) _____
- 5-9 years (2) _____
- 10-14 years (3) _____
- 15-17 years (4) _____

Display This Question:

If Do you have children (under age 18) currently living in your household? If you are a blended/ste... = Yes

Q25 Are you the parent/caregiver of the children?

- Yes (1)
- No (2)

End of Block: Demographics

Start of Block: Employment

Q26 The following questions focus on employment in order to understand how the COVID-19 pandemic has affected your work situation.

Q27 What is your employment status?

- Not working (student/home carer/retired) (1)
- Never worked or long-term unemployed (4)
- Unemployed and looking for work (not due to COVID-19 crisis) (2)
- Out of work, furloughed, or given leave of absence, due to COVID-19 (3)
- Unable to work because of sickness or disability (5)
- Employed (6)
- Self-employed/freelance (7)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q28 What is your occupation group?

- Routine and manual occupations (e.g. HGV driver, van driver, cleaner, porter, sewing machinist, messenger, labourer, waiter/waitress, bar staff) (1)
- Intermediate occupations (e.g. secretary, personal assistant, clerical worker, office clerk, call centre agent, healthcare assistant, nursery nurse) (2)
- Managerial/professional occupations (e.g. teacher, nurse, physiotherapist, social worker, welfare officer, artist, musician, police officer (sergeant or above), software designer) (3)

Q29 Some questions will refer to prior the COVID-19 pandemic. Please answer for the time period November 2019 to January 2020 - the three months preceding the date of the first identified transmitted coronavirus case in the UK.

Q30 Was your employment status different before the COVID-19 pandemic?

- Yes (1)
- No (2)

Display This Question:

If Was your employment status different before the COVID-19 pandemic? = Yes

Q31 What was your employment status before the COVID-19 pandemic?

- Not working (student/home carer/retired) (1)
- Unemployed and looking for work (not due to COVID-19 crisis) (2)
- Never worked or long-term unemployed (3)
- Unable to work because of sickness or disability (4)
- Employed (5)
- Self-employed/freelance (6)

Display This Question:

If What was your employment status before the COVID-19 pandemic? = Employed

Or What was your employment status before the COVID-19 pandemic? = Self-employed/freelance

Q32 What was your occupation group before the COVID-19 pandemic?

- Routine and manual occupations (e.g. HGV driver, van driver, cleaner, porter, sewing machinist, messenger, labourer, waiter/waitress, bar staff) (1)
- Intermediate occupations (e.g. secretary, personal assistant, clerical worker, office clerk, call centre agent, healthcare assistant, nursery nurse) (2)
- Managerial/professional occupations (e.g. teacher, nurse, physiotherapist, social worker, welfare officer, artist, musician, police officer (sergeant or above), software designer) (3)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q33 In what location are you working?

- At home - I've always worked at home (1)
- At home - I'm working at home due to COVID-19 (2)
- Not at home - in my usual workplace (3)
- Not at home - in a different workplace to normal (4)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q34 Have your actual hours worked (rather than contracted hours) increased or decreased since the COVID-19 pandemic?

- Decreased considerably (1)
- Decreased somewhat (2)
- Stayed the same (3)
- Increased somewhat (4)
- Increased considerably (5)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q35 Has your income increased or decreased since the COVID-19 pandemic?

- ○ Decreased considerably (1)
- ○ Decreased somewhat (2)
- ○ Stayed the same (3)
- ○ Increased somewhat (4)
- ○ Increased considerably (5)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q36 Are you having to take care of children during your usual (pre COVID-19) work hours?

- ○ Yes (1)
- ○ No (2)

Display This Question:

If What is your employment status? = Employed

Or What is your employment status? = Self-employed/freelance

Q37 Are you a "key worker"? (e.g. NHS workers, social care workers, teachers, police officers, supermarket staff, delivery staff, infrastructure staff)

- ○ Yes. Please give your job role: (1) _____
- ○ No (2)

Q38 Have you applied for, or are you currently receiving, financial support from the Government as a result of the COVID-19 pandemic?

- ○ Yes. Please describe support scheme/benefit: (1) _____
- ○ No (2)

Q39 What was your household's average net (after tax) monthly income in March 2020? Please include any benefits your household members received.
If you are a single person living in a shared house/lodging please base this on your individual income.

