THE ROLE OF DIET-DERIVED INFLAMMATION IN THE RELATIONSHIP BETWEEN DIETARY PATTERNS, MOOD AND SLEEP QUALITY

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ABSTRACT

Close relations exist between diet, mood and sleep. Healthy dietary behaviours are associated with good mental health, and interventions to improve diet quality are effective adjuvant treatments for major depressive disorder. Diet is also related to sleep: short sleep duration is associated with unhealthy diets, weight gain and obesity, and emerging evidence suggests that this relationship is reciprocal, with diet quality affecting sleep, in terms of both duration and quality. However, these relationships may not be simple and binary – they are likely to be multi-dimensional, but studies investigating these potentially more complex interactions are scarce, so mechanisms driving them are poorly understood.

Substantial research evidence links chronic inflammation to the pathophysiology of numerous serious diseases, including cardiovascular disease, and in the last decade, diet has been recognised as a major modulator of the chronic inflammatory process. In the current thesis I present evidence from three diverse samples, that diet-derived inflammation is a key mechanism driving the connection between habitual diet quality, mood and sleep quality.

The first study involved a group of employees working standard daytime hours, the second was a sample of shift workers, almost one-third of whom worked regular night shifts, and the third study consisted of a general population sample, including students and retired people, as well as those in a range of employments. High quality dietary patterns, including Mediterranean-style diets, rich in fruit, vegetables, fibre, fish and polyunsaturated fats, were

consistently associated with better mood (fewer anxiety and depressive symptoms) and better sleep quality. Further, the relationships observed were fully mediated by the anti-inflammatory properties of these dietary patterns. Conversely, diets which included a high intake of fast food were associated with higher levels of depression and poorer sleep quality, and these associations were partly mediated by the pro-inflammatory properties of regular fast food intake. Mood disorders and problematic sleep are highly prevalent and comorbid conditions, with significant societal costs, yet diet-derived inflammation is itself asymptomatic. Diet is an unavoidable daily health exposure, but it is also a modifiable behaviour. Thus, dietary interventions to reduce the silent inflammatory burden in individuals who habitually consume a poor quality diet, may help to reduce the risk of mental illness and problematic sleep before clinical disease manifests. There is a long-established direct link between diet quality and cardiovascular disease risk. A further, novel thesis is that healthy dietary patterns may also reduce cardiovascular disease risk indirectly, via improvements in both mood and sleep quality, and these relations may be driven by the inflammatory potential of the diet.

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PREFACE

The aim of this early narrative is to introduce the aims, objectives and central hypothesis of the research, to summarise the structure of the thesis and signpost to where the working hypotheses are tested in subsequent chapters.

Close relations exist between diet, mood and sleep. Healthy dietary behaviours are associated with good mental health (Lassale et al., 2019) and interventions to improve diet quality are effective in improving mood (Kris-Etherton et al., 2021). Diet is also associated with sleep: short sleep duration is associated with unhealthy diets, weight gain and obesity (St-Onge, 2017), and emerging evidence suggests that this relationship is reciprocal, with diet affecting sleep, in terms of both quality and duration (Binks et al., 2020). There is also a reciprocal relationship between mood and sleep: poor quality sleep is associated with subsequent poor mood, and poor mood also affects sleep, again in terms of both quantity and quality (Konjarski et al., 2018).

What are the mechanisms driving these interactions? A large body of research has investigated the bivariate, correlational associations between diet and mood, diet and sleep, and mood and sleep. However, these relationships may not be simple and binary (Du et al., 2021). They are likely to be multi-dimensional, but studies investigating these more complex relationships are scarce, so mechanisms driving them remain poorly understood (Bremner et al., 2020; Campanini et al., 2017; Mamalaki et al., 2018; Molendijk et al., 2018).

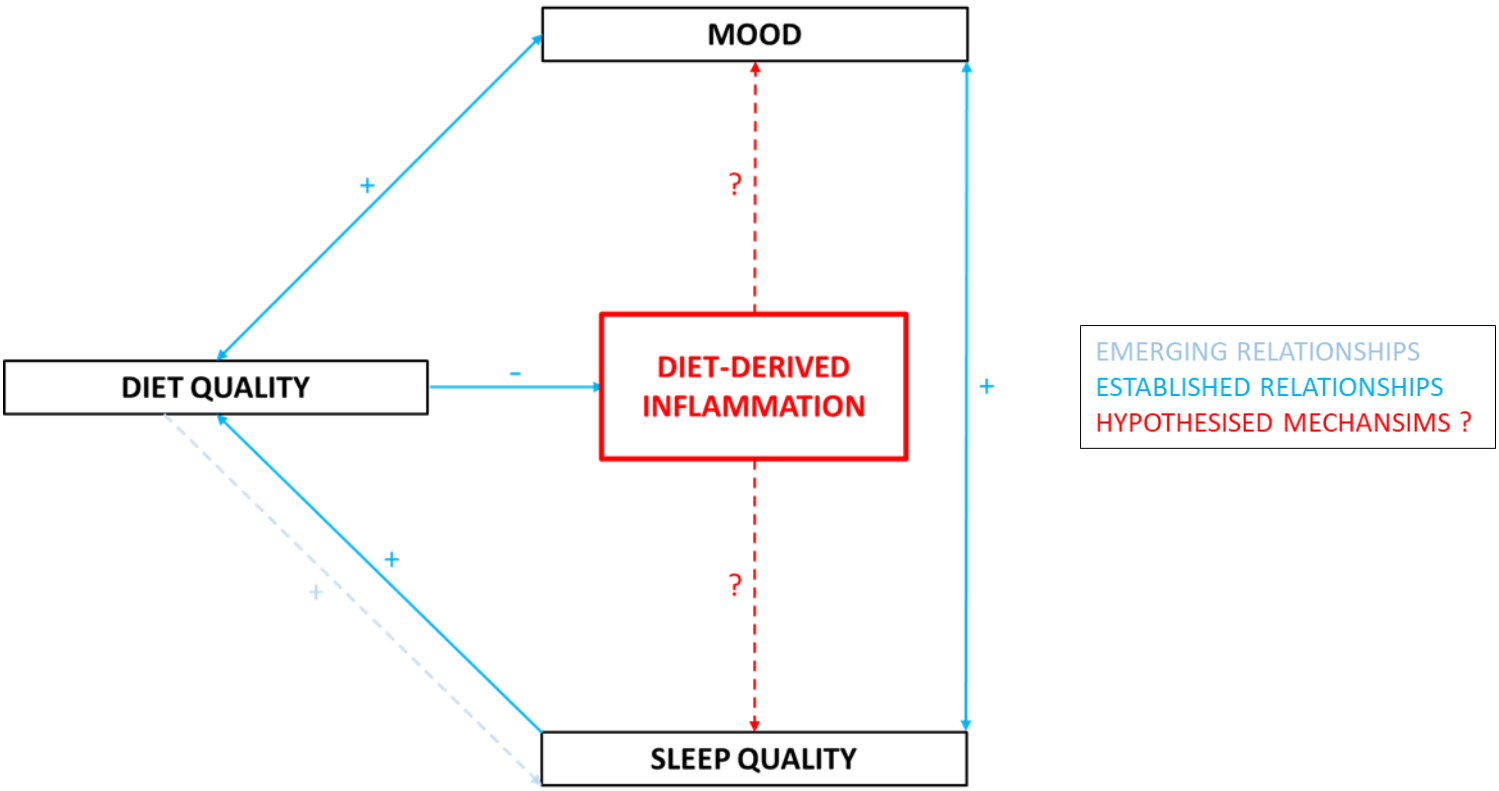
Why is this important? Understanding what drives these interrelations is vital because poor diet, poor mood and poor sleep are all risk factors for a number of serious but common diseases that inflict middle- and high-income nations. These range from cardiovascular disease (Castro-Diehl et al., 2018; Ham et al., 2017) to major depressive disorder (Godos et al., 2020a; Kris-Etherton et al., 2021). Together, cardiovascular disease and depression share the highest burden of non-communicable, chronic disease in developed nations across the world (O'Neil et al., 2013). The World Health Organisation (WHO) also predicts that this pattern will extend to all countries by the year 2030 (WHO, 2011). Thus, there is an urgent need for improved management and effective preventative strategies. Investigating what links this triad of risk factors mechanistically may improve our understanding of their shared contribution to chronic disease. This may lead to improved strategies to mitigate against these increasingly prevalent and disabling conditions.

Given that diet, mood and sleep are common risk factors for a number of chronic diseases, it is plausible that common mechanisms drive the risks they pose. One such pathological mechanism is chronic, systemic inflammation. Chronic inflammation is a major driver of cardiovascular disease (Casas et al., 2018), and is also now recognised as a risk factor for pathological states involving the brain, including depression (Godos et al., 2020a; Maeng & Hong, 2019). It is also associated with poor quality sleep (Godos et al., 2019b; Kanagasabai & Ardern, 2015a, 2015b), including sleep disturbance (Irwin et al., 2016).

Interventions to improve diet quality have long been known to improve cardiovascular disease risk profiles (Casas et al., 2018), and are now also considered effective interventions

for depression and anxiety (Firth et al., 2019; Kris-Etherton et al., 2021). As these conditions have known inflammatory elements, dietary interventions may work by reducing chronic inflammation. Diet is now recognised as a major regulator of systemic inflammation (Baer et al., 2004; Cavicchia et al., 2009; Cui et al., 2012; Giugliano et al., 2006). Evidence has accumulated over the past decade that poor quality diets, high in saturated animal fats, processed foods and snacks, and low in fresh fruit, vegetables and dietary fibre, contribute a low-level, systemic inflammatory burden. This low-grade inflammation is asymptomatic, but chronic exposure to a pro-inflammatory dietary pattern may ultimately culminate in overt inflammatory disease. Fortunately, the inflammatory potential of the diet can now be measured on a numeric scale, using a recently developed population-based index called the Dietary Inflammatory Index® (Shivappa et al., 2014a). Recent meta-analyses have connected higher Dietary Inflammatory Index scores to increased risk of depression (Wang et al., 2019). Emerging data also link them to problematic sleep (Godos et al., 2019b), but evidence is lacking because studies are scarce. The principal hypothesis of the current research is that asymptomatic diet-derived inflammation drives the cycle that connects diet quality to mood and sleep quality. A visual depiction of the emerging and established pathways, and hypothesised mechanisms is presented below.

Figure 1. Schematic showing emerging and established pathways, and hypothesised mechanisms connecting diet quality to mood and sleep quality.



Diet is an unavoidable daily health exposure, so if the hypothesis is supported, habitual poor diet can be considered a chronic inflammatory exposure that increases the risk of mood disorders and problematic sleep. But diet is also a modifiable behaviour, so interventions to reduce diet-derived inflammation could improve symptoms in individuals suffering from poor mood and problematic sleep. Further, population-based preventative strategies to reduce asymptomatic dietary inflammation and improve risk profiles before inflammatory disease manifests, may be valuable on an epidemiological level.

The thesis is structured as follows. **Chapter 1** provides key background information on diet, mood and sleep. Methods used to assess each are described and evaluated. The aim of this background material is to introduce the reader to the three major topics and to set the scene for the whole thesis.

Chapter 2 is a literature review of studies examining the bivariate, correlational relationships between the three subjects. The aim is to provide a context for the empirical research that follows. Thus, it begins by summarising the evidence that diet is associated with mood, and that interventions to improve diet can improve mood; evidence that mood impacts diet is also presented. The chapter goes on to discuss the bidirectional relationship between sleep quality and mood, and finally, the relationship between diet and sleep quality. A large body of research indicates that sleep (quality and quantity) impacts dietary behaviours, and emerging evidence also suggests that diet quality impacts sleep. This literature is reviewed in detail in the final section of the chapter.

Chapter 3 discusses inflammatory mechanisms that may underlie the cycle that links diet, mood and sleep. It therefore begins by defining the immune system and inflammation. Connections are made between diet and the immune system, and the Dietary Inflammatory Index® is introduced. Evidence to support the role of diet-derived inflammation in mood and sleep is reviewed in detail. This contextualises the principal hypothesis of the thesis, and orients the reader towards the empirical research, in which the working hypotheses are tested in three different samples.

Chapter 4 describes the first empirical study, a survey of diet, mood and sleep in *N* = 180 university employees working standard daytime hours. Thus, all participants were of working age. Most worked full time, and although no selection criteria were applied to education and work role, the vast majority of participants were educated to degree level or beyond.

Chapter 5 describes an equivalent study of diet, mood and sleep, in a sample of *N* = 410 police shift workers, 28% of whom worked regular night shifts. So, as before, all participants were of working age. Again, no selection criteria were applied to education and work role, but far fewer participants were educated to degree level than in the university sample.

Chapter 6 describes the final empirical study, a survey of a similar design, but no selection criteria were set regarding employment status. So this was a general population sample, including students ($\geq$ age 18), working adults and retired people (*N* = 466). The age range was therefore wider than the first two samples.

Chapter 7 draws the narrative to a close by bringing the three studies together into a final synthesis. The implications of the work are discussed, followed by its limitations, and finally, future directions for the research.

1 DIET, MOOD AND SLEEP: AN OVERVIEW

1.1 AIMS

The aim of Chapter 1 is to introduce the three major topics of the thesis. Thus, it is divided into three parts. Part one introduces and defines diet, nutrition, balanced diets and dietary patterns. It goes on to describe dietary assessment and its challenges, and to evaluate the dietary tools used in the studies described in the literature review and the empirical research that follows. Part two introduces depressive and anxiety disorders. Risk factors and symptoms are discussed, followed by an evaluation of the assessment methods, with a focus on those used in the current work. Finally, part three introduces and defines sleep, and summarises its structure and functions. It then describes and critically evaluates the sleep assessment methods referred to in the literature review and used in the empirical research. This background material lays the foundations of the thesis and orients the reader towards the relevant terminology and research methods used herein.

1.2 DIET AND NUTRITION

1.2.1 DEFINITIONS

Diet defines what we eat and drink on a day-to-day basis. Nutrients are the individual components of foods, that when consumed in appropriate quantities, confer health benefits and reduce the risk of disease. They are required for normal physiology (i.e., growth, repair and metabolism) and are considered “essential” if the amounts needed to maintain optimum health exceed the body’s capacity to synthesise them endogenously. Seven essential nutrients make up the human diet, as follows: proteins, carbohydrates, fats, fibre, vitamins, minerals and water, and these can be further divided into macronutrients and micronutrients. Micronutrients are primarily vitamins and minerals, and are generally required in very small quantities; macronutrients are required in larger amounts and also provide energy.

1.2.2 BALANCED DIETS AND DIETARY GUIDELINES

A “balanced” diet is one that provides the optimum levels of all the essential nutrients and energy required to support growth and repair, maintain homeostasis and reduce the risk of diet-related disease. No single food item contains all the essential nutrients, so a wide variety (“dietary diversity”) is needed to obtain the required range (Kant et al., 1995).

Dietary guidelines provide information and advice about how to eat a healthy, balanced diet, with the aim of reducing diet-related disease in the population. Recommendations evolve as nutritional understanding advances, and tend to vary slightly from country to country and between cultures, but generally include the following five "food groups" in specific proportions: fruit and vegetables, proteins, grains, dairy products and fats. Examples of dietary guidelines include Public Health England's "Eatwell Guide" (2018) and associated "Eatwell Plate", which provides a visual depiction of the proportions of the five food groups that are recommended in each meal.

At least five fresh fruit or vegetable portions a day are recommended and should make up half the Eatwell Plate. Proteins make up one-quarter of the plate and should consist of lean/low fat sources such as fish, poultry and pulses (legumes). Carbohydrates contribute the remaining quarter, and are found in wholegrains and refined grains. Wholegrains contain all the edible parts of the grain; refined grains (e.g., white rice, white flour) have been processed to remove the germ and bran. Processing also removes fibre and protein, so refined grains should make up less than half the total carbohydrate intake due to their poorer nutritional value.

Foods containing carbohydrate can also be described in terms of their glycaemic index (GI), which is a measure of the increase in plasma glucose levels two hours after consuming a carbohydrate-containing food (Jenkins et al., 1981). Values are compared to pure glucose as the reference carbohydrate, which is assigned the maximum score of 100. The GI of a particular food is related not only to the amount of available carbohydrate it contains, but the type. Carbohydrates that are digested quickly, causing a rapid rise in plasma glucose levels

have a high GI (i.e., > 70), whereas those taking longer to digest, with a correspondingly slower rise in plasma glucose, have a lower GI (i.e., < 55). Glycaemic index is introduced here because some of the studies discussed in Chapter 2 manipulated carbohydrate intake in terms of the GI of the test food.

Dairy products are an important source of calcium, but are also typically high in fat, so the Eatwell Guide recommends consuming them in moderation. Fats and oils are also an essential part of a balanced diet, but have the highest energy density of the macronutrients. Therefore, consuming fats in excess of energy requirements leads to weight gain, so these are recommended in moderation. The basic structural component of all fats is the fatty acid, which is a chain of carbon atoms linked (bonded) together by either single or double carbon-carbon bonds. They are classified according to the degree of "saturation" of the carbon atoms in the chain. Saturated fats contain single carbon-carbon bonds because each carbon is saturated with hydrogen atoms. Monounsaturated fats have one double (i.e., unsaturated) carbon-carbon bond and polyunsaturated fats have two or more unsaturated carbon-carbon double bonds. The degree of saturation determines the physical properties of the fat: highly saturated fats tend to be solid at room temperature while polyunsaturated fats are generally liquids (i.e., oils). Dietary fats usually contain both saturated and unsaturated fats, but in different proportions. Those containing predominantly saturates are typically derived from animal products, such as butter, cream and lard. Monounsaturated fats usually come from plant-based sources, such as sunflower and olive oil. The Eatwell Guide recommends consuming primarily unsaturated, plant-based oils rather than saturated animal fats. There is no dietary requirement for saturated fats because the body can synthesise all that is required (European Food Safety Authority, 2017). However, two long-chain polyunsaturated

fats are essential dietary nutrients because they cannot be synthesised endogenously: linoleic acid (LA), an omega-6 polyunsaturated fatty acid, and alpha-linolenic acid (ALA), an omega-3 polyunsaturated fat (Dhull & Punia, 2020); the omega prefix refers to the position of the first carbon-carbon double bond in the chain. Foods rich in LA include soy, safflower, sunflower and corn oils; those with a high ALA content include walnut, linseed (flaxseed), sesame and rapeseed (James et al., 2000). ALA is the metabolic precursor of two more long-chain polyunsaturated fats that are required for human health: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which are omega-3 fatty acids. ALA is metabolised to EPA and DHA endogenously in small amounts, by elongation and desaturation enzymes, but both are also readily absorbed from the gut. Foods rich in pre-formed EPA and DHA include fatty fish, such as trout, salmon, mackerel, herring and sardine (Patterson et al., 2012). Marine animals concentrate the fatty acids in their tissues by feeding on micro-organisms that readily manufacture them, such as phytoplankton, thereby introducing them into the food chain (Jacob et al., 2013).

The four long-chain fatty acids described above are highly metabolically active molecules and integral components of almost all cell membranes throughout the body. Some specialised tissues/cells such as myocardium, retina and neurones have particularly high concentrations of omega-3 fatty acids (Bazan et al., 1990; Knochel et al., 2015). Lipids make up 50 to 60% of the dry weight of the adult brain. DHA is the most prevalent fatty acid in brain cell membrane phospholipids (Robinson et al., 2010) and is particularly abundant at neuronal synapses (Bourre & Dumont, 2002). It is essential for normal human development and organogenesis (Calder & Yaqoob, 2009).

1.2.3 DIETARY PATTERNS

A large volume of nutritional research has investigated the health effects of individual foods and nutrients. However, foods are generally not consumed in isolation, and when consumed together, nutrients can interact to have synergistic or antagonistic effects. Thus, dietary patterns are also studied in nutritional epidemiology. These reflect combinations of foods that are typically consumed together on a regular basis, to form overall, or habitual diet (Biró et al., 2002). Studying dietary patterns is therefore more informative of diet-related disease risk (Hu et al., 2001; Jacka et al., 2010), and for this reason, many systematic reviews exclude studies that focus solely on individual foods or nutrients (Rahe et al., 2014). Examples of dietary patterns commonly studied in nutritional epidemiology include traditional diets, such as the Nordic, Oriental, Mediterranean and Western-style diet (Huang et al., 2019). Mediterranean and Western-style diets are discussed further in the next section, as they are particularly relevant to the thesis.

1.2.3.1 MEDITERRANEAN-STYLE DIET

The Mediterranean-style diet is based on traditional dietary practices of the people of rural Southern Italy (Trichopoulou et al., 2003). It is low in saturated animal fats, refined carbohydrates and highly processed foods, and rich in natural, plant-based nutrients. It is characterised by high intakes of fruit, vegetables, wholegrains, legumes and unsaturated fats (especially olive oil), low or moderate intakes of dairy products, consumption of fish rather

than meat as a protein source, and regular but moderate alcohol intake, mainly wine with meals. Following landmark research by Trichopoulou and colleagues (2003), it is now recognised around the world as one of the healthiest dietary patterns (Martinez-Lacoba et al., 2018). A substantial evidence base links Mediterranean-style diets to a lower risk of numerous chronic diseases, including metabolic (Godos et al., 2017) and cardiovascular disease (Katz & McHorney, 1998; Grosso et al., 2017; Estruch et al., 2018), cognitive decline (Valls-Pedret et al., 2015), dementia (Petersson & Philippou, 2016), depression (Psaltopoulou et al., 2013) and overall mortality (Dinu et al., 2018).

1.2.3.2 WESTERN-STYLE DIET

The Western-style diet, also known as the "standard American" diet, is now the predominant dietary pattern in most high-income countries, including the UK (Odermatt, 2011). In contrast to the Mediterranean diet, it is low in wholegrains, fibre, fruit, vegetables, fish and unsaturated fats, and high in saturated fats from animal sources, refined grains, red and processed meats, salt and sugar; it is therefore also known as the "meat-sweet" diet. Most people in the UK eat too much saturated fat (NHS.UK, 2020) and high intakes are linked to obesity, hypercholesterolaemia and increased cardiometabolic disease risk. High salt intake is linked to hypertension, another risk factor for cardiovascular disease, and refined grains and added sugars are associated with obesity, insulin resistance and metabolic disease. In contrast to the Mediterranean-style diet, the Western diet has become the principal driver of cardiometabolic disease (Odermatt, 2011) and a significant contributor to many other chronic diseases, including certain cancers (e.g., colorectal: Fan et al., 2017; Jakszyn et al., 2020),

depression (Oddy et al., 2018) and all-cause mortality (Heidemann et al., 2008; Odermatt, 2011).

The Western-style diet is partly the product of agricultural advances in the mid-twentieth century, which brought major changes to food production in high-income countries (Simopoulos, 2011). Traditional farming on a local level gave way to mass processing, including a sharp rise in the mass production of seed-based cooking oils such as soybean and corn oil (Blasbalg et al., 2011). These are cheap to produce and relatively resistant to spoilage. They are therefore ideal ingredients for low cost/high revenue, processed products with long shelf lives, such as "ready meals", packaged snacks and baked goods. They are convenient because they require little or no preparation, and are usually designed to be highly palatable (i.e., high in fat and sugar or salt). This tests dietary restraint and encourages over-eating and weight gain. Packaged snacks, in particular, are eaten for pleasure rather than nutrition, and generally contain little or no nutritional value. Also known as "junk food", these products are mass produced, readily available and often marketed aggressively, and consumption has increased substantially in high-income countries over the last century (Blasbalg et al., 2011). "Fast food" has also become an integral part of Western culture. This is a multi-billion pound industry (Lock, 2021) involving the mass production of highly palatable hot food, quickly and cheaply. Again, these products tend to be energy-dense and high in saturated fat and salt or sugar (Min et al., 2018).

As well as the mass production of seed-based cooking oils, the food industry also manufactures *trans* fatty acids for use in processed foods. This involves chemically altering the unsaturated fatty acids using hydrogen gas, heat and pressure, or a metal catalyst, in a

process called “partial hydrogenation”. This alters the physical properties of the fat, changing liquid oils into semi-solids with a smooth, buttery consistency. This improves the texture and taste of the product, and stabilises the fat, thus prolonging its shelf life. When they were first manufactured, partially hydrogenated fats were thought to be a healthier alternative to saturated fats (Iqbal, 2014). However, the process alters the structure of the molecules (changing the position of some of the unsaturated double bonds from the *cis* to *trans* configuration), and it is now known that *trans* fats are significantly more harmful than saturates, and a serious risk factor for cardiovascular disease (Islam et al., 2019). A number of countries have banned them in food manufacturing. In the UK, a ban has not been introduced, but the food industry has been asked to reduce them on a voluntary basis. Most manufacturers have done so, and levels in UK diets are now thought to be well within safe limits (BDA.UK, 2022). However, heating cooking oils to high temperatures, and reheating them, increases *trans* fat levels (Bhardwaj et al., 2016). There is no requirement for ingredients and nutritional information to be listed on restaurant/takeaway menus, and many fast-food outlets preferentially use *trans* fats in their deep fat fryers because they can be reheated and re-used many times, so fast food may be a particular problem (Pipoyan et al., 2021). According to one source, “fast food chains have been notorious for their use of *trans* fats” and although many “have agreed to reduce” them, “few of the leading chains have completely cut out the use of partially hydrogenated oils” (Diabetes.co.uk, 2022).

1.2.4 ASSESSING DIET

Assessing diet is challenging as there is no convenient gold standard method (Burrows et al., 2020). Objective assessment, such as independent observation of an individual's habitual intake, is generally impractical, so it is usually assessed with subjective instruments. These can be retrospective or prospective, and the main methods include diet history, 24-hour dietary recall, food record/diet diaries, food frequency questionnaires and dietary screeners.

All subjective assessments include a degree of measurement error (Kipnis et al., 2003). The major limitation is that most methods rely on participants' memory of what they have consumed, and reports cannot be independently verified, so validity (accuracy) is hard to assess. Furthermore, within-person food/nutrient intake often varies significantly from one day to the next (Tarasuk & Beaton, 1999) due to a number of physiological factors that can also vary considerably, such as activity levels, health status, and climatic factors (e.g., ambient temperature, season etc.). As such, a one-off assessment is subject to random error and may not provide a valid reflection of usual/habitual diet. Rather than assessing *actual* intake over a few days, methods that estimate *average* intake over an extended period (e.g., food frequency questionnaires) may be a better measure of habitual diet, but are more prone to systematic error in the form of recall bias. Assessments may also be prone to social desirability bias, in which subjects respond in ways that conform to societal norms to avoid criticism from others (Hebert et al., 1997). For instance, over-weight/obese individuals may under-report consumption of high calorie foods, leading to energy intakes being underestimated, particularly in interviewer-led assessments.

A vast body of research has compared the validity and reliability (reproducibility) of dietary assessment tools, some of which have been tested against objective recovery biomarkers (e.g., 24-hour urinary nitrogen excretion); others compare estimates between two or more instruments. Many review articles have been published, including a systematic review of systematic reviews (Hooson et al., 2016). A detailed discussion of this literature is beyond the scope of the current thesis, but interested readers are referred to Hooson and colleagues' review and the associated "Nutritools" website (www.nutritools.org), or the recent overview of dietary assessment tools by Dao and co-workers (2019). The following section evaluates instruments used in studies featured in the current literature review and empirical research to follow.

1.2.4.1 24-HOUR DIETARY RECALL

This is a retrospective assessment in which subjects recall everything they ate and drank over a 24-hour period. It can be self-report or administered via structured interview. Every item is recorded, typically from midnight to midnight the previous day. Portion sizes are approximated using visual aids such as images of standard measures, or different quantities of food on a standard size plate. 24-hour recalls yield detailed dietary information and some quantitative data, and if interviewer-led, clarifications and further information can be sought, such as preparation/cooking method; they can also be tailored to ethnic diets. The method relies on specific memory of what and how much has been consumed, so it is vulnerable to reporting bias. Furthermore, it only captures the previous 24 hours, so to provide a valid assessment of habitual intake, it needs to be repeated (Basiotis et al., 1987). Dietary recalls

have a relatively low participant burden, taking around 20 to 40 minutes to complete if self-administered, so completion rates can be relatively high compared to some methods. Response data from all dietary instruments require processing to generate quantitative nutritional data, but computerised, self-report versions with automatic coding of responses into nutrient values are increasingly available. This greatly reduces researcher workload and facilitates the acquisition of multiple records. Examples include "Intake24" (intake24.co.uk) which is an online, 24-hour dietary recall system developed by Cambridge and Newcastle Universities. It is used in the UK National Diet and Nutrition Survey, which is a rolling programme of research into the diet and nutritional status of the UK population (GOV.UK, 2017). It is also now available to researchers as open-source software, and it was used in the final study of the current work. Further details are provided in the Materials and Methods section of Chapter 6.

1.2.4.2 FOOD RECORDS/DIET DIARIES

Food records, also known as diet diaries, are a prospective method in which participants diarise everything they consume, at the time of consumption, over a specified number of days. All food items and details of preparation methods are recorded, and leftovers are also documented. Some require every item to be weighed – known as weighed food records, these are often considered the gold standard (Carlsen et al., 2010; Nightingale et al., 2016), or "imperfect" gold standard dietary assessment (Coulston et al., 2017), because they afford greater quantitative accuracy than estimated portion sizes. An example is the Medical Research Council Epidemiology Unit 7-day Weighed Food Diary (www.mrc-

epid.cam.ac.uk/research/nihr-cbrc-measurement-platform/dietary-assessment). Diaries are usually kept for three, seven, or fourteen days, which may or may not be consecutive, and include weekends as well as weekdays. If diaries are completed on multiple occasions, they may well be representative of habitual intake, and because they are completed prospectively, they are the only instrument that is not dependent on participant memory. They are also more flexible than finite food lists (e.g., food frequency questionnaires), allowing unlimited reporting, so participants have the opportunity to record everything they consume. However, to obtain complete records, participants need to be highly motivated and report all dietary information accurately and consistently; they therefore tend to have lower completion rates than some methods. The predominant measurement error is random, although systematic error due to reporting bias can occur. They are also prone to reactivity bias, where respondents transiently alter their dietary behaviours in response to completing the record, and they may underestimate total energy intake (US Institute of Medicine, 2002).

1.2.4.3 FOOD FREQUENCY QUESTIONNAIRES

Food frequency questionnaires are retrospective instruments consisting of a comprehensive list of individual food items and foods groups, against which the participant selects (via tick box or equivalent) their frequency of consumption over a designated period, typically the previous month or year. Examples include the European Prospective Investigation into Cancer and Nutrition Norfolk Food Frequency Questionnaire (EPIC-Norfolk FFQ, Mulligan et al., 2014). This is a semi-quantitative questionnaire consisting of a tick-box list of 130 foods commonly consumed in the UK, plus a free text section on brands and types/quantities of

milk and fats consumed. Finite food lists may not include items consumed in non-standard or ethnic diets, so FFQs should be validated in the population (or type of population) under study (Sharma, 2011; Aoun et al., 2019). If so, they usually reflect habitual intake and provide a good qualitative estimate of a wide range of foods that are consumed daily, occasionally or not at all. Some, including the EPIC-Norfolk instrument, also provide semi-quantitative information based on estimated portion sizes. FFQs rely on generic memory, so estimating the frequency of intake of numerous items over long periods may be inaccurate, and the principal type of measurement error encountered is random error (D. A. Bennett et al., 2017). Some overestimate energy intake, as much as 50% in some studies (US Institute of Medicine, 2002), and underestimation is also well recognised (Carlsen et al., 2010; Mahabir et al., 2006). However, FFQs are relatively quick and easy to use, taking around 40 to 60 minutes to complete. The EPIC-Norfolk instrument was used in the current research and further details are provided in the Materials and Methods section of Chapter 4.

1.2.4.4 DIETARY SCREENERS

Dietary screeners are generally brief food frequency questionnaires designed to capture intake of specific nutrients, or dietary behaviours. Examples include the Three Factor Eating Questionnaire, which assesses dietary behaviours including “dietary disinhibition” (over-consumption of highly palatable foods likely to test dietary restraint and lead to overeating (Karlsson et al., 2000). Others assess adherence to specific dietary patterns, such as the Mediterranean-style diet, or healthy eating guidelines. They are hypothesis driven, i.e., developed from a priori knowledge of what constitutes the dietary pattern of interest.