- ○ £0-£500 (1)
- ○ £501-£999 (2)
- ○ £1000-£1499 (3)
- ○ £1500-£1999 (4)
- ○ £2000-£2499 (5)
- ○ £2500-£2999 (6)
- ○ £3000-£3499 (7)
- ○ £3500-£3999 (8)
- ○ £4000-£4499 (9)
- ○ £4500-£4999 (10)
- ○ £5000+ (11)
- ○ Prefer not to say (12)

Q40 Has your household income changed since the COVID-19 pandemic?

- Yes (1)
- No (2)

Display This Question:

If Has your household income changed since the COVID-19 pandemic? = Yes

Q41 What was your household's average monthly net income (after tax) in January 2020 (before the COVID-19 pandemic)? Please include any benefits your household members received.
If you are a single person living in a shared house/lodging please base this on your individual income.

- £0-£500 (1)
- £501-£999 (2)
- £1000-£1499 (3)
- £1500-£1999 (4)
- £2000-£2499 (5)
- £2500-£2999 (6)
- £3000-£3499 (7)
- £3500-£3999 (8)
- £4000-£4499 (9)
- £4500-£4999 (10)
- £5000+ (11)
- Prefer not to say (12)

End of Block: Employment

Start of Block: Nutrition and exercise

Q42 We are very interested in how COVID-19 may have impacted on your health behaviours. The next questions ask about your nutrition and physical activity.

Q43 We would like to know your BMI (body mass index) both now and at the end of the 12 week period. To work this out we need to know your height and weight.

Do you measure your height in feet and inches or cm?

- Feet and inches (1)
- cm (2)

Display This Question:

If We would like to know your BMI (body mass index) both now and at the end of the 12 week period. T... = Feet and inches

Q44 What is your height in feet and inches?

- Feet (1) _____
- Inches (2) _____

Display This Question:

If We would like to know your BMI (body mass index) both now and at the end of the 12 week period. T... = cm

Q45 What is your height in cm?

_____

Q46 Do you measure your weight in stones and pounds or kg?

- Stones and pounds (1)
- kg (2)

Display This Question:

If Do you measure your weight in stones and pounds or kg? = Stones and pounds

Q47 What is your weight in stones and pounds?

○ Stones (1) _____

○ Pounds (2) _____

Display This Question:

If Do you measure your weight in stones and pounds or kg? = kg

*

Q48 What is your weight in kgs?

_____

*

Q49 Prior to the COVID-19 pandemic, on average how many portions of fruit did you eat per day? (e.g. 5, 0, 1) A portion of fruit is 80g (about a handful). Fresh, frozen, canned, dried and juiced fruit all count. 30g of dried fruit is equivalent to around 80g of fresh fruit. You can include fruit juice or smoothies once. For example, if you have 2 glasses of fruit juice and a smoothie in one day, this still counts as 1 portion.

_____

*

Q50 Prior to the COVID-19 pandemic, on average how many portions of veg did you eat per day? (e.g. 5, 0, 1) A portion of vegetables is 80g (about 3 heaped tablespoons or a cup of salad vegetables). Fresh, frozen and canned vegetables all count.

_____

*

Q51 Prior to the COVID-19 pandemic, on average how many times per day (e.g. 5, 0, 1) did you eat foods high in sugar such as chocolate (regular bar), cakes, biscuits (3), sweets (1 small packet), sugary drinks and jams (3 teaspoons).
Include chocolate spreads (3 teaspoons), honey (2 teaspoons), table sugar (3 teaspoons), squash cordials and fruit juice.

_____

Q52 Prior to the COVID-19 pandemic, on a typical day, how healthy was your overall diet? Would you say:

- ○ Excellent (1)
- ○ Very good (2)
- ○ Good (3)
- ○ Fair (4)
- ○ Poor (5)

Q53 Before the COVID-19 pandemic, how many days a week did you do a total of 30 minutes or more of physical activity, which was enough to raise your breathing rate?

This may include exercise, and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that may be part of your job.

▼ 0 days a week (4) ... 7 days a week (12)

Q54 Before the COVID-19 pandemic, how many days a week would you have done an activity to improve your strength, such as yoga, resistance training, the gym or bowls?

▼ 0 days a week (4) ... 7 days a week (11)

End of Block: Nutrition and exercise

Start of Block: Smoking and Cessation

Q55 We are very interested in how COVID-19 may have impacted on your health behaviours. The following questions ask you about any smoking, drinking, and recreational drug use.