Examples include the "Healthy Eating Index, 2015", which is based on the latest dietary guidelines for Americans, and includes a wide range of healthy and unhealthy foods (Krebs-Smith et al., 2018). Several a priori screeners to assess adherence to the Mediterranean-style diet have been developed for use in different populations (Hidalgo-Mora et al., 2020; Zaragoza-Martí et al., 2018), including children and adolescents (e.g., KIDMED, Serra-Majem et al., 2004). Others have been adapted to non-Mediterranean populations, such as the ten-item "Alternative Mediterranean Diet" (aMed) questionnaire (Abiemo et al., 2013; Castro-Diehl et al., 2018) which was adapted from a Greek instrument for use in American samples; both were used in studies discussed in the upcoming literature review. The "Mediterranean Diet Adherence Screener" (MEDAS) is a fourteen-item questionnaire originally developed in Spain (Martínez-González et al., 2012; Monteagudo et al., 2015; Schröder et al., 2011) and later adapted and validated for UK samples. It was used in the current research, and further details are provided in the Materials and Methods section of Chapter 6.

Dietary screeners do not usually assess total diet, or capture portion size, so their quantitative value is limited. However, they are quick and easy to administer, typically taking less than fifteen minutes to complete, so participant burden is low. Like food frequency questionnaires, screeners rely on generic memory of what has been consumed over time, and the type of measurement error most commonly encountered is random error.

1.2.4.5 DIETARY PATTERN ANALYSIS

This is an empirically derived method based on a posteriori/post-hoc statistical modelling of response data obtained from standard questionnaires such as food frequency questionnaires (Hu, 2002). The statistical techniques used include principal components analysis and factor analysis. This method helps to identify specific dietary patterns/behaviours in the sample under study, but these are not necessarily generalisable to the wider population. Principal components analysis was used in the current research, and further details are provided in the Materials and Methods section of Chapter 4.

1.2.4.6 DIETARY INFLAMMATORY INDEX®

A recent addition to nutritional assessment is an a priori, whole-diet analysis called the Dietary Inflammatory Index (DII®) (Shivappa et al., 2014a). A large evidence base confirms that diet is a major modulator of chronic inflammation (Baer et al., 2004; Cavicchia et al., 2009; Cui et al., 2012; Giugliano et al., 2006). Thus, different foods can exert pro- or anti-inflammatory effects on the body on a systemic level. Diets high in processed products, animal-derived saturated fats and refined carbohydrates have pro-inflammatory effects, while unprocessed diets, high in fresh fruit, vegetables, wholegrains and lean protein sources (e.g., fish, pulses) have anti-inflammatory effects. The index provides an individual-level numerical score of the inflammatory potential of the diet, and can be calculated from standard self-report instruments (e.g., FFQs, diet diaries etc.). DII was used the current work and further information can be found in Chapter 3.

In summary, a wide range of assessment tools are available for use in nutritional research, each with its own strengths and weaknesses. Both a posteriori (principal components analysis) and a priori methods (MEDAS, DII, Epic-Norfolk FFQ), including an online, automated 24-hour dietary recall (Intake24) were used in the current research.

1.3 MOOD: DEPRESSION AND ANXIETY

1.3.1 INTRODUCTION

Depression and anxiety are the commonest mental illnesses worldwide (Amirul Islam, 2019; WHO, 2021). Major depressive disorder contributes the largest societal burden of all psychiatric illnesses in high-income nations (Lassale et al., 2019), and undiagnosed, subclinical depression is also highly prevalent (Johnson et al., 1992; Rodríguez et al., 2012). Lower socioeconomic status, chronic physical illness/disability and female sex are well documented risk factors (Lincoln et al., 2011; Mahedy et al., 2013).

In terms of symptomology, depression is a serious and debilitating illness that affects the way the patient feels, thinks and behaves, and significantly impairs daily functioning. In severe cases it can lead to suicide. Symptoms are diverse, ranging from emotional, cognitive, behavioural and physical. Emotional symptoms include feelings of hopelessness, anhedonia (lack of pleasure) and persistent sadness; cognitive problems include difficulty concentrating and making decisions; depressive behaviours manifest in a loss of motivation to carry out activities of daily living, eating more or less than usual, and avoiding social situations; fatigue and sleep disturbance are common physical symptoms.

Individuals suffering from depression often experience comorbid anxiety (Kessler et al., 1996). Anxiety affects mood, but it is not a mood disorder per se: it is a normal emotion if it occurs

in proportion to the stressor that precipitates it and resolves soon after the stressor is removed (American Psychiatric Association, 2022). Conversely, anxiety disorders are characterised by extreme and persistent emotional symptoms, including worry, dread and fear, in the absence of an ongoing stressor. The individual is unable to control the anxiety, which may impair their ability to carry out routine daily activities. Cognitive, behavioural and physical symptoms often accompany the emotional disturbances. Cognitive symptoms include racing thoughts and rumination; changes in behaviour might manifest in drinking excessive amounts of alcohol or smoking more than usual; muscle tension, restlessness, tachycardia and sleeping difficulties are all common physical symptoms. The lifetime incidence of anxiety disorders is 33.7% in epidemiological studies and women are approximately twice as likely to be affected than men (Bandelow & Michaelis, 2015).

1.3.2 ASSESSING DEPRESSION AND ANXIETY

Structured instruments are used to diagnose and assess depression and anxiety disorders in clinical settings. Self-report instruments are often used in research, for example the four-item Brief Case-Finding Instrument for Depression (Clarke et al., 1994), which is a validated screening tool that takes about a minute to complete. Screeners and short scales are convenient, but may be lacking in psychometric performance. For example, they may be reasonably sensitive in detecting psychological distress, but inadequate in terms of specificity, with high rates of false positives (Mitchell, 2007). They may also be unsuitable in some studies because they are generally limited to one psychological domain (e.g., depression). Medium-length instruments have more scope to capture a range of psychological domains. They may

also perform well in terms of validity and reliability, and make up for what short scales lack in specificity. Examples include the fourteen-item Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith 1983) which was used in the current research. HADS is a well validated and reliable self-report measure of psychological distress experienced over the previous week. It consists of seven items relating to anxiety (HADS-A) and seven to depressive symptoms (HADS-D), and further details are provided in the Materials and Methods section of Chapter 4.

1.4 SLEEP

1.4.1 DEFINITIONS

Sleep has been described in numerous ways, including "profound behavioural shutdown" (Aulsebrook et al., 2016), and "a rapidly reversible state of immobility and greatly reduced sensory responsiveness" (Siegel, 2008). It is a recurring and quickly reversible state of altered consciousness, and a universal need in almost all animals (Omond et al., 2017; Trojanowski & Raizen, 2016). It is behaviourally and physiologically distinct from other apparently similar states, such as dormancy, hibernation, coma or other disorders of consciousness. Sleep requirements vary across the lifespan and between individuals, and tend to decrease with age (Li et al., 2018). In adults, the average length of a sleep episode is 7 to 8.5 hours (Carskadon & Dement, 2010), and the recommended duration is 7 to 9 hours for individuals aged 26 to 64 years (Chaput et al., 2018).

1.4.2 FUNCTION

Humans spend approximately one third of their lives sleeping, yet despite well over a century of research, its exact functions remain debated (Scharf et al., 2008). Sleep is a state of physical vulnerability in which the individual remains predominantly immobile, with greatly reduced awareness of changes in their environment (Lima et al., 2005). Yet, evolutionarily it is a highly

conserved behaviour cross-species (Joiner, 2016), one that is considered far more than just a passive, resting state. It is a highly metabolically active state serving a diverse range of functions. These include modulation of synaptic transmission, consolidation of memory for long term storage, removal of toxins and waste products of neuronal metabolism, and anabolic replenishment of endocrine, immunological and musculoskeletal function (Xie et al., 2013).

1.4.3 STRUCTURE

Sleep structure, or architecture, describes the composition, organisation and evolution of a typical sleep episode (Carley & Farabi, 2016). There are two broad types, rapid eye-movement (REM) and non-rapid eye-movement (NREM) sleep (Aserinsky & Kleitman, 1953), each of which is behaviourally and physiologically distinct (Colten & Altevogt, 2006). NREM is further divided into three chronological stages (N1, N2, N3) of increasing "depth". N3 corresponds to deep sleep and is also known as slow wave sleep (SWS) (Schulz, 2008). It is considered "restorative" sleep which enables the individual to wake up feeling refreshed (Reither et al., 2021). A normal sleep episode consists of cycles of alternating NREM and REM sleep that repeat across the night. NREM accounts for approximately 80% of total sleep time in adults (Berry et al., 2018), with REM contributing the remaining 20% (Colten & Altevogt, 2006). The physiological stages can be distinguished by measuring brain electrical activity and its corresponding waveforms using electroencephalography (EEG). An in-depth discussion of sleep structure is beyond the scope of this thesis, but several comprehensive overviews are available (e.g., Carskadon & Dement, 2011; Hirshkowitz, 2004).

1.4.4 SLEEP HEALTH AND SLEEP DISORDERS

Sleep health is defined as the ability to obtain sufficient sleep at an appropriate time, with a high sleep efficiency. The operational definition of sleep efficiency is the ratio of time spent asleep to the total time spent in bed (Reed & Sacco, 2016). Good sleep health ensures a lack of daytime sleepiness and optimal physical and mental wellbeing during waking hours (Buysse, 2014).

Chronic poor sleep health can culminate in a sleep disorder. These are a set of conditions which prevent the patient from sleeping well on a regular basis, with significant physical and psychological consequences (Xie et al., 2017). Insomnia is the commonest sleep disorder (Himelfarb & Shatkin, 2021). It is characterised by chronic poor sleep efficiency, difficulties falling asleep (i.e., prolonged sleep onset latency), difficulties staying asleep (e.g., early morning waking) and non-restorative sleep (i.e., feeling unrefreshed in the morning), despite having the opportunity and conditions conducive to good sleep. Symptoms culminate in distress and/or impairment in daytime functioning (Roth, 2007), and over time the condition can lead to significant morbidity, including increased risk of cardiovascular disease (Ham et al., 2017), diabetes (Vgontzas et al., 2009), cognitive impairment (Fernandez-Mendoza et al., 2010) and all-cause mortality (Vgontzas et al., 2010). Insomnia is included here not only because it is the commonest sleep disorder, but because it is used as a measure of sleep health in many of the studies presented in the literature review. Other sleep disorders include narcolepsy, circadian rhythm sleep-wake disorders, obstructive sleep apnoea and the parasomnias (see Xie et al., 2017 for a comprehensive review of sleep disorders).

1.4.4.1 ASSESSING SLEEP

Sleep can be assessed in terms of its structure, quantity and quality. There are numerous methods, and a diverse range of objective and subjective instruments is available. Objective measures include polysomnography, multiple sleep latency testing and actigraphy; self-report questionnaires and sleep diaries are examples of subjective methods. Selection of the most appropriate instrument(s) depends upon the research question(s) under scrutiny, the study population and environment. The following section describes the measures referred to in the literature review and used in the present research.

1.4.4.1.1 OBJECTIVE MEASURES

1.4.4.1.1.1 POLYSOMNOGRAPHY

The most sophisticated sleep assessment is polysomnography (PSG; Ibáñez et al., 2018). Also used clinically to diagnose sleep disorders, PSG is considered the gold standard method (Blackwell et al., 2008). It is a multiparametric test involving simultaneous electrophysiological recording of brain electrical activity, heart rate, eye movements and skeletal muscle activity to detect sleep and distinguish its stages. PSG studies are typically conducted over night in a sleep laboratory (Lab-PSG), although unattended, fully ambulatory systems (Amb-PSG) are now available (Andrade & Paiva, 2018). Ambulatory systems, although costly, are advantageous, because sleep is known to change when individuals are

exposed to a new sleeping environment, such as a sleep laboratory. Known as “first night effect” (Webb & Campbell, 1979), changes include increased sleep onset latency and arousals, and relatively less slow wave sleep (Tamaki et al., 2016; Tamaki & Sasaki, 2019). Confining participants to the artificial environment of a sleep laboratory also prevents them from following their usual routines, so the ecological validity of laboratory-based studies is somewhat limited.

1.4.4.1.2 ACTIGRAPHY

Actigraphy is an ambulatory method of recording rest/activity cycles (Blackwell et al., 2008). An actigraph is a small electronic device, resembling a wristwatch, that is worn continuously throughout the study period. It records gross motor activity, ambient light exposure and temperature. It can be used to assess circadian rhythms and chronotype, sleep latency, efficiency, duration and disturbance (Martin & Hakim, 2011), but it does not measure the electrophysiological parameters that determine sleep structure and stage (Ancoli-Israel et al., 2015). However, it is cheaper and more versatile than PSG, and several individuals can be monitored simultaneously over prolonged periods, so it is particularly useful in research settings. Further, being ambulatory, participants can remain in their natural environments rather than being confined to the sleep laboratory. Actigraphic studies are therefore often considered to have higher ecological validity than those using laboratory-based PSG (Blackwell et al., 2008; Tang & Harvey, 2004).

As illustrated, there are various objective methods of sleep assessment, each with its own advantages and disadvantages, and whilst objective assessments are considered the most accurate and reliable in terms of sleep physiology and its behavioural correlates, they do not assess how individuals rate their own sleep and whether they are satisfied with it – that can only be ascertained with subjective measures.

1.4.4.2 SUBJECTIVE MEASURES

In some studies participants are simply asked to report how many hours they typically sleep, or the hours slept over a specified number of nights. In others, including the current work, validated self-report instruments are used, of which there are several to choose from.

1.4.4.2.1 SLEEP QUESTIONNAIRES

Self-report questionnaires assess various aspects of sleep, including duration, quality, daytime sleepiness and insomnia symptoms. Some have been validated against other questionnaires, in healthy and clinical populations; others are validated against objective instruments such as PSG or actigraphy. The following sections describe two of the most widely used questionnaires, both of which were used in studies discussed in the literature review and in the current research.

1.4.4.2.1.1 PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) is one of the most well validated instruments, widely regarded as the gold standard self-report measure in both clinical and research settings. Nineteen questions about sleep habits and sleep difficulties experienced over the previous month are summed to yield seven component scores and a global score between 0 and 21. Global scores greater than five differentiate good from poor quality sleep. PSQI was used in the current research, and further details are provided in the Materials and Methods section of Chapter 4.

1.4.4.2.1.2 EPWORTH SLEEPINESS SCALE

The Epworth Sleepiness Scale (ESS; Johns, 1991) is a well validated and widely used self-report measure of daytime sleepiness. Consisting of eight common daytime scenarios (e.g., sitting and reading), participants rate their chances of "dozing off", under normal circumstances. Scores range from 0 to 24, with higher scores indicating more daytime sleepiness. ESS was used in the current research, and as before, further information is available in the Materials and Methods section of Chapter 4.

1.4.4.2.1.3 SLEEP DIARIES

Self-report sleep diaries, or sleep logs, are often used in combination with actigraphy, and there are at least twenty-five to choose from (Ibáñez et al., 2018). The diary is completed daily, just after waking, and includes information such as evening caffeine/alcohol intake, perceived sleep latency, sleep disturbance, how refreshed the participant felt on waking, daytime sleepiness and overall perceived quality of the previous night's sleep. Diaries offer a number of advantages over questionnaires, and are considered the gold standard subjective measure (Buysse et al., 2006). Questionnaires are normally completed once, and therefore only capture a snapshot of overall sleep quality, whereas diaries are kept for several days, over which sleep quality may vary considerably. They are therefore more accurate and detailed, and rely less on memory than questionnaires. Available in both paper and electronic format, they are cheap and easy to implement. However, they require ongoing commitment, so data might be incomplete if participants fail to complete them in full (American Psychiatric Association, 2022).

Subjective sleep measures do not always coincide with objective measures. Studies have shown that healthy sleepers do not diarise sleep latency and arousals accurately when compared to polysomnographic data from the same sleep episode (Baker et al., 1999). Others report only moderate correlations between actigraphic and self-report sleep duration (Lauderdale, 2008). That said, subjective measures still provide important information: they capture individuals' unique sleep experience (Konjarski et al., 2018), sleep satisfaction, and how their perceived sleep quality impacts their daily life.

1.5 SUMMARY

This first chapter introduced the three major topics of the thesis: diet, mood (depression and anxiety) and sleep. Each was described, and assessment methods were discussed and evaluated. The various methods have different strengths and weaknesses, and those best suited to a particular study depend on many factors relating to the research questions under investigation, the study sample and environment. The present research used two, well-validated, self-report instruments, both of which were discussed herein. By introducing the terminology and methodologies early, this background material lays the foundations of the thesis and sets the scene for subsequent chapters.

2 DIET, MOOD AND SLEEP: A REVIEW OF RELATIONSHIPS

2.1 AIMS

Close relations exist between diet, mood and sleep, and the main aim of this research was to investigate biological mechanisms that link them. Substantial published research has examined binary associations between the variables, using correlational designs (Konjarski et al., 2018), and the aim of the current chapter is to review this literature. Thus, it is organised as follows: the first section examines correlational diet/mood relations; part two summarises binary mood/sleep associations, and the final section reviews correlational diet/sleep relations.

2.2 RELATIONSHIPS BETWEEN DIET AND MOOD

The relationship between diet and mood is complex, and has been the subject of intense investigation for many decades (Bremner et al., 2020). It has evolved into a discipline known as “nutritional psychiatry” (Marx et al., 2017) which encompasses not only disorders of mood, but all aspects of psychological health and its interaction with diet. The following section summarises the evidence, starting with reviews of cross-sectional studies.

One of the earlier reviews and meta-analyses found that both high and moderate adherence to a Mediterranean-style diet was associated with reduced risk of depression (Psaltopoulou et al., 2013). A systematic review the following year suggested that the Mediterranean diet might be protective of mood, but that design limitations and heterogeneity between studies made them difficult to compare. The authors therefore stopped short of attempting a meta-analysis, and called for well designed, longitudinal prospective studies with homogeneous methodologies (Rahe et al., 2014).

A subsequent review of longitudinal prospective studies reported that healthier diets, particularly those high in fish and vegetables, were associated with a lower incidence of depressive symptoms, in a linear, dose-response relationship (Molendijk et al., 2018). Poor quality diets, such as the Western-style diet, were not, however, associated with a higher risk of depressive symptoms.

A further meta-analysis (Li et al., 2017) and narrative review (Huang et al., 2019) both reported that diets high in fruit and vegetables, fish, olive oil and wholegrains, and low in animal products, conferred a significantly lower risk of depression. In contrast to Molendijk and colleagues, a Western-style diet, high in saturated fats, red/processed meat, refined carbohydrates and confectionary, was associated with an increased risk (Li et al., 2017).

In a review of both prospective and cross-sectional studies, Lassale and colleagues found a significant negative relationship between healthy diets and risk of depression. The strongest evidence was for a Mediterranean-style diet, in longitudinal data (Lassale et al., 2019).

Methodological considerations included adjustment for confounders, and selection of studies with at least five years follow-up, to reduce the probability of reverse causation.

Most of the studies included in the above reviews adjusted for demographic (e.g., age, sex, socioeconomic status etc.) and non-dietary lifestyle factors (e.g., physical activity, smoking status). Lifestyle behaviours can themselves be correlates of diet quality, so controlling for these can establish whether the observed outcomes are independently related to diet, or whether healthy diets are a proxy for other healthy lifestyle behaviours that also impact mood, such as physical exercise. The accumulated evidence suggests that the relationship between diet and depression is independent of non-diet related health behaviours (Lassale et al., 2019).

Some reviews excluded studies with "patient samples" (Rahe et al., 2014), but many studies that did include subjects with baseline or incident co-morbidities, such as cardiovascular disease, did not adjust for them. Cardiovascular disease and depression are highly correlated/co-morbid (Halaris, 2009, 2017), so residual confounding may be a limitation of these studies. The two conditions share some biological symptoms (e.g., fatigue, sleep disturbance, weight gain), so controlling for cardiovascular disease would help to distinguish whether subjects reporting these biological symptoms in depression questionnaires are in fact suffering from cardiovascular disease rather than depression. Poor habitual diet is a strong predictor of incident cardiovascular disease (Casas et al., 2018), so future longitudinal studies should stratify data for baseline and new onset cardiovascular disease.

Randomised controlled trials are the gold standard test in medical research (Fritsche, 2014), and trials of dietary interventions support the epidemiological diet/mood evidence (Francis et al., 2019; Marx et al., 2017; Parletta et al., 2019). A meta-analysis of randomised controlled trials found that interventions to improve diet quality are effective adjuvant treatments for depressive symptoms (Firth et al., 2019). Kris-Etherton and colleagues went further in their recent review, concluding that healthy dietary behaviours may help to prevent, as well as treat, anxiety and depression, but that further controlled trials are required to explore underlying mechanisms (Kris-Etherton et al., 2021).

The relationship between diet and mood is reciprocal. Mood influences food choices, for example, depression can reduce the motivation to adopt and maintain healthy eating behaviours (Begdache et al., 2019). Anxiety and depression can lead to overeating (Valassi et al., 2008; van Oudenhove et al., 2011), binge eating (Fowler et al., 2019) and increased intake of highly palatable junk food in an attempt to counteract negative emotions and reduce psychological distress (Freeman & Rapaport, 2011). Consuming palatable, high fat and/or high sugar foods increases activation in reward-sensitive brain areas (Stice et al., 2013) and triggers dopamine release in the striatum, with the amount released correlating with energy density (Ferreira et al., 2012) and pleasure ratings (Small et al., 2003).

In summary, the accumulated evidence demonstrates close links between diet and mood. Poor quality diets, such as the Western-style diet, are associated with an increased risk of depression, while healthy dietary patterns, including the Mediterranean-style diet, are inversely associated. Research in nutritional psychiatry has also established that interventions to improve diet quality are successful treatments for anxiety and depression,

and recently, that healthy dietary habits may also have a preventative role. The relationship is also reciprocal, with poor mood leading to unhealthy dietary choices and emotional eating. Mechanisms underlying these associations are likely to be multifactorial rather than binary, but remain poorly understood (Molendijk et al., 2018). Further studies are therefore needed to determine the drivers of these relationships.

2.3 RELATIONSHIPS BETWEEN MOOD AND SLEEP

A strong body of evidence indicates that mood and sleep are closely related (Buysse et al., 1997; Pandina et al., 2010; Totterdell et al., 1994; Triantafillou et al., 2019). The following section summarises the evidence, which comes mainly from studies using subjective measures, such as sleep diaries and self-administered mood scales.

Short sleep duration has been linked to subsequent poor mood in both observational (Bixler, 2009) and interventional studies (Banks & Dinges, 2007). Sleep disturbance has been shown to worsen next-day mood and increase stress levels (Blaxton et al., 2017), and poor quality sleep (difficulty falling asleep, restless sleep and severe tiredness) has been associated with depressive symptoms, regardless of sleep duration (C.J. Bennett et al., 2017). Correspondingly, improved sleep quality can lead to better mood (Asarnow et al., 2014). The associations persist after controlling for confounding factors that might affect both sleep and mood, such as age, sex and physical exercise (Triantafillou et al., 2019).

Sleep disturbance is a characteristic feature of mood disorders (Asarnow et al., 2014). Often described by patients as one of the most distressing symptoms (Pandina et al., 2010), one study found 92% of those with depression also complained of sleeping problems (Goodyer et al., 2017). Previously considered only to be a consequence of mood disorders, sleep disturbance is now implicated in their development and persistence (Harvey, 2008; Konjarski et al., 2018; Watling et al., 2017). In a meta-analysis of twenty-one studies, Baglioni and

colleagues (2011) found that individuals suffering from insomnia were twice as likely to develop depression than those reporting good sleep.

Some studies report a reciprocal relationship between mood and sleep quality. de Wild-Hartmann and co-workers (2013) found that positive mood was associated with subsequent good sleep quality, although this is not a universal finding. Studies are limited in number and heterogeneous methods make them difficult to compare. A systematic review of prospective studies in naturalistic settings found that the relationship is indeed bidirectional (Konjarski et al., 2018). Only studies of healthy subjects or those diagnosed with major depressive disorder or insomnia were included, so other conditions that may impact both sleep and mood, such as cardiovascular disease, could not act as confounders. However, the authors noted that other variables that can independently affect both, including chronotype, having a bed partner or young children, were not adjusted for in many of the studies. Evidence also indicates that sleep may be a stronger predictor of subsequent mood than mood is of sleep (Blaxton et al., 2017; Bower et al., 2010; de Wild-Hartmann et al., 2013; Galambos et al., 2009; Sonnentag et al., 2008; Totterdell et al., 1994; Triantafillou et al., 2019).

Several PSG studies have been conducted in patients with mood disorders, and a meta-analysis concluded that mood and anxiety disorders are associated with altered sleep architecture, inhibition of sleep depth, and sleep continuity problems (Baglioni et al., 2016). The objective evidence therefore supports the subjective, self-reports that poor mood is closely linked to poor sleep quality.

The mood/sleep literature is not without limitations. Triantafillou and colleagues (2019) noted that some studies did not differentiate between anxiety and depressive disorders, and others did not adjust for confounding variables, as discussed (Konjarski et al., 2018). The observational studies typically only assessed sleep and mood at one time point, or over short periods. However, single assessments are susceptible to recall bias (Konjarski et al., 2018) and both sleep and mood can fluctuate on a daily basis, so repeat assessment is preferable. They can also be biased by individuals' implicit feelings about mood and sleep rather than their actual experiences at the time of the assessment (Wilson et al., 1982). As explained in Chapter 1, studies conducted in a sleep laboratory are necessarily short, and may not capture habitual sleep due the "first night effect" (Webb & Campbell, 1979). Confining participants to a sleep laboratory prevents them from pursuing their normal activities, and this may also impact both mood and sleep. Thus, the ecological validity of laboratory-based mood/sleep studies is somewhat limited. Technological advances now allow studies to be conducted in naturalistic settings, and over longer periods of time (e.g., 6 weeks), using daily assessments of mood and sleep delivered via mobile phone apps and/or actigraphy. These may yield more accurate and complete data, and can be easier to administer than traditional paper-based assessments such as sleep diaries (Triantafillou et al., 2019).

In summary, the literature demonstrates a reciprocal relationship between mood and sleep. Poor sleep quality, and short sleep duration, are independently associated with subsequent poor mood, and insomnia is a risk factor for depression. Poor mood can also lead to disturbed and poor quality sleep. The remainder of this chapter explores the final bivariate relationship under investigation, the association between diet and sleep.

2.4 RELATIONSHIPS BETWEEN DIET AND SLEEP

2.4.1 EPIDEMIOLOGICAL STUDIES

Eating and sleeping are two innate and essential human behaviours, and numerous cross-sectional studies have examined the relationship between them. Table 2.1 provides a summary of studies that were selected for their size and for specifically examining the diet/sleep relationship. Some investigated sleep duration only, while others considered sleep quality as well as duration.

Table 2.1. Cross-sectional studies of self-reported* diet and sleep in adults.

STUDY REFERENCE	PARTICIPANTS	DIET MEASURES	SLEEP MEASURES	ADJUSTMENTS	FINDINGS
Shi et al., 2008	*N* = 2828 Chinese adults (sub-sample from Chinese national Nutrition and Health Study); 54.1% female, age 20+	Food weighing & 3-day food records (consecutive)	Self-reported habitual SD	Sex, age, income, education level, residence, occupation, smoking status, alcohol intake, energy intake	Short SD (<7 h) associated with lower carbohydrate & higher fat intakes compared to average SD (7-9 h); sleep quality not assessed
Grandner et al., 2010	*N* = 423 American females, post-menopausal (sub-sample from US Women's Health Initiative), age 50+	Semi-quantitative FFQ over previous 3 months	1 week actigraphy *not self-report, sleep diary; SD, WASO, naps	Age, education level, income, BMI, physical activity, grams food consumed/day	Actigraphic SD negatively correlated with total fat intake & energy-adjusted fat intake; subjective (not actigraphic) napping correlated positively with fat & meat intake
Haghighat-doost et al., 2012	*N* = 410 female Iranian university students, age 18-28	Semi-quantitative FFQ	Self-reported habitual SD	Energy intake	Short SD (<6 h) associated with higher carbohydrate & energy intake, lower fruit, pulses, wholegrain & fibre intake compared to average (6-8 h) or long SD (>8 h); sleep quality not assessed
Grandner et al., 2013	*N* = 4548 American adults (sub-sample from annual US National Health &	Structured interviewer-led 24-h dietary recall	Self-reported habitual SD	Model 1: unadjusted; Model 2: dietary pattern (energy intake, dietary variety,	Short sleep duration (5-6 h) associated with higher energy intake compared to average sleep duration (7-8 h); 7-8 h sleep associated with more varied diet than very short (<5 h),

	Nutrition Examination Survey 2007-2008); 53.1% female, age 20+			diet type; Model 3: sex, age, income, education level, BMI, physical activity	short (5-6 h) or long sleep duration (9+ h); sleep quality not assessed
Katagiri et al., 2014	*N* = 3129 Japanese females (sub-sample from 3-generation Study of Women on Diet & Health), age 34-65	Japanese DHQ	PSQI (Japanese version)	Age, BMI, physical activity, alcohol intake, employment status, smoking status, depression score (CES-D)	Poor sleep quality (PSQI $\geq$5.5) associated with higher refined carbohydrate intake (noodles, sweets, energy drinks) & lower fish & vegetable intake; no significant relationships reported between diet & SD or any other PSQI subcomponents
Yoneyama et al., 2014	*N* = 1848 Japanese adults; 37% female, age 20-60	Japanese DHQ	PSQI (Japanese version)	Sex, age, BMI, smoking status, physical activity, alcohol intake, frequency of breakfast consumption	Poor sleep quality (PSQI >5.5) associated with higher noodle intake; noodle intake correlated positively with PSQI sub-components sleep latency, use of sleeping medications, poorer sleep quality (subcomponent), sleep disturbances & daytime dysfunction; higher rice intake correlated positively with good sleep quality & longer SD
Del Brutto et al., 2016	*N* = 677 Ecuadorian adults; 56% female, age 40+	Frequency of oily fish intake	PSQI (Spanish version)	Sex, age, education level, alcohol intake, smoking status, physical activity, BMI, fasting plasma glucose, cholesterol, blood pressure	Good sleep quality (PSQI $\leq$6) associated with higher oily fish intake; no PSQI sub-components reported
C.J. Bennett et al., 2017	*N* = 6594 Australian females of childbearing age (sub-sample from Australian Longitudinal Study on Women's Health), age 31-36	74-item FFQ (Dietary Questionnaire for Epidemiological Studies)	Self-reported habitual SD, "restless" sleep", DIS, and "severe tiredness"	Model 1: unadjusted; Model 2: smoking status, residential area, socio-economic status, education level, depression score (CES-D $\geqslant$10); Model 3: as model 2 plus BMI	Short SD (6 h), DIS & severe tiredness associated with higher energy intake, higher saturated, monounsaturated & total fat intake compared to 8 h sleep
Komada et al., 2017	*N* = 1902 Japanese adults; 45.9% female; age 30–69	Japanese brief DHQ	PSQI (Japanese version)	Variations in sleep timing (midpoint of sleep); energy-adjusted nutrients	SD positively associated with bread, pulses & fish intake in men only; no associations with other PSQI subcomponents or global scores reported
Noorwali et al., 2018	*N* = 1612 UK adults (sub-sample from UK National Diet and Nutritional Survey); 57% female, age 19-65	4-day estimated diet diary	Self-reported SD over the previous 7 days	Model 1: sex and age; model 2: sex, age, socio-economic status, smoking status, ethnicity, energy intake	Short (<7 h) & long (>8 h) SD associated with lower fruit & vegetable intake compared to average sleep duration (7–8 h); sleep quality not assessed

SD = sleep duration; BMI = body mass index; DHQ = diet history questionnaire; h = hours; DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakening; FFQ = food frequency questionnaire; NS = non-significant; PSQI = Pittsburgh Sleep Quality Index; WASO = wake after sleep onset; CES-D = Center for Epidemiologic Studies Depression Scale.

Shi and colleagues were the first to produce large cross-sectional data linking sleep duration with dietary fat intake (Shi et al., 2008). In a study of almost 3000 Chinese adults, self-reported short sleep (< 7 hours) was associated with lower carbohydrate and higher fat intake compared to sleeping seven to nine hours, after adjusting for demographic factors, alcohol intake and smoking status. These findings conflict with other studies (to follow), in which short sleep was associated with higher carbohydrate intake (e.g., Haghighatdoost et al., 2012). The authors posited that these inconsistencies may reflect differences in ethnicity and dietary patterns of their Asian cohort compared to samples with different dietary patterns, such as Western-style diets.