Q56 Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking')

- Yes - I smoke (2)
- No - I have given up since the COVID-19 pandemic (1)
- No - I gave up before the COVID-19 pandemic (4)
- No - I have never smoked (3)

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

Or Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = No - I have given up since the COVID-19 pandemic

*

Q57 Before the COVID-19 pandemic, how many cigarettes/rollups per day did you usually smoke?
(If you didn't smoke every day, please add up the number of cigarettes you usually smoked over a week and divide by 7)

_____

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

Or Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = No - I have given up since the COVID-19 pandemic

Q58 Before the COVID-19 pandemic, where would you usually smoke? Please select all that apply.

- [ ] Indoors at home (include smoking out of a window) (1)
- [ ] Outdoors at home (e.g. doorstep, garden, balcony) (2)
- [ ] In car (3)
- [ ] In public places in designated smoking areas (e.g. work/pub smoking shelter) (4)
- [ ] In public spaces in the open (e.g. park, beer garden, pavement, outside office building) (5)
- [ ] Other. Please state: (6) _____

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

Q59 Where do you usually smoke now? Please select all that apply.

- [ ] Indoors at home (include smoking out of a window) (1)
- [ ] Outdoors at home (e.g. doorstep, garden, balcony) (2)
- [ ] In car (3)
- [ ] In public places in designated smoking areas (e.g. work/pub smoking shelter) (4)
- [ ] In public spaces in the open (e.g. park, beer garden, pavement, outside office building) (5)
- [ ] Other. Please state: (6) _____

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

*

Q60
How many cigarettes/rollups per day do you usually smoke currently?
(If you don't smoke every day, please add up the number of cigarettes you smoke over a week and divide by 7)

_____

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

Q61 How soon after you wake up do you smoke your first cigarette?

- Within 5 minutes (1)
- 6-30 minutes (2)
- 31-60 minutes (3)
- More than 60 minutes (4)

Display This Question:

If Do you smoke any tobacco? (e.g. cigarettes, rollups, include 'social smoking') = Yes - I smoke

Q62 How much do you want to quit?

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Quite a bit (4)
- Extremely (5)

Q63 Did you use any of the following in the three months before the COVID-19 pandemic (Nov 2019 to Jan 2020)?

- [ ] E-cigarettes / vapes (1)
- [ ] Heated tobacco products (e.g. heat-not-burn products, non-combustible cigarettes) (2)
- [ ] Nicotine replacement (e.g. gum, patches) (3)
- [ ] Stop smoking medication (e.g. Champix) (4)
- [ ] None (5)

Display This Question:

If Did you use any of the following in the three months before the COVID-19 pandemic (Nov 2019 to Ja... = E-cigarettes / vapes

Q64 How often did you use e-cigarettes before the COVID-19 pandemic?

- ○ Less than once a month (6)
- ○ Once a month (1)
- ○ Two to four times a month (2)
- ○ Two to three times per week (3)
- ○ Four to six times a week (4)
- ○ Every day (5)

Display This Question:

If Did you use any of the following in the three months before the COVID-19 pandemic (Nov 2019 to Ja... = Heated tobacco products (e.g. heat-not-burn products, non-combustible cigarettes)

Q65 How often did you use heated tobacco products before the COVID-19 pandemic?

- Less than once a month (6)
- Once a month (1)
- Two to four times a month (2)
- Two to three times per week (3)
- Four to six times a week (4)
- Every day (5)

Display This Question:

If Did you use any of the following in the three months before the COVID-19 pandemic (Nov 2019 to Ja... = Nicotine replacement (e.g. gum, patches)

Q66 How often did you use nicotine replacement therapy before the COVID-19 pandemic?

- Less than once a month (6)
- Once a month (1)
- Two to four times a month (2)
- Two to three times per week (3)
- Four to six times a week (4)
- Every day (5)

End of Block: Smoking and Cessation

Start of Block: Drugs and alcohol

Q67 Before the COVID-19 pandemic, how often on average did you have a drink containing alcohol?

- ○ Never (1)
- ○ Once a month (2)
- ○ Two to four times a month (3)
- ○ Two to three times per week (4)
- ○ Four or more times per week (5)

Skip To: Q70 If Before the COVID-19 pandemic, how often on average did you have a drink containing alcohol? = Never

Q68 Before the COVID-19 pandemic, how many drinks did you have on a typical day when you were drinking?

- ○ 1-2 (1)
- ○ 3-4 (2)
- ○ 5-6 (3)
- ○ 7-9 (4)
- ○ 10+ (5)

Q69 Before the COVID-19 pandemic, how often did you usually have six or more drinks on one occasion?

- ○ Never (1)
- ○ Once a month (2)
- ○ Weekly (3)
- ○ Almost daily (4)
- ○ Daily (5)

Q70 Have you used any recreational drugs (e.g. cannabis, MDMA, opioids, LSD, new psychoactive substances) within the 3 months preceding the COVID -19 pandemic? (Nov 2019 to Jan 2020)
Please note that the study is confidential and your anonymised data will only be used for research.

- ○ Yes (1)
- ○ No (2)
- ○ Prefer not to say (4)

Display This Question:

If Have you used any recreational drugs (e.g. cannabis, MDMA, opioids, LSD, new psychoactive substan... = Yes

Q71 What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic? (Nov 2019 to Jan 2020)
Please note that the study is confidential and your anonymised data will only be used for research.

- ☐ Cannabis (1)
- ☐ Stimulants (e.g. MDMA, speed, cocaine) (2)
- ☐ Depressants (e.g. Valium, Xanax, GHB, opioids, heroin) (3)
- ☐ Hallucinogens (e.g. magic mushrooms, LSD, ketamine, DMT) (4)
- ☐ New Psychoactive Substances (5)
- ☐ Prefer not to say (7)

Display This Question:

If What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic?... = Cannabis

Q72 How often did you use cannabis during the 3 months preceding the COVID-19 pandemic?

- ○ Less than once a month (1)
- ○ Once a month (2)
- ○ Two to four times a month (3)
- ○ Two to three times per week (4)
- ○ Four or more times a week (5)

Display This Question:

If What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic?... = Stimulants (e.g. MDMA, speed, cocaine)

Q73 How often did you use stimulants (e.g. MDMA, speed, cocaine) during the 3 months preceding the COVID-19 pandemic?

- ○ Less than once a month (1)
- ○ Once a month (2)
- ○ Two to four times a month (3)
- ○ Two to three times per week (4)
- ○ Four or more times a week (5)

Display This Question:

If What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic?... = Depressants (e.g. Valium, Xanax, GHB, opioids, heroin)

Q74 How often did you use depressants (e.g. Valium, Xanax, GHB, opioids, heroin) during the 3 months preceding the COVID-19 pandemic?

- Less than once a month (1)
- Once a month (2)
- Two to four times a month (3)
- Two to three times per week (4)
- Four or more times a week (5)

Display This Question:

If What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic?... = Hallucinogens (e.g. magic mushrooms, LSD, ketamine, DMT)

Q75 How often did you use hallucinogens (e.g. magic mushrooms, LSD, ketamine, DMT) during the 3 months preceding the COVID-19 pandemic?

- Less than once a month (1)
- Once a month (2)
- Two to four times a month (3)
- Two to three times per week (4)
- Four or more times a week (5)

Display This Question:

If What type of recreational drugs did you use within the 3 months preceding the COVID -19 pandemic?... = New Psychoactive Substances

Q76 How often did you use new psychoactive substances during the 3 months preceding the COVID-19 pandemic?

- Less than once a month (1)
- Once a month (2)
- Two to four times a month (3)
- Two to three times per week (4)
- Four or more times a week (5)

End of Block: Drugs and alcohol

Start of Block: Debrief block

Q77 Thank you for volunteering to take part in the UEA COVID-19 Wellbeing Study. Your input will help researchers, policy makers, and government to understand how best to plan for long-term health and wellbeing support. You will be sent a text message with a daily survey link at your specified time (8pm, 9pm, or 10pm) for the next 12 weeks (84 days) starting tomorrow or as soon as possible after tomorrow if we are experiencing a high volume of responses. For further information see: https://www.uea.ac.uk/medicine/research/addiction You can access support for any of the topics covered by following the links below: NHS COVID-19 advice Government guidance for the public on the mental health aspects and wellbeing aspects of the coronavirus (COVID-19) NHS mental wellbeing while staying at home tips NHS general health behaviours and wellbeing advice: NHS quitting smoking advice NHS alcohol use advice Substance misuse support

End of Block: Debrief block

Appendix 31. C-19 Daily questionnaire

Q1

Welcome back to the COVID-19 Wellbeing Study daily survey!
Everyone taking part in the study is asked the same questions so that we can capture changes in behaviour. This may mean that you are asked questions about behaviour that you have previously told us that you don't do.
We ask you about your health behaviours and wellbeing for 'today' – this includes the time frame from the moment you got up to just before you go to bed.
It would be helpful if you could complete the measures in the evening before bedtime.