Grandner and colleagues (2010) studied diet and sleep using objective (actigraphy) as well as subjective methods (sleep diaries). Actigraphic, but not subjective total sleep time was inversely associated with total calorie and fat intake in a cohort of *N* = 423 American women. Subjective napping was also positively correlated with fat and meat intake, but objective napping was not. The authors suggested that subjective napping may be indicative of daytime sleepiness, and that future studies should include direct assessments of daytime sleepiness. Further, because the relationship between fat intake and sleep was only observed in the objective data, they also argued that future studies should include objective measures of sleep. This study is noteworthy for using objective as well as subjective sleep measures, although it was limited to post-menopausal women, so the findings may not translate to the wider population.

In a subsequent study by the same group (Grandner et al., 2013), adults who habitually slept seven or eight hours per night consumed a wider variety of foods than those who reported

habitual short (5 - 6 hours) or long (≥ 9 hours) sleep duration. As discussed in Chapter 1, consuming a wide variety of foods (dietary diversity) ensures that adequate quantities of all essential nutrients are obtained (Kant et al., 1995). The authors also reported that short sleep duration was associated with higher energy intakes compared to seven or eight hours.

In a study of circa 400 female university students, those reporting habitual short sleep duration (< 6 hours) consumed more carbohydrates and total calories than those who slept for more than six hours. They also consumed less fruit, fibre, wholegrains and pulses, and were more likely to be overweight or obese (Haghighatdoost et al., 2012). However, as the study was limited to female university students, the findings may not be representative of the wider population.

In a sample of *N* = 3129 Japanese females, Katagiri and colleagues reported that poor sleep quality (global PSQI scores ≥ 5.5) was associated with higher consumption of processed carbohydrates (noodles, sweets, sugary drinks) and lower intakes of fish and vegetables (Katagiri et al., 2014). The authors hypothesised that the high glycaemic index of refined carbohydrates might account for their detrimental effect on sleep quality. The study was limited to Japanese females, so again, the findings may not translate to the wider population, or other groups with different dietary patterns.

Yoneyama and colleagues (2014) conducted a similar study of just under 2000 Japanese workers, in males as well as females. Higher intake of noodles was associated with poorer sleep quality (global PSQI scores > 5.5), which mirrors Katagiri's findings in Japanese females (Katagiri et al., 2014). Higher noodle intake also correlated positively with the PSQI

subcomponents sleep latency, use of sleeping medication, sleep quality, sleep disturbance and daytime dysfunction. Conversely, higher rice consumption was associated with good sleep quality and longer sleep duration. Higher GI diets were associated with good sleep quality, which is at odds with Katagiri's hypothesis that high GI diets are associated with poorer sleep quality. However, some types of rice contain high levels of melatonin, so the authors posited that consuming rice rather than noodles as a source of carbohydrate may increase melatonin levels, therefore increasing sleep propensity.

Del Brutto and co-workers investigated oily fish consumption and sleep quality in a sample of *N* = 677 Ecuadorians (del Brutto et al., 2016). Higher intakes were associated with significantly lower global PSQI scores, indicating that oily fish was associated with better sleep quality. The authors conceded that the cross-sectional design of the study meant that causality could not be established, but that it is unlikely that better quality sleep would cause individuals to consume more oily fish.

In a cross-sectional analysis of circa 6500 Australian females of childbearing age, those reporting short sleep duration (6 hours), difficulties falling asleep and severe daytime sleepiness, consumed significantly more energy and fat (saturated, monounsaturated and total fat) than those sleeping an average of 8 hours (C.J. Bennett et al., 2017). As before, the ecological validity of this study may be limited by the fact that it was confined to women of a relatively narrow age range.

In a cohort of almost 2000 Japanese adults, Komada and colleagues (2017) reported significant positive correlations between sleep duration and consumption of fish, shellfish,

bread and pulses, but only in males. The authors were unable to account for the sex-specific effects, but reasoned that food choices might be related to sex, and concluded that further studies were needed to explore underlying mechanisms.

Noorwali and colleagues used data from the UK National Diet and Nutrition Survey to examine the relationship between sleep duration and fruit and vegetable intake (Noorwali et al., 2018). Both short (< 7 hours) and long (> 8 hours) sleepers consumed significantly less fruit and vegetables than those sleeping seven to eight hours. This study is noteworthy for being the first to examine the relationship between sleep duration and disaggregated, rather than composite dietary data for fruit and vegetable intake in a UK population. Composite foods are ones that contain multiple ingredients, for example, chicken and mushroom pie and fruit cake. Dietary analysis of composite foods may overestimate meat intake (Prynne et al., 2009) and underestimate fruit and vegetable intake (Fitt et al., 2010) because the fruit and vegetable content of composite foods can remain hidden (Whybrow et al., 2015). Thus, disaggregating composite foods into their individual ingredients provides a more complete and accurate reflection of total diet.

Dashti and co-workers (2015) reviewed 16 cross-sectional studies of the relationship between diet and sleep duration. Short sleep (< 7 hours) was consistently associated with higher intakes of calories, energy-dense snacks and total fat; it was also associated with lower fruit consumption and irregular eating patterns.

Children are not the focus of this research, however, findings in children support those in adults. Córdova and co-workers conducted a systematic review of thirty cross-sectional

studies in children (2 - 18 years), and a metanalysis of ten. Short sleep duration was consistently associated with unhealthy eating patterns, including snacking and lower intakes of fruit and vegetables (Córdova et al., 2018).

Cross-sectional studies generally only assess diet at one time point and are therefore particularly vulnerable to recall bias (Li et al., 2017). Furthermore, they cannot assess the temporality of the relationships under scrutiny. Longitudinal prospective studies, with repeat observation, are less prone to recall bias and allow relationships to be explored over time, such as the development of a disease when individuals are exposed to risk factors over months or years (Caruana et al., 2015). To this end, Gangwisch and colleagues followed a large cohort of circa 78,000 postmenopausal women prospectively for three years, to investigate high GI diets as potential risk factors for the development of insomnia (Gangwisch et al., 2020). Higher intakes of added sugar and refined carbohydrates, and higher GI diets correlated positively with prevalent and incident insomnia in both cross-sectional and longitudinal analyses. In contrast, higher consumption of fruit, vegetables, wholegrains and fibre correlated negatively with prevalent insomnia, and fruit and vegetable intake was inversely associated with incident insomnia over the three-year follow-up period.

Finally, for this section, numerous longitudinal prospective studies, with follow-ups ranging from 2 to 16 years, confirm that habitual short sleep independently and consistently predicts weight gain and the development of obesity over time (C. J. Bennett et al., 2017; Blumfield et al., 2018; Chaput et al., 2008; Gangwisch et al., 2005; Hasler et al., 2004; Markwald et al., 2013; Patel et al., 2006). The sleep/obesity literature has been reviewed extensively, and interested readers are directed towards a comprehensive review by St-Onge (2017).

In summary, a large body of evidence from observational studies indicates that short and/or poor quality sleep is associated with poor quality diets, high in saturated fats, added sugars and other processed carbohydrates, and low in fresh fruit and vegetables, wholegrains and fish. Short sleep duration in the longer term is also consistently associated with weight gain and obesity. Conversely, longer sleep duration, better quality sleep and lower rates of insomnia are associated with diets low in saturated fats and processed carbohydrates, and high in fruit, vegetables, wholegrains and fish.

Epidemiological studies provide valuable insights into diet-sleep relations in naturalistic settings. Inclusion of large numbers of participants allows adjustment for a wide range of potential covariates and confounding factors, and longitudinal studies allow relationships to be observed over time. Although most of the studies presented above controlled for demographic factors and total energy intake, the vast majority did not adjust for mood. One study found no significant differences in sleep between individuals with and without a "probable current mood disorder" and therefore did not adjust for mood (Grandner et al., 2010). However, most did not assess mood, despite the fact that subclinical/undiagnosed depression is common (Rodríguez et al., 2012). As discussed in detail earlier in this chapter, mood is associated with both diet and sleep, so it may be a major confounder in studies investigating the relationship between diet and sleep. Further, although approximately half the studies adjusted for energy intake and BMI, only one (del Brutto et al., 2016) adjusted for other cardiovascular risk factors (e.g., cholesterol, fasting glucose, blood pressure) and none controlled for diagnosed cardiovascular disease or other common physical illnesses that may affect sleep and diet. Yet, with the majority of studies focussing on middle aged and older age groups, some participants may have been suffering from cardiovascular disease. As

discussed, cardiovascular disease is associated with both poor diet and poor sleep, so it may be a confounder in studies investigating the relationship between diet and sleep. Another limitation is that many studies did not use validated instruments to assess diet and sleep, and very few used objective sleep measures, such as actigraphy. Grandner and colleagues used actigraphic as well as subjective sleep assessments, and found significant diet/sleep relations only in actigraphic data (Grandner et al., 2010).

Directionality cannot be established from observational studies, but interventional trials, in which independent variables are manipulated under controlled conditions, can corroborate the observational studies and address some of their limitations. They facilitate objective assessment of the dependent/outcome variable(s) and can help distinguish cause from effect. The following section reviews laboratory-based studies of the effects of sleep manipulation on feeding behaviours.

2.4.2 STUDIES OF THE EFFECTS OF SLEEP MANIPULATION ON DIET

Table 2.2 summarises laboratory-based controlled trials of the effects of experimental sleep restriction on dietary intake in healthy adults.

Table 2.2. Laboratory-based controlled trials of the effects of sleep restriction on dietary intake in healthy adults.

STUDY REFERENCE	DESIGN	SUBJECTS	INTERVENTION	FINDINGS
Bosy-Westphal et al., 2008	Controlled 3-condition intervention over 8 nights	*N* = 14 females, age 23-38	2 nights CC (>8 h TIB) followed by 4 nights increasing SR (7 h, 6 h, 5 h, 4 h TIB) followed by 2 recovery nights (>8 h TIB); ad libitum access to food	Increased calorie intake (+20%) & body weight (+0.4 kg) after SR compared to CC
Nedeltcheva et al., 2009	Randomised controlled 2-condition crossover of 14 nights each	*N* = 11 adults (6 males), mean ± *SD* age 39 ± 5	14 nights SR (5.5 h TIB) vs. 14 nights CC (8.5 h TIB); ad libitum access to palatable food and snacks	Increased consumption of snacks and total calorie intake after SR compared to CC
Brondel et al., 2010	Randomised controlled 2-condition crossover of 1 night each	*N* = 12 males, mean ± *SD* age 22 ± 3	1 SR night (4 h TIB) vs. 1 control night (8 h TIB); ad libitum breakfast, lunch & dinner	Higher pre-prandial hunger & increased calorie intake (+22%) after SR compared to CC
St-Onge et al., 2011	Randomised controlled 2-condition crossover of 5 nights each	*N* = 30 adults (15 males), age 30-49	5 SR nights (4 h TIB) vs. 5 control nights (9 h TIB); controlled diet for 4 days (31% of energy from fat, 53% from CHO, 17% from protein); ad libitum access to self-selected food on day 5	Increased fat (especially saturated) & total calorie intake after SR compared to CC; higher total energy intake on day 5 (self-selected diet) after SR compared to CC, mainly from fat (especially saturated)
Markwald et al., 2013	Randomised controlled 2-condition crossover of 5 nights each	*N* = 16 adults (8 males), mean ± *SD* age 22.4 ± 4.8	5 nights SR (5 h TIB) vs. 5 nights CC (9 h TIB); ad libitum break-fast, lunch, dinner and snacks	Increased calorie intake (+6%) & 0.82 ± 0.47 kg weight gain after SR compared to CC
Spaeth et al., 2013	Randomised controlled 3-condition intervention over 9 nights	*N* = 225 adults (109 males), age 22–50	2 baseline nights followed by 5 nights SR (4 h TIB) followed by 2 recovery nights (*n* = 198) vs. CC (10 h TIB, *n* = 27); ad libitum access to food	Increased calorie intake & 0.97 ± 1.4 kg weight gain after SR compared to CC (0.11 ± 1.9 kg weight gain after CC)
Spaeth et al., 2014	2-condition intervention over 7 nights	*N* = 44 adults (23 male), mean ± *SD* age 32.7 ± 8.7	2 baseline nights (10 or 12 h TIB) followed by 5 nights SR (4 h TIB); ad libitum access to food	Increased intake of desserts, salty snacks, fat & total calories after SR compared to baseline

TIB= time in bed; SR= sleep restriction; CC= control condition

Table 2.2 indicates that experimental sleep restriction alters dietary behaviours. These studies all screened participants for physical and mental illnesses, and most also excluded irregular sleepers, extreme chronotypes, shift workers and recent travel across multiple time zones. Increased intakes of fat (Spaeth et al., 2014; St-Onge et al., 2011), energy-dense snacks (Nedeltcheva et al., 2009; Spaeth et al., 2014) and total calories (Bosy-Westphal et al., 2008;

Brondel et al., 2010; Markwald et al., 2013; Nedeltcheva et al., 2009; Spaeth et al., 2013, 2014; St-Onge et al., 2011) were observed after experimental sleep restriction under laboratory conditions. These findings corroborate the observational evidence presented earlier in the chapter.

Tajiri and colleagues studied the effects of sleep restriction under free-living conditions, rather than confining participants to a laboratory (Tajiri et al., 2018). In a randomised crossover design, sixteen healthy females restricted their sleep to four hours, or slept as normal, for three consecutive nights. They slept at home and purchased their own food, according to their normal routines, and compliance with the sleep schedule was monitored with actigraphy. In contrast to the majority of laboratory-based sleep studies, energy intake was not significantly different between the sleep restricted and control condition. Laboratory studies usually provide buffet-style meals with ad libitum access to palatable foods that individuals may not normally have access to. This encourages overeating of tasty but unhealthy foods (Allirot et al., 2012), irrespective of any sleep-related changes in dietary behaviour. Purchasing their own food as normal, may explain why participants in this study did not overeat while sleep restricted. That said, in the laboratory-based studies presented in Table 2.2, all of which provided ad libitum access to food, dietary behaviours still differed between the two sleep conditions, with significantly higher intakes of snacks, fat and calories after sleep restriction compared to the non-sleep-restricted condition.

Finally, for this section, Al Khatib et al (2017) conducted a systematic review of seventeen controlled trials of the effects of experimental sleep restriction on diet, and meta-analysis of eleven. Partial sleep restriction predicted higher fat and energy intake (+385 kcal/day), and

net positive energy balance. Positive energy balance is where energy intake exceeds expenditure, resulting in weight gain over time (Hill et al., 2012; Hill & Commerford, 1996).

Although the interventional studies described above were conducted in healthy adults screened for mental illnesses, none assessed participants' mood during the experiment. Confining people to a laboratory and subjecting them to acute sleep restriction may have a detrimental effect on mood. As discussed, mood affects dietary behaviours, so anxiety and/or depressed mood, rather than the sleep restriction, may have driven the observed dietary changes, or contributed to them to some degree. Furthermore, the majority of these studies restricted sleep severely and acutely, to four or five hours over a few nights. However, mild, chronic sleep restriction is more prevalent than severe, acute restriction (Alhola & Polo-Kantola, 2007), and it is unclear whether there is a cumulative, dose-response relationship when mild sleep restriction becomes chronic.

The relationship between sleep and diet is also likely to be reciprocal, with dietary composition affecting sleep (Godos et al., 2020b; St-Onge et al., 2016a; St-Onge & Zuraikat, 2019). So, although experimental sleep restriction has been shown to increase fat and calorie intake, it is also plausible that dietary manipulation impacts sleep, and the next section reviews the evidence.

2.4.3 STUDIES OF THE EFFECTS OF DIETARY MANIPULATION ON SLEEP

In contrast to the robust evidence of the effects of sleep on diet, studies of the reciprocal relationship are relatively limited, so the effects of diet on sleep are less clear (Campanini et al., 2017; Mamalaki et al., 2018). Studies are mainly short randomised controlled trials of dietary interventions in small groups of healthy adults. Examples include trials of dietary supplements (e.g., tryptophan, melatonin, B vitamins, magnesium, zinc) and specific whole foods (e.g., tart cherry juice, milk, kiwi fruit), with some evidence of improved sleep quality (see St-Onge et al., 2016a, for a comprehensive review). However, whole foods may contain several different nutrients, any of which might affect sleep, so other studies have focussed on macronutrients. Table 2.3 summarises laboratory-based trials of the effects of macronutrient interventions on sleep indices in healthy individuals. Studies were selected for assessing sleep objectively, mainly with polysomnography.