Q2 Have you been tested and diagnosed as having a COVID-19 infection today? Please only select yes if you received your diagnosis today.

- ○ Yes (1)
- ○ No (2)

Q3 Have you experienced any possible COVID-19 symptoms today? e.g. a high temperature and/or new and continuous cough?

- ○ Yes (1)
- ○ No (2)

Q4 Did you leave your home today?

- ○ No - I'm self isolating and not leaving the house (1)
- ○ No - but not because I'm self-isolating (2)
- ○ Yes - for exercise, to go shopping, to pick up medication, or to go to work. (3)
- ○ Yes - for another reason. Please state: (5) _____

Page Break

Q5 How would you rate your sleep quality last night?

- ○ Very good (1)
- ○ Fairly good (2)
- ○ Fairly bad (3)
- ○ Very bad (4)

*

Q6 How many portions of fruit did you eat today? (e.g. 5, 0, 1) A portion of fruit is 80g (about a handful). Fresh, frozen, canned, dried and juiced fruit all count. 30g of dried fruit is equivalent to around 80g of fresh fruit. You can include fruit juice or smoothies once. For example, if you have 2 glasses of fruit juice and a smoothie in one day, this still counts as 1 portion.

_____

*

Q7 How many portions of veg did you eat today? (e.g. 5, 0, 1) A portion of vegetables is 80g (about 3 heaped tablespoons or a cup of salad vegetables). Fresh, frozen and canned vegetables all count.

_____

*

Q8 How many times today (e.g. 5, 0, 1) did you eat foods high in sugar such as chocolate (regular bar), cakes, biscuits (3), sweets (1 small packet), sugary drinks and jams (3 teaspoons). Include chocolate spreads (3 teaspoons), honey (2 teaspoons), table sugar (3 teaspoons), squash cordials and fruit juice.

_____

Q9 How would you describe your overall diet today? Would you say:

- ○ Excellent (1)
- ○ Very good (2)
- ○ Good (3)
- ○ Fair (4)
- ○ Poor (5)

*

Q10 How many alcoholic drinks did you have today so far? (e.g. 0, 2, 6)

_____

*

Q11 How many alcoholic drinks do you plan to have later? (e.g. 0, 2, 6)

_____

Q12 Have you done any physical activity today, which was enough to raise your breathing rate? This may include exercise, and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that may be part of your job.

- ○ No (1)
- ○ Yes. Please state the approximate number of minutes in the box: (2)

_____

Q13 Have you done any exercise today to improve your strength and flexibility, such as weights, yoga or a fitness app?

- ○ Yes (1)
- ○ No (2)

Q14 If you track your daily steps (using app/watch/phone), how many steps did you achieve today approximately (so far)?

If you don't track your steps please add in a 0.

_____

Q15 On a scale of 0 - 10, did you feel happy in general today?

- ○ 0 Unhappiest (1)
- ○ 1 (2)
- ○ 2 (3)
- ○ 3 (4)
- ○ 4 (5)
- ○ 5 (6)
- ○ 6 (7)
- ○ 7 (8)
- ○ 8 (9)
- ○ 9 (10)
- ○ 10 Happiest (11)

Q16 How would you rate the amount of stress you have experienced today?

- ○ No stress (1)
- ○ A little (2)
- ○ Moderate (3)
- ○ A lot (4)
- ○ Extreme (5)

Q17 How low do you feel right now?

- ○ Not at all (1)
- ○ Slightly (2)
- ○ Somewhat (3)
- ○ Very (4)
- ○ Extremely (5)

Q18 How anxious do you currently feel about you or one of your family contracting coronavirus?

- ○ Not at all (1)
- ○ Slightly (2)
- ○ Somewhat (3)
- ○ Very (4)
- ○ Extremely (5)

Page Break

Q19 Have you smoked tobacco today? (e.g. cigarettes, rollups)

- ○ Yes (1)
- ○ No (2)

Display This Question:
If Have you smoked tobacco today? (e.g. cigarettes, rollups) = Yes

Q20 How many cigarettes/rollups have you smoked today?

_____

Q21 Have you used any of the following today?

- ☐ None (5)
- ☐ E-cigarettes / vapes (1)
- ☐ Heated tobacco products (2)
- ☐ Nicotine replacement (e.g. gum, patches) (3)
- ☐ Stop smoking medication (e.g. Champix) (4)

Display This Question:
If Have you used any of the following today? = E-cigarettes / vapes

Q22 What strength nicotine eliquid did you mainly use today in mg/ml? (e.g. 18, 3.5)

_____

Display This Question:

If Have you used any of the following today? = E-cigarettes / vapes

*

Q23 Approximately how much e-liquid you have used today (in ml)? (e.g. 0.5, 4, 8)

_____

Q24 Have you taken any recreational drugs today? (e.g. cannabis, MDMA, opioids, LSD, new psychoactive substances) Please note that the study is confidential and your anonymised data will only be used for research.

- Yes (1)
- No (2)

Display This Question:

If Have you taken any recreational drugs today? (e.g. cannabis, MDMA, opioids, LSD, new psychoactive... = Yes

Q25 What type of recreational drugs did you take today? Please note that the study is confidential and your anonymised data will only be used for research.

- [ ] Cannabis (2)
- [ ] Stimulants (e.g. MDMA, speed, cocaine) (3)
- [ ] Depressants (e.g. Valium, Xanax, GHB, opioids, heroin) (4)
- [ ] Hallucinogens (e.g. magic mushrooms, LSD, ketamine, DMT) (5)
- [ ] New Psychoactive Substances (6)
- [ ] Prefer not to say (7)

Q26 How motivated have you felt to engage in healthy behaviours today? (e.g. eat well, avoid alcohol, be physically active, avoid tobacco if a smoker, etc.)

- ○ Not at all (1)
- ○ Slightly (2)
- ○ Somewhat (3)
- ○ Very much (4)
- ○ Extremely (5)

Q27 Do you feel you have had the opportunity to engage in healthy behaviours today? (e.g. having the right facilities, equipment, food and support from others)

- ○ Not at all (1)
- ○ Slightly (2)
- ○ Somewhat (3)
- ○ Very much (4)
- ○ Extremely (5)

Q28 Do you feel you have had the ability to engage in healthy behaviours today? (e.g. knowing what to do or having the right mindset)

- ○ Not at all (1)
- ○ Slightly (2)
- ○ Somewhat (3)
- ○ Very much (4)
- ○ Extremely (5)

Q29 Please use this space if you have any further comments you would like to add relating to your wellbeing or health behaviour today.

_____

_____

_____

_____

_____

Q30 Please click next to submit your daily UEA COVID-19 Wellbeing Study response - thank you! We look forward to your responses tomorrow.

We really appreciate your involvement in this important study which will help researchers, policy makers, and government understand how best to plan for health and wellbeing support.

Please contact c.notley@uea.ac.uk if you have any questions or you would like to withdraw from the study.

Skip To: End of Survey If Please click next to submit your daily UEA COVID-19 Wellbeing Study response - thank you! We look... Is Displayed

End of Block: Daily measures block

Appendix 32. C-19 Nutritional analysis Statistical Analysis Plan (Uploaded onto OSF)

Version control

Version and date	Change from previous version
V1.0 10/10/2022	NA
V1.1 21/11/2022	The plans to conduct an exploratory data analysis (EDA) has been removed.

Overview of the project

In rapid response to the COVID-19 pandemic and the sweeping changes to healthcare and restrictions on daily living, we set up a UK intensive longitudinal study to understand the impact on health behaviours and mental health/wellbeing.

This study has four components:
1) A baseline cohort of 1,044 people with assessments of participants' circumstances and health behaviours before the COVID-19 pandemic
2) Daily surveys for 12 weeks among the cohort tracking health behaviours and wellbeing, including COVID-19 symptoms, smoking and alternative nicotine device use, alcohol and substance use, physical activity, diet, sleep and theory-informed psychosocial determinants of health behaviours.
3) A 3, 6, 12, and 24 month follow up questionnaire to establish longer term changes in behavioural, health and mental health patterns and outcomes
4) Detailed qualitative feedback via interviews to provide contextualised explanations for self-recorded behavioural and mental health changes.