Table 2.3. Laboratory-based* controlled trials of the effects of macronutrient interventions on objective sleep measures (polysomnography or actigraphy) in healthy subjects.

STUDY REFERENCE	SUBJECTS	DIETARY INTERVENTION	FINDINGS
Phillips et al., 1975	*N* = 8 "young" adult males (age not stated)	Isocaloric high carbohydrate/low fat, low carbohydrate/high fat or control, balanced diet over 2 days; sleep monitored with PSG for 2 nights in each condition	Less SWS & more REM with high carbohydrate/low fat diet compared to low carbohydrate/high fat or control diet; SL & SD not significantly different between diets
Hartmann et al., 1979	*N* = 12 males, age 18-25	Single isocaloric high protein, high fat or high carbohydrate drink with evening meal; PSG to assess % REM time for 1 night in each condition	No significant differences in % REM between the 3 conditions (only % REM time measured)
Porter & Horne, 1981	*N* = 6 "young" adult males (age not stated)	Single high carbohydrate, low carbohydrate, or carbohydrate free meal (not isocaloric) before bed; PSG for 1 night in each condition	Less SWS, more REM & more arousals with high carbohydrate meal compared to low or carbohydrate free meal; SL not significantly different between conditions
Afaghi et al., 2007	*N* = 12 males, age 18-38	Single isocaloric high GI or low GI meal before bed; PSG for 3 nights in each condition	Shorter SL with the high GI meal compared to the low GI meal

Afaghi et al., 2008	*N* = 14 adult males, age 18-35	Single very low carbohydrate meal or isocaloric control meal before bed; PSG for 2 nights in each condition	Less REM, more NREM (all stages) and trend towards greater SE with very low carbohydrate meal compared to isocaloric control meal; SL not significantly different between conditions
St-Onge et al., 2016b	*N* = 26 adults (13 females), age 30-45;	Balanced (control) diet for 4 days (31% of energy from fat, 53% from carbohydrate, 17% from protein); ad libitum, self-selected diet on day 5 & 6; PSG for 5 nights	Less SWS & longer SL after self-selected diet compared to control diet; less SWS with higher % energy from saturated fat; less N1 & more SWS with higher fibre intake; more arousals with higher sugar/refined carbohydrate intake; no change in sleep duration between conditions
Lindseth et al. (2013)	*N* = 44 adults (sex not stated); age 19 - 22 y; BMI mean ± *SD* 24.8 ± 3.5	Isocaloric high fat, high CHO, high protein or control diet over 4 days; participants slept at home* not laboratory-based, sleep monitored with actigraphy for 3 nights in each condition	Shorter SOL with the high CHO diet compared to the high fat, high protein or control diet; fewer arousals with high protein diet compared to the high fat, high CHO or control diet; sleep duration not reported
Jalilolghadr et al., 2011	*N* = 8 children (4 females), age 8-12	High GI or low GI milk before bed; PSG for 2 nights in each condition	More NREM arousals and total arousals with high GI milk compared to low GI milk; SOL, REM-SL, SD, TWT & SE not significantly different between conditions
Misra et al., 2015	*N* = 56 toddlers (sex not stated), age 14-24 mo	High GI or low GI milk for 3.5 days; participants slept at home* not laboratory-based, sleep monitored with actigraphy for 4 days	No significant differences in sleep parameters (SL, SD, SE, number of arousals) between high & low GI milk condition

SWS = slow wave sleep; REM = rapid eye movement sleep; NREM = non-rapid eye movement sleep; PSG = polysomnography; SL = sleep latency; GI = glycaemic index; SD = sleep duration; TWT = total wake time; SE = sleep efficiency; mo = months.

In a pioneering early study to assess the effects of dietary manipulation on polysomnographic sleep architecture, *N* = 8 healthy young adult males consumed either a high carbohydrate/low fat, low carbohydrate/high fat or a balanced, isocaloric control diet over two days (Phillips et al., 1975). The high carbohydrate/low fat diet was associated with significantly more REM and less SWS compared to the low carbohydrate/high fat diet or the isoenergetic control diet.

In another early trial, Hartmann and colleagues randomised twelve healthy men to either a high protein, high carbohydrate or high fat drink with an evening meal and measured REM sleep time (Hartmann et al., 1979). None of the macronutrient drinks had any effect on the amount of REM sleep as a percentage of total sleep time. The authors acknowledged that the study was short (1 night), and called for future trials to include more test nights.

Again over one night, but in contrast to Hartmann and colleagues, Porter and Horne reported a significant effect of high carbohydrate intake on sleep architecture in six healthy adult males (Porter & Horne, 1981). Compared to a low carbohydrate or carbohydrate free meal, a single, high carbohydrate meal before sleep was associated with more arousals, increased REM sleep in the first half of the night and less slow wave NREM sleep across the whole night. However, the three meals were not isocaloric, so the findings could be attributed to differences in calorie intake rather than the macronutrient content of the meals.

In a study of twelve healthy young males, subjects were randomised to consume either a high GI or an isoenergetic, low GI meal at bedtime for three nights (Afaghi et al., 2007). Sleep latency was significantly shorter after the high GI meal compared to the low GI meal. In a follow-up study by the same group, fourteen healthy young males consumed either a very low carbohydrate meal or an isocaloric control meal at bedtime (Afaghi et al., 2008). Subjects consuming the low carbohydrate meal had less REM and more NREM sleep (all stages) than those consuming the control meal.

St-Onge and colleagues gave *N* = 26 healthy adults a controlled, balanced diet for four days, followed by ad libitum, self-selected food on day five (St-Onge et al., 2016b). Participants were allowed a nine-hour sleeping opportunity each night. Sleep duration did not differ significantly between the two dietary conditions, but sleep latency increased, and subjects had significantly less SWS after the ad libitum diet. Total energy intake was significantly higher in the self-selected condition than the controlled diet, mainly due to increased fat intake (especially saturated fat). Those consuming more saturated fat under the self-selection condition had less SWS, while a higher self-selected fibre intake was associated with

more SWS and less N1 sleep. Higher intakes of sugar and other refined carbohydrates were associated with more sleep disturbance/arousals.

In one of the larger dietary manipulation studies, Lindseth and colleagues randomised *N* = 44 healthy adults to receive either a high fat, high carbohydrate, high protein, or a balanced, isoenergetic control diet over four days (Lindseth et al., 2013). Participants slept in their own homes rather than the laboratory and sleep was monitored with actigraphy. Sleep duration was not reported, but under the high protein condition there were fewer arousals, and the high carbohydrate diet was associated with significantly shorter sleep latency than the other three dietary interventions. This study is noteworthy for being one of the only dietary manipulation studies to assess sleep objectively under free-living conditions.

Some studies examined the effects of macronutrient intake on sleep in children. Jalilolghadr and colleagues assessed the effects of a high versus low GI milk drink at bedtime over two consecutive nights in eight children aged eight to twelve (Jalilolghadr et al., 2011). Those consuming the high GI drink had significantly more NREM arousals and total arousals than those in the low GI group. Also in children, Misra and co-workers randomised *N* = 56 toddlers to receive either high or low GI milk for four days. Participants slept at home and sleep was monitored with actigraphy (Misra et al., 2015). In contrast to Jalilolghadr et al., there were no significant differences in any sleep indices between the two groups. The authors postulated that the lack of significant differences could be due to the short duration of the study.

Vlahoyiannis and colleagues conducted the first, and to my knowledge, only systematic review and meta-analysis of interventional trials of the effects of carbohydrate manipulation on sleep structure (Vlahoyiannis et al., 2021). High carbohydrate intake was associated with significantly more REM sleep (relative to total sleep time), while low intakes were associated with more NREM slow wave sleep. The authors noted that mechanisms driving the relationships remain unclear, and should be tested in extended interventional trials.

In summary, experimental studies of the effects of macronutrient interventions on sleep are limited, but some evidence supports a role for carbohydrate intake on sleep latency, arousals and architecture. Some studies reported shorter sleep latency with a high carbohydrate/high GI intake (Afaghi et al., 2007; Lindseth et al., 2013); others reported no significant effects of high versus low carbohydrate intake on sleep latency (Afaghi et al., 2008; Jalilolghadr et al., 2011; Misra et al., 2015; Porter & Horne, 1981). Some reported more arousals with a high GI/high carbohydrate intake (Porter and Horne, 1981; Jalilolghadr et al., 2011; St-Onge et al., 2016b) while others found no difference (Misra et al., 2015). In terms of sleep architecture, some studies reported more REM and less SWS with a high carbohydrate intake (Phillips et al., 1975; Porter & Horne, 1981), supported by others that found less REM and more NREM sleep (all stages) with very low carbohydrate intake (Afaghi et al., 2008). The systematic review and meta-analysis by Vlahoyiannis and colleagues (2021) support the sleep architecture/carbohydrate intake findings. Studies in children generally support the findings in adults, but overall, results are mixed. The inconsistencies might reflect heterogeneity between study designs, such as variations in the number of test nights, timing and composition of test meals (e.g., quantity/proportion of nutrients, variations in the GI of carbohydrates etc.), different demographic characteristics and generally very small numbers

of participants. Laboratory-based trials are necessarily small, and in all the polysomnography studies, participants were extracted from their natural environments and confined to the artificial surroundings of a sleep laboratory. As discussed, first night effects can disrupt sleep (Webb & Campbell, 1979), and this is particularly relevant in shorter studies, especially those limited to one or two nights.

Given that macronutrients are generally not consumed in isolation, findings should be considered in the wider context of total/habitual diet. Evidence presented thus far indicates that unhealthy dietary patterns, such as those high in saturated fats and refined carbohydrates, and low in fresh fruit and vegetables, wholegrains and lean protein sources, are associated with short and/or poor quality sleep. The Western-style diet is an example of this type of dietary pattern. In contrast, diets low in saturated fats and refined carbohydrates, and high in unrefined wholegrains, fish, fruit and vegetables, are associated with longer sleep duration, better quality sleep and lower rates of insomnia. The Mediterranean-style diet is an example of this type of dietary pattern, and a small but growing number of studies over the past decade have investigated the relationship between Mediterranean diet adherence and sleep quality. The following section reviews the evidence.

2.4.4 EPIDEMIOLOGICAL EVIDENCE OF MEDITERRANEAN DIET/SLEEP RELATIONSHIPS

Table 2.4 summarises epidemiological studies examining the relationship between Mediterranean diet and sleep quality across the age spectrum.

Table 2.4. Observational (cross-sectional and prospective) studies of the effects of Mediterranean-style diet on sleep quality.

STUDY REFERENCE AND DESIGN	PARTICIPANTS	SLEEP MEASURES	DIET MEASURES	ADJUSTMENTS	FINDINGS
Jaussent et al., 2011 Cross-sectional	*N* = 5886 French adults, 3213 females (French multi-centre 3C Study), age 65+	Self-reported insomnia symptoms (DIS, DMS, EMA, sleeping medication, daytime sleepiness)	FFQ for calculation of 11-item MD adherence score	Chronic disease, depression (CES-D score >16) caffeine & alcohol intake, BMI	MD adherence inversely associated with insomnia symptoms in females; SD not reported
Ferranti et al., 2016 Cross-sectional	*N* = 1586 Italian adolescents, 716 females, age 11-14	Self-report bed /wake time for SD; Paediatric Daytime Sleepiness Scale	FFQ; KIDMED	Sex, age, physical activity, parents' education & occupation	Adherence to MD correlated positively with SD & negatively with daytime sleepiness; SD correlated positively with fruit & vegetable intake & negatively with snacks, sweets & eating out; no other measures of sleep quality assessed
Campanini et al., 2017 Prospective (2 time points: 2012 and 2015)	*N* = 1596 Spanish adults, (sex not stated); (ENRICA study of lifestyle & healthy ageing in older Spanish adults), age 60+	Self-reported SD, sleep quality, DIS, DMS, EMA, hypnotic drug use, daytime sleepiness, snoring, ESS	Computer-assisted face-to-face diet history & MEDAS	Model 1: sex, age, education; Model 2: as Model 1 plus BMI, physical activity, smoking status, energy & caffeine intake, baseline/incident CVD, DM, cancer, depression, Parkinson's disease, SD (≤6 h, 7-8, ≥9 h)	Higher MEDAS score associated with lower risk of changes in SD over time; higher MEDAS score at baseline associated with better sleep quality at follow-up
Castro-Diehl et al., 2018 Prospective (2 time points: 2000 and 2010)	*N* = 2007 US adults, 1076 females (US Multi-Ethnic Study of Atherosclerosis) age 45-84 at baseline	Self-reported insomnia symptoms (Women's health Insomnia Rating Scale; WHIIRS), actigraphy & sleep diary (7 days) for SD	Semi-quantitative FFQ; alternate Mediterranean Diet (aMed) score	Model 1: sex, age, ethnicity; Model 2: as Model 1 plus education; Model 3: as Model 2 plus energy intake, physical activity, smoking status; Model 4: as Model 3 plus BMI, DM, HT, apnoea score, depression (CES-D score ≥16), antidepressant/ antipsychotic use	Higher aMed scores associated with longer SD & fewer insomnia symptoms; changes in aMed scores over time not associated with sleep
Mamalaki et al., 2018	*N* = 1639 Greek adults (Hellenic Longitudinal Study), age 65+	Self-reported SD (previous 4 weeks); 6 questions from Medical Outcomes Study self-report sleep scale	Semi-quantitative FFQ for calculation of 11-item MD adherence	Sex, age, education (years), physical activity, BMI, energy intake, diagnosed depression/anti-depressant use,	Adherence to MD correlated positively with better sleep quality in ≤75 year-olds; no associations between MD & SD

		(previous 4 weeks) for sleep quality	score	depression score (GDS score >6)	
Godos et al., 2019a	*N* = 1936 Sicilian adults, 1132 females, age 18+	PSQI	FFQ; Medi-lite for MD adherence score	Model 1: unadjusted; Model 2: sex, age, BMI, physical activity, education, occupation, smoking status, alcohol & energy intake, chronic diseases (cardio-metabolic, cancer); Model 3: as Model 2 plus MD score	For each point increase in MD score, individuals were 10% more likely to have adequate sleep quality (PSQI score <5), SD, efficiency & latency
Zuraikat et al., 2020 Prospective (1 year follow-up)	*N* = 432 US women; age 20-76	PSQI	FFQ; aMed score	Age, ethnicity, education, health insurance status, energy intake, BMI	Higher fruit & vegetable intake & higher aMed scores at baseline predicted better sleep quality at follow-up (lower global PSQI scores, fewer sleep disturbances, higher sleep efficiency); higher intakes of pulses predicted higher sleep efficiency at follow-up

FFQ = food frequency questionnaire; MD = Mediterranean diet; MEDAS = Mediterranean Diet Adherence Screener; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; SD = sleep duration; DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakening; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; GDS = Geriatric Depression Scale; CVD = cardiovascular disease; DM = diabetes mellitus; HT = hypertension.

In the first observational study to claim a sleep protective effect of the Mediterranean diet, Jaussent and colleagues analysed cross-sectional data from *N* = 5886 adults over the age of 65. Insomnia symptoms were inversely associated with adherence to a Mediterranean-style diet in women, but not in men (Jaussent et al., 2011). As discussed in Chapter 1, the Mediterranean diet is protective against cardiovascular disease (Grosso et al., 2017), a condition that is also associated with insomnia (Javaheri & Redline, 2017; Katz & McHorney, 1998) and commoner in those over 65. But the association endured after controlling for cardiovascular disease, so the authors reasoned that the relationship was unlikely to be driven by the reduced prevalence of cardiovascular disease in followers of a Mediterranean-style diet. They did not, however, attempt to explain the sex differences. Validated measures of sleep and diet were not used, and as the sample was limited to older adults, findings may not extend to younger age groups. Also, although the authors claimed that the Mediterranean

diet was protective of sleep, as this was a cross-sectional study, reverse causation could have occurred. So, it is possible that having better quality sleep (i.e., fewer insomnia symptoms) predicts healthier dietary behaviours (i.e., higher adherence to a Mediterranean-style diet).

In a cross-sectional study of *N* = 1369 Greeks over the age of 65, higher adherence to a Mediterranean-style diet was associated with better sleep quality in those aged under 76 (Mamalaki et al., 2018). Validated measures of sleep and diet were used, but again, the study was limited to older individuals, so findings may not extend to younger age groups.

In another cross-sectional study (*N* = 1936), Godos and colleagues (2019a) reported that for every point increase in Mediterranean diet score, individuals were 10% more likely to have good quality sleep (global PSQI scores < 5). Validated self-report measures were used, and this study had a much wider age range (18+) than the previous two (65+), so the findings are more generalisable to the wider population.

In a longitudinal prospective study of *N* = 1596 Spanish seniors (60+ years) observed at two time points three years apart, higher adherence to a Mediterranean-style diet was associated with better sleep quality and lower rates of change (increases or decreases) in sleep duration at follow-up (Campanini et al., 2017). The study population was limited to an older age group, so again, the findings may not extend to younger groups, but the prospective design enabled diet/sleep associations to be examined over time.

In one of the first cross-sectional studies of its kind in children and adolescents, Ferranti and colleagues found that higher adherence to a Mediterranean-style diet was associated with

longer sleep duration and less daytime sleepiness in circa 1500 Sicilians, even though only 6% reported high adherence (Ferranti et al., 2016). Southern Italy is where the traditional Mediterranean-style diet originated, so it is noteworthy that only 6% of participants reported high adherence, given the Southern Italian demographic of the sample. There was also a positive correlation between sleep duration and fruit and vegetable intake, and a negative association between sleep duration and intake of packaged snacks and sweets.

To my knowledge, only a handful of studies have investigated relations between Mediterranean diet adherence and sleep in non-Mediterranean populations. These include two cross-sectional studies in Sweden (Theorell-Haglöw et al., 2020; van Egmond et al., 2019), two in Arab nations (Naja et al., 2021; Zaidalkilani et al., 2022) and two longitudinal studies in Americans (Castro-Diehl et al., 2018; Zuraikat et al., 2020). All but one (van Egmond et al., 2019) reported better sleep quality in individuals with higher adherence to a Mediterranean-style diet.

Castro-Diehl and colleagues were the first to use actigraphy to study Mediterranean diet/sleep relations prospectively, in a non-Mediterranean sample (Castro-Diehl et al., 2018). A cohort of *N* = 2007 middle-aged and older Americans were observed twice over a ten-year period. Higher adherence to a Mediterranean-style diet was associated with longer sleep duration and fewer insomnia symptoms, but changes in Mediterranean diet scores over the ten years were not significantly associated with sleep variables. This study was the first of its kind to be conducted in a non-Mediterranean population not renowned for consuming a Mediterranean-style diet, but a “standard American” (i.e., Western-style) diet. The authors

identified a need for further studies to explore possible mechanisms underlying the associations.

To my knowledge, only one other study has investigated Mediterranean diet/sleep relations prospectively, in a non-Mediterranean sample. Zuraikat and colleagues observed *N* = 432 American females at two time points one year apart, using validated measures. Higher adherence to a Mediterranean-style diet at baseline predicted better sleep quality at follow-up (Zuraikat et al., 2020). However, the sample was limited to women, so the findings may not extend to the whole population.

The studies presented in this final section are not without limitations. Although some adjusted for diagnosed depression, fewer than half controlled for mood. Given the high prevalence of undiagnosed/subclinical depression (Rodríguez et al., 2012), some participants may have been suffering from undiagnosed or subthreshold depression. As mood is associated with both diet and sleep, it could have confounded the relationships observed between diet and sleep in studies that did not adjust for it. Similarly, cardiovascular disease is associated with both diet and sleep, yet fewer than half the studies controlled for cardiovascular disease. Although Mediterranean diet reduces the risk of cardiovascular disease (Grosso et al., 2017), the risk still increases with age, and over half the studies in Table 2.4 were limited to middle-aged and older subjects. Thus, some participants may have been suffering from cardiovascular disease, but without statistical adjustment, this may have confounded the relationships observed between diet and sleep quality.

In summary, emerging cross-sectional evidence suggests that higher adherence to a Mediterranean-style dietary pattern is associated with less daytime sleepiness, fewer insomnia symptoms, longer sleep duration and better overall sleep quality. Studies in children appear to support those in adults, but more are needed. Prospective evidence is particularly limited, and more studies are required in both males and females, across the age spectrum and in non-Mediterranean populations, including the UK.

2.5 SUMMARY

The aim of this chapter was to review the literature examining binary relationships between diet, mood and sleep. The evidence supports a strong, bidirectional relationship between diet quality and mood, with healthy dietary patterns, including the Mediterranean diet, associated with lower rates of depression (Lassale et al., 2019; Molendijk et al., 2018). Conversely, poor quality diets, such as the Western-style diet, are associated with an increased risk (Huang et al., 2019; Y. Li et al., 2017). Interventions to improve diet quality are now recognised as successful treatments for depression (Firth et al., 2019), and healthy dietary patterns may also have a preventative role in both depression and anxiety (Kris-Etherton et al., 2021). The relationship is reciprocal, because mood can also influence dietary behaviours, with poor mood leading to unhealthy dietary choices and emotional eating (Begdache et al., 2019).

There is also a bidirectional relationship between sleep quality and mood, although sleep may be a stronger predictor of subsequent mood than mood is of sleep (Totterdell et al., 1994; Buysse et al., 1997; Pandina et al., 2010; Triantafillou et al., 2019). Short sleep duration is associated with poor mood in both observational and interventional studies (Banks and Dinges, 2007). Poor sleep quality is also associated with subsequent poor mood, and insomnia/sleep disturbance is implicated in the development and maintenance of mood disorders in clinical samples (Harvey, 2008a; Watling et al., 2017).

A substantial body of evidence supports a close relationship between diet and sleep. Cross-sectional studies indicate that habitual short (Shi et al., 2008; Grandner et al., 2010; Haghighatdoost et al., 2012) and poor quality sleep (Katagiri et al., 2014; Yoneyama et al., 2014) are associated with unhealthy dietary patterns such as a Western-style diet. Conversely, longer sleep duration and better sleep quality are associated with healthy dietary patterns, although directionality cannot be ascertained from cross-sectional studies. Interventional studies demonstrate that sleep restriction can alter dietary behaviours, leading to higher intakes of calories, fat, snacks, sugar and other refined carbohydrates (Markwald et al., 2013; Al Khatib et al., 2017; Spaeth et al., 2014; Gangwisch et al., 2020). The relationship is also reciprocal, with diet, and dietary manipulation, impacting sleep (Shi et al., 2008; St-Onge et al., 2016a; St-Onge & Zuraikat, 2019), although the experimental evidence is currently limited by small sample sizes, heterogeneous methodologies and inconsistent results (Campanini et al., 2017; Mamalaki et al., 2018). More research in larger samples, with prospective designs and homogeneous methodologies would help to substantiate the emerging evidence and explore underlying mechanisms. Evidence is also emerging that a Mediterranean-style diet may be protective of sleep (Godos et al., 2019a), but again, more prospective studies are needed, including in non-Mediterranean populations such as the UK.

If poor quality diets are detrimental to mood and sleep quality, and good quality diets are protective, what underlying mechanisms are responsible for these effects? The next chapter examines biological mechanisms that may drive these associations.

3 INFLAMMATORY MECHANSIMS CONNECTING DIET, MOOD AND SLEEP

3.1 AIMS

It is clear from the studies presented in Chapter 2 that diet impacts mood and sleep, although the underlying mechanisms remain unclear (Bremner et al., 2020). This chapter introduces diet as a stimulus that has the potential to induce a state of pathological inflammation. This orients the reader towards the hypothesis that chronic, diet-derived inflammation is one of the biological mechanisms linking diet quality to mood and sleep quality. The first section introduces the immune system, and one of its major functions, inflammation.

3.2 THE IMMUNE SYSTEM

The immune system is a vital host-defence mechanism composed of a vast network of molecular messengers, cells, tissues and organs that act in concert to provide protection against pathological stimuli that can cause injury. These stimuli include chemical toxins, physical irritants and insults (e.g., pressure, trauma, ultra-violet light, heat), and infective agents (e.g., fungi, yeasts, bacteria, viruses).

The immune system has two major divisions, the innate and adaptive system. The innate, or non-specific immune system, provides a rapid, generic response to pathogenic stimuli (Litman et al., 2005). It is the first line of internal defence if a pathogen breaches the external barrier of the skin or mucosal surfaces. If the pathogen is not neutralised by this initial response, the system then triggers activation of the adaptive immune response. This provides a more sophisticated response, with immunological "memory" for the specific pathogen, so that if it is re-encountered, it is recognised, and a targeted response is launched (Kurosaki et al., 2015). It is also known as acquired immunity, as memory for the pathogen is acquired and maintained after it has been eliminated. The innate system does not provide immunological memory, but both systems work in tandem to produce a coordinated response.

3.2.1 ACUTE INFLAMMATION

Acute inflammation is one of the first host-defence responses to pathological stimuli and tissue injury. It is a vital protective mechanism, not confined to microbial infections, as it is triggered by any stimulus that can damage cells. It is initiated within a few minutes to hours of the insult, and the cardinal signs and symptoms are pain, oedema, redness, heat and loss of function (Ferrero-Miliani et al., 2007). Normally a self-limiting process, cells of the innate immune system, blood vessels, inflammatory mediators and cell-signalling molecules (cytokines) work together to neutralise the noxious agent, remove dead cells/cellular debris and promote cellular proliferation, tissue repair and restoration of function (Kawai and Akira, 2006; Kumar et al., 2004). The principal cell types involved in an acute inflammatory response are neutrophils, mononuclear monocytes and macrophages, and the main mediators of the

process are eicosanoids, vasoactive amines, hydrolytic enzymes and reactive oxygen species. Acute inflammation starts rapidly and is normally a self-limiting process (Eming et al., 2007), lasting from a few days to a few weeks, depending on the nature and extent of the stimulus than needs to be removed. But if the stimulus persists and the acute response is unable to resolve it, there is a gradual shift in the types of immune cells recruited into the inflamed tissue. This transforms the process into a chronic inflammatory state.

3.2.2 CHORNIC INFLAMMATION

Chronic inflammation is a pathological, unresolving immune response that can persist for months or years (Pahwa et al., 2020). The principal cell types are fibroblasts, monocytes, macrophages, plasma cells and lymphocytes, with macrophages predominating. The main mediators are growth factors, hydrolytic enzymes, reactive oxygen species and inflammatory cytokines. Cytokines can be detected in the circulation, as soluble biomarkers of inflammation. Normally circulating at very low levels in peripheral blood, if plasma levels are persistently elevated, this indicates a state of chronic, systemic inflammation. Chronic inflammation is characterised by elevations in the predominantly pro-inflammatory cytokines interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and other inflammatory markers such as C-reactive protein (CRP) (Petersen and Pedersen, 2005). The hydrolytic enzymes and reactive oxygen species released during an acute inflammatory reaction are toxic to infectious agents and instrumental in their elimination. However, exposure to them on a sustained basis (i.e., chronic inflammation) damages healthy host tissue (Wang et al., 2021).

3.2.2.1 DIET-DERIVED CHRONIC INFLAMMATION

As discussed in Chapter 1, unhealthy dietary patterns, such as the Western-style diet, are major risk factors for a range of chronic, non-communicable diseases that inflict high-income nations, including cardiometabolic disease (Odermatt, 2011), certain cancers (Jakszyn et al., 2020). Chronic inflammation is a pathophysiological mechanism common to all these diseases (Phillips et al., 2019), and a large evidence base has established that habitual diet is one of the strongest modulators of chronic inflammation (Baer et al., 2004; Cavicchia et al., 2009; Cui et al., 2012; Giugliano et al., 2006; Libby, 2007; Lopez-Garcia et al., 2004; Wirth et al., 2017). Thus, in the absence of an ongoing infectious agent, poor quality diets can stimulate the immune system into a state of silent/asymptomatic chronic inflammation. Elevated levels of pro-inflammatory cytokines can be detected in the blood of apparently healthy/asymptomatic, but at-risk individuals, not (yet) suffering from diet-driven clinical inflammatory disease (Giugliano et al., 2006). Making the connection between poor quality diets and chronic inflammation paved the way for a new and rapidly evolving field of research into the inflammatory potential of the diet. Research in the area has grown exponentially over the past decade, with more than 30,000 peer-reviewed scientific papers now published on the subject (Hébert et al., 2019).

3.2.2.1.1 DIETARY INFLAMMATORY INDEX

Recognition of diet as an immunomodulator led to the development of the Dietary Inflammatory Index (DII) as a method of quantifying the inflammatory potential of the diet on

an individual level. Its design and development have been described in detail by Shivappa et al. (2014a), and it has been validated against cellular and plasma biomarkers of inflammation, including TNF-α, CRP and IL-6 (Shivappa et al., 2014b; Shivappa et al., 2018; Tabung et al., 2015; Wirth et al., 2014b). It is a literature review-based index derived from a review of almost 2,000 journal articles (dated between 1950 and 2010) assessing the inflammatory properties of 45 different food parameters. These include a range of micronutrients, macronutrients, ten whole foods, alcohol, caffeine and energy (see Table 3.1 for the full list of 45 food parameters and their inflammatory effect scores). Thus, the index is a whole diet measure, not just confined to a few specific foods or nutrients. A battery of six well established inflammatory markers were considered in the literature search (CRP, TNF-α, IL-1β IL-4, IL-6 and IL-10), and studies were weighted according to the robustness of their design, in order to derive an overall inflammatory effect score for each food parameter. Individual-level nutrient intakes are estimated from standard dietary instruments (e.g., diet diaries or FFQs), and standardised to mean (± *SD*) global daily intakes (in grams, mg and μg) for each of the 45 food parameters. These mean global daily intakes were obtained from 11 different countries and compiled into a reference database. To generate standardised intakes, the mean global intake is subtracted from the individual-level intake of each food parameter, and divided by the standard deviation of the global intake. The resulting standardised intakes (*z*-scores) are converted to proportions/percentiles and centred around zero by multiplying by two and subtracting one. They are then multiplied by the literature-derived inflammatory effect score for that food parameter. All food parameter scores and then summed to give an estimate of the overall inflammatory potential of the individual's diet. Scores for each nutrient are calculated per 1,000 kcal of food consumed to control for individual variations in total energy intake ("E-DII").

Table 3.1. Inflammatory effect scores of the 45 dietary parameters used to calculate Dietary Inflammatory Index.

Dietary parameter	Inflammatory effect score
Saturated fat (g)	+0.373 (most pro-inflammatory)
Total fat (g)	+0.298
Trans fat (g)	+0.229
Energy (kcal)	+0.180
Cholesterol (mg)	+0.110
Vitamin B_{12} (cobalamin) (μg)	+0.106
Carbohydrate (g)	+0.097
Iron (mg)	+0.032
Protein (g)	+0.021
Monounsaturated fat (g)	-0.009
Rosemary (mg)	-0.013
Vitamin B_2 (riboflavin) (mg)	-0.068
Vitamin B_1 (thiamine) (mg)	-0.098
Thyme/oregano (mg)	-0.102
Caffeine (g)	-0.110
Anthocyanidins (mg)	-0.131
Pepper (g)	-0.131
Eugenol (mg)	-0.140
Saffron (g)	-0.140
Omega-6 polyunsaturated fat (g)	-0.159
Folic acid (μg)	-0.190
Selenium (μg)	-0.191
Niacin (mg)	-0.246
Flavanones (mg)	-0.250
Alcohol (g)	-0.278

Onion (g)	-0.301
Zinc (mg)	-0.313
Total polyunsaturated fat (g)	-0.337
Vitamin B_6 (pyridoxine) (µg)	-0.365
Vitamin A (retinol) (RE)	-0.401
Garlic (g)	-0.412
Flavan-3-ol (mg)	-0.415
Vitamin E (mg)	-0.419
Vitamin C (mg)	-0.424
Omega-3 polyunsaturated fat (g)	-0.436
Vitamin D (µg)	-0.446
Ginger (g)	-0.453
Flavanols (mg)	-0.467
Magnesium (mg)	-0.484
Green/black tea (g)	-0.536
Beta carotene (µg)	-0.584
Isoflavones (mg)	-0.593
Flavones (mg)	-0.616
Fibre (g)	-0.663
Turmeric (mg)	-0.785 (most anti-inflammatory)

RE = retinol equivalents.

At least 20 dietary parameters are required to calculate DII scores, and if calculated from all 45, scores can range from + 7.98 to - 8.87. Positive scores indicate a higher level of diet-derived inflammation and negative scores a more anti-inflammatory dietary pattern (Shivappa et al., 2014a). Scores of < -3.0 are “very anti-inflammatory”, -3.0 to -1.01 are “moderately anti-inflammatory”; scores of -1 to 0.99 are “neutral”, while 1.0 to 3.0 are

"moderately pro-inflammatory" and >3 are "very pro-inflammatory" (Wirth et al., 2021). Saturated fat has the highest inflammatory effect score (+0.373), and is therefore the most pro-inflammatory of the 45 dietary parameters, followed by *trans* fat (+0.229). In contrast, other dietary fats have negative inflammatory effect scores, and omega-3 polyunsaturated fat has the most anti-inflammatory effect score of all the fats (-0.436). Thus, different types of dietary fat have very different inflammatory properties.

Western-style diets, typically high in pro-inflammatory, animal-derived saturated fats and refined carbohydrates, and low in fresh fruit, vegetables and dietary fibre, are pro-inflammatory dietary patterns, while those high in plant-derived, anti-inflammatory unsaturated fats, such as olive oil (high in MUFA) or seed-based oils (high in omega-3 or omega-6 PUFA), oily fish (high in omega-3 PUFA), wholegrains, fruit and vegetables, such as the Mediterranean-style diet, are anti-inflammatory (Ahluwalia et al., 2013).

3.2.2.1.2 SUBCELLULAR INFLAMMATORY MECHANISMS

Why do dietary patterns high in fruit, vegetables, dietary fibre and oily fish have low (anti-inflammatory) DII scores? Fruit and vegetables contain high levels of polyphenols and flavonoids, which are associated with reduced levels of circulating pro-inflammatory markers (de Mello et al., 2011). The antioxidant activity of these phytochemicals may be responsible for their anti-inflammatory effects (de Mello et al., 2011; Harms et al., 2020; Huang et al., 2019). Hi levels of vitamins (e.g., vitamin C, E and some B-group vitamins) and minerals (e.g., iron, zinc, selenium) in plant-based diets may also protect against inflammation by inhibiting

oxidative stress (Crispo et al., 2021), particularly in the brain (Miquel et al., 2018). High fibre diets may also impact immune responsiveness by influencing the composition of commensal microbial species that inhabit the human gut (the gut microbiome), favouring eubiosis (microbial balance) and species with anti-inflammatory actions, although further research into these mechanisms is required (Berk et al., 2013; Young et al., 2021).

As discussed in Chapter 1, oily fish is a rich source of the long-chain omega-3 fatty acids EPA and DHA (Patterson et al., 2012). These are highly metabolically active lipids that form major functional components of all cell membranes, and it is widely acknowledged that membrane omega-3 polyunsaturated fats are metabolised to anti-inflammatory and inflammation-resolving eicosanoids (resolvins and protectins) (Balta et al., 2021; Souza et al., 2020). In contrast, the inflammatory properties of membrane omega-6 polyunsaturated fats are debated. High intakes of omega-6 linoleic acid are thought by some to promote inflammation (Patterson et al., 2012), and critics argue that Western dietary intakes should be reduced substantially (Hamazaki & Okuyama, 2003; Mariamenatu & Abdu, 2021; Simopoulos, 2008). However, other evidence suggests that they are involved in both pro- and anti-inflammatory signalling pathways in cell membranes (Fritsche, 2008). Review evidence indicates that higher linoleic acid intakes are not significantly associated with inflammation, and many studies reported that individuals with the highest intakes had the lowest inflammatory status (Fritsche, 2014). The latest advice from the American Heart Association (AHA, 2019) is that omega-6 fats either reduce biomarkers of inflammation or leave them unchanged, and that they are beneficial to cardiovascular health (Harris et al., 2009). This is also supported by the moderately negative (anti-inflammatory) DII effect score of omega-6 polyunsaturated fat (see Table 3.1).

In contrast to unsaturated fats, dietary saturated fatty acids have primarily pro-inflammatory properties, and a substantial evidence base indicates that activation of toll-like receptor-4 (TLR-4) is a major mechanism underlying these effects (Lee et al., 2001; Milanski et al., 2009). TLR-4 is present on numerous cells of the innate immune system, leading to activation of nuclear factor-kappaB (NF-kB), a transcription factor that switches on the expression of a wide variety of pro-inflammatory cytokines (Fritsche, 2015). Unsaturated fats do not have the same effect on this cytokine expression pathway (Lee et al., 2001), and omega-3 polyunsaturated fats are thought to down-regulate the NF-kB pathway, thus exerting anti-inflammatory effects (Balta et al., 2021; Li et al., 2020; Rogero & Calder, 2018). See Balta et al., 2021 for a comprehensive review of the biological mechanisms of action of essential fatty acids.

Studies have linked Dietary Inflammatory Index to obesity, metabolic disease, cardiovascular disease (Garcia-Arellano et al., 2015; Parimisetty et al., 2016; Goldfine et al., 2017), telomere length (Garcia-Calzon et al., 2015), various cancers (Maisonneuve et al., 2016; Wirth et al., 2015; Zitvogel et al., 2017) and all-cause mortality (Shivappa et al., 2016). In the case of cardiovascular disease, the evidence is particularly robust: three meta-analyses examining the relationship between DII and cardiovascular disease found that higher scores were associated with both increased risk (Aslani et al., 2020; Ji et al., 2020; Shivappa et al., 2018) and mortality from cardiovascular disease (Aslani et al., 2020; Okada et al., 2019; Shivappa et al., 2018).

3.2.2.1.3 DIETARY INFLAMMATORY INDEX AND MOOD

A robust evidence base also links Dietary Inflammatory Index to mood (Philips et al., 2019). Wang and colleagues conducted a systematic review and meta-analysis of almost 50,000 individuals from cross-sectional and prospective studies. Those in the highest category of DII (i.e., the most pro-inflammatory diets) had a 23% higher risk of depression than those in the lowest category (Wang et al., 2019). Similarly, a meta-analysis of sixteen studies found that compared to an anti-inflammatory diet, a pro-inflammatory diet was significantly associated with anxiety and depression (Chen et al., 2021). A one-unit increase in DII score was associated with a 6% higher risk of depressive symptoms, suggesting a linear, dose-response relationship.

It is clear from the review evidence that DII scores are strongly related to mood; emerging data also suggests that they are associated with sleep. It is widely acknowledged that there is a reciprocal relationship between sleep and the immune system (Besedovsky et al., 2019; Irwin, 2019). Sleep strengthens the immune response, and afferent (incoming) signals from immune cells to the central nervous system facilitate sleep (Irwin, 2019). Some interventional studies found that sleep restriction increases circulating pro-inflammatory cytokines (e.g., Vgontzas et al., 2004; Haack et al., 2007; Pejovic et al., 2013) and the inflammatory biomarker CRP (Meier-Ewert et al., 2004; Leproult et al., 2014). Others, however, report no significant associations (e.g., Schmid et al., 2011; Faraut et al., 2011; Lekander et al., 2013). These inconsistencies may be due to differences in study design, such as the number of hours sleep was restricted by (e.g., total sleep deprivation, severe sleep restriction or mild sleep restriction), the number of days of sleep restriction and differences in how and when

inflammatory markers were measured. A systematic review and meta-analysis concluded that long sleep duration and sleep disturbance, but not short sleep duration, are risk factors for increased circulating pro-inflammatory markers (Irwin et al., 2016). Long sleep duration may be the result of other factors associated with inflammation, such as obesity and chronic inflammatory disease. Furthermore, although short sleep was not *directly* related to increased cytokine levels in peripheral blood, acute partial sleep restriction upregulated transcriptional (gene expression) measures of inflammation and activation of inflammatory signalling pathways. Thus, the authors reasoned that downstream increases in plasma inflammatory markers may be undetectable until sometime later, or may require longer periods of sleep restriction than is generally practicable under laboratory conditions (Irwin et al., 2016).

3.2.2.1.4 DIETARY INFLAMMATORY INDEX AND SLEEP

As discussed, inflammation and sleep, inflammation and diet, and diet and sleep are associated, yet research into the relationship between dietary inflammation and sleep is scarce. When I first embarked on this work in 2018, there were no published articles, and to my knowledge, there are now (March 2022) only a handful. Table 3.2 summarises the total studies examining the relationship in adults, all of which reported statistically significant associations.

Table 3.2. Studies (observational and interventional) investigating the relationship between Dietary Inflammatory Index and sleep quality in adults.

STUDY REFERENCE and DESIGN	PARTICIPANTS	DIET MEASURE FOR DII CALCULATION	SLEEP MEASURES	ADJUSTMENTS	FINDINGS
Godos et al., 2019b Cross-sectional	*N* = 1936 Italian adults (804 males) from the Mediterranean healthy Eating, Aging, and Lifestyle (MEAL) study, age 18+	Validated FFQ, Mediterranean diet adherence score	PSQI (sleep quality)	Sex, age, BMI, education, occupation, physical activity, alcohol intake, energy intake, Mediterranean diet adherence, smoking, diabetes, hypertension, dyslipidaemias, cardiovascular disease, cancer	Higher DII scores associated with lower likelihood of good sleep quality (global PSQI score < 5)
Wirth et al., 2020 Cross-sectional and longitudinal (3-month follow-up)	*N* = 95 American adults, 18 males at baseline; *n* = 79 (follow-up) from the Inflammation Management Intervention Study (IMAGINE), mean (± *SD*) age = 46.9 (13.4)	3 x 24-hour dietary recalls	Continuous actigraphy (7 days); plasma inflammatory biomarkers (CRP, IL-6, TNF-α)	Sex, age, ethnicity, education, employment status, physical activity, smoking, perceived health, social desirability, aspirin use, shift work exposure (γ), perceived stress (PSS), depression scores (CES-D scale)	Cross-sectionally, higher levels of TNF-α associated with longer SL; higher IL-6 and CRP associated with more WASO; lower CRP associated with higher SE; longitudinally, those with post-intervention anti-inflammatory changes (lower DII scores at 3 months compared to baseline) had improved SE and less WASO compared to those with pro-inflammatory changes (higher DII scores at 3 months compared to baseline)
Wirth et al., 2021 Cross-sectional and longitudinal (15-year follow-up)	*N* = 464 active-duty police officers, 295 males at baseline; *n* = 240 (follow-up), mean (± *SD*) age = 41.5 (6.7)	FFQ	Continuous actigraphy (15 days), PSQI	Sex, ethnicity, education, CES-D score, Beck Anxiety Inventory, Impact of Events, BMI, sleep medications, blood pressure, alcohol intake, smoking, waist circumference	Cross-sectionally, higher DII scores associated with more actigraphic WASO but lower PSQI scores. At follow-up, for each 1-unit increase in DII scores, WASO increased by almost 1.4 min (p = .07) but sleep quality improved (lower PSQI scores)
Masaad et al., 2021 Cross-sectional	*N* = 379 United Arab Emirates university students (36% male), age 18-30	Semi-quantitative FFQ	PSQI	None	Higher DII scores associated with more daytime dysfunction; trend association between DII and global PSQI scores
Kase et al., 2021 Cross-sectional	*N* = 30,121 American adults (48.1% male) from the 2005-2016 National Health and Nutrition Examination Survey (NHANES), age 20+	1 x 24-hour dietary recall	*"How much sleep do you usually get at night on weekdays or workdays?" "Have you ever told a*	Sex, age, ethnicity, education, BMI, marital status, chronic medical conditions	Subjects in highest quintile of DII had 40% increased odds of short sleep (≤6 hours) compared to lowest quintile; highest quintile associated with more sleeping troubles; long sleep duration (≥ 9 h)

			doctor or other health professional that you have trouble sleeping?"		associated with higher DII quintiles
Bazyar et al., 2021 Cross-sectional	*N* = 249 Iranian female college students, age 18-35	Validated FFQ	PSQI	Model 1: unadjusted, Model 2: energy intake, Model 3: energy intake, age, education, physical activity	Higher DII scores associated with poor sleep quality (global PSQI scores > 5). In the fully adjusted model, subjects in the highest quartile of DII had higher global PSQI scores than those in quartile 1
Setayesh et al., 2021 Cross-sectional	*N* = 219 overweight and obese Iranian females, mean (± *SD*) age = 36.49 (8.38)	Semi-quantitative FFQ	PSQI	Model 1: unadjusted, Model 2: energy intake, age, physical activity, BMI	Higher DII scores associated with poor sleep quality; 58% of subjects in highest DII quartile had inadequate sleep quality (PSQI scores > 5)

DII = Dietary Inflammatory Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; CES-D = Center for Epidemiologic Studies Depression scale; PSG = polysomnography; FFQ = food frequency questionnaire; BMI = body mass index; TNF-α = tumour necrosis factor-alpha; SL = sleep latency; IL-6 = interleukin-6; CRP = C-reactive protein; WASO = wake-after-sleep-onset; SE = sleep efficiency; mo = month(s); PHQ-9 = 9-item Patient Health Questionnaire.

Godos and colleagues were the first to show that higher DII scores were associated with poorer sleep quality (higher global PSQI scores and longer sleep latency) in *N* = 1936 Italian adults (Godos et al., 2019b). Data were adjusted for a wide range of demographic and inflammation-related confounders including smoking status, cardiometabolic disease and cancer. Further, after adjusting for adherence to Mediterranean diet, the relationship between sleep and DII strengthened, so the authors argued that if both dietary assessments represent a measure of dietary-related inflammation, the DII is a "stronger predictor" than Mediterranean diet. However, given the cross-sectional design of this study, it may be difficult to argue that DII/Mediterranean diet are predictors of sleep quality. This study is noteworthy for controlling for a number of inflammatory-related confounders, although it did not adjust for subclinical or diagnosed anxiety and depression, which may also have been related to both sleep and DII.

In one of the only longitudinal studies of Dietary Inflammatory Index and objective (actigraphic) sleep quality, Wirth and colleagues conducted an anti-inflammatory diet and lifestyle intervention in *N* = 95 healthy American adults. At baseline, higher levels of the pro-inflammatory cytokine TNF-α were associated with longer sleep latency, and higher IL-6 and CRP levels were associated with more wake-after-sleep-onset (i.e., more disturbed sleep); lower CRP was associated with higher sleep efficiency (Wirth et al., 2020). At follow-up (3 months), participants with anti-inflammatory changes (i.e., reductions in DII scores at follow-up), had improved sleep efficiency and less wake-after-sleep-onset compared with those exhibiting pro-inflammatory changes after three months. The study excluded individuals with chronic disease and controlled for a number of demographic and health factors, including mood and stress.

In the only other published longitudinal study of Dietary Inflammatory Index and objective (and subjective) sleep quality, also by Wirth and colleagues (2021), higher DII scores at baseline were associated with more actigraphic wake-after-sleep-onset (i.e., poorer objective sleep quality) but lower global PSQI scores (i.e., better subjective sleep quality). Similarly, at follow up (15 years), increasing DII scores were associated with more actigraphic wake-after-sleep-onset, but lower global PSQI scores, as before. These apparent contradictions are consistent with other studies reporting that objective and subjective measures of sleep quality do not always coincide (e.g., Baker et al., 1999; Lauderdale, 2008). The study controlled for variables identified as confounders, including depression, anxiety and cardiovascular disease risk factors.

Masaad and co-workers examined the relationship between Dietary Inflammatory Index and sleep quality in a cross-sectional study of *N* = 379 university students from the United Arab Emirates (Masaad et al., 2021). A significant positive association was found between DII scores and the PSQI subcomponent daytime dysfunction, and a trend relationship between DII and global PSQI scores in the same direction. However, no statistical adjustments were made for potential confounding factors that might be related to diet and sleep, including mood and cardiovascular disease status.

Kase and colleagues conducted a large cross-sectional study of circa 30,000 Americans (Kase et al., 2021). Individuals in the highest quintile of DII had a 40% increased odds of self-reported short sleep duration (≤ 6 hours) and reported having more "trouble sleeping" compared to those in the lowest quintile. Subjects with long sleep durations (≥ 9 hours) were also more likely to score in higher quintiles. Adjustments were made for potential confounders including chronic medical conditions. This is the only study of the six to report a significant relationship between DII scores and sleep duration, although a validated scale was not used to assess sleep duration.

In a sample of *N* = 249 female college students from Iran, Bazyar and co-workers reported that individuals in the highest quartile