Objectives

The primary aim of the current analysis, which will form a part of a PhD, is to:

- test the association between short term fruit and vegetable intake (FVI) and happiness using daily survey data.

The secondary aims are to

- test the association between short term dietary intake dietary intake (FVI, high sugar foods and overall diet quality score) and low mood and stress using daily survey data.

- test the association between short term dietary intake (FVI, high sugar foods and overall diet quality score) and sleep quality using daily survey data.

Statistical methods

To achieve the objectives:

- A lagged analysis will be investigated in relation to the primary objective (470).
    - Multilevel modelling will be used to predict ecological momentary assessment (EMA) end-of-day happiness from the FVI, with a lag duration of 24 hours (lag 1) as the colonic transit appears to mainly occur around 24 hours (385, 471, 472). The same approach will also be taken for the secondary outcomes (low mood, stress and sleep rating).
    - Fruit and vegetable intakes will be added together for each day for each person as well as to be analysed separately.

- Secondary analyses;
    - 4 additional lags (days 2, 3, 4 and 5) will be investigated as the whole gut transit may occur up to 5 days for those with slower colonic movements (385, 471, 472).
    - A cross-sectional (same-day) analysis will also be conducted in order to assess the associations between the independent and dependent variables, with an attempt to examine individual confounding factors such as age, sex, mental health status, baseline BMI status and baseline diet quality, which will be applied to the secondary analyses.

The analysis will be adjusted for the below covariates.

Covariates:

From the baseline survey which will be used to inform descriptive of the sample: Sex, age, deprivation status, work and income status, ethnicity, marital status, weight, BMI status, diagnosed mental health reporting, baseline FVI.

From the daily survey: Sleep, exercise, smoking, alcohol, Covid-19 diagnosis

Variables:

Primary independent variable:

- FVI

Secondary independent variables:

- High sugar food intake
- Overall diet quality score

According to our systematic review findings, contentment can be improved over a short period of time (473). Therefore;

Primary dependent variable:

- Happiness (Did you feel happy in general today? (0-10))

Secondary dependent variable:

- Low mood (How low do you feel right now? (1-5))
- Stress (How would you rate the amount of stress you have experienced today? (1-5)),
- Sleep quality

Questions of interest

Baseline variables will be used to produce descriptives, and to explore random effects in the model i.e. time-invariant individual characteristics which may predict the strength of the associations.

Baseline questionnaire		
Nutritional behaviour	Prior to the pandemic 1) How many portions of fruit … ? 2) How many portions of vegetable … ? 3) How many times per day foods high in sugar … ? 4) How health was your overall diet?	
Mental health	"Please state any health condition(s) in the box below"	
Potential covariates	Sex (male, female, non-binary) Age (date of birth) Postcode – deprivation status Work and income status Ethnicity Marital status Weight BMI status Diagnosed mental health issue reporting	

Daily surveys		
Nutritional behaviour	Today 1. How many portions of fruit …? (474) 2. How many portions of vegetable …? (474) 3. How many times per day foods high in sugar …? 4. How healthy was your overall diet? (407, 475)	Independent variables
Mental wellbeing	1. Did you feel happy in general today? (0-10) (476) 2. How would you rate the amount of stress you have experienced today? (1-5) (477) 3. How low do you feel right now? (1-5) (478)	Dependent variables
Sleep	1. How would you rate your sleep quality last night? (1 to 4 points) (291)	Covariate
Exercise	1. Have you done any physical activity today, which was enough to raise your breathing rate? This may include exercise, and brisk walking or cycling for recreation or to get to and from places. But should not include housework or physical activity that may be part of your job. (No; Yes, please state the approximate number of minutes in the box))	Covariate

	2. Have you done any exercise today to improve your strength and flexibility, such as weights, yoga or a fitness app? (Yes, No) 3. If you track your daily steps (using app/watch/phone), how many steps did you achieve today approximately (so far)? If you don't track your steps please add in a 0. (479)	
Smoking	1. Have you smoked tobacco today? 2. How many cigarettes/rollups have you smoked today? (480)	Covariate
Alcohol	1. How many alcoholic drinks did you have so far? 2. How many alcoholic drinks do you plan to have later? (481)	Covariate

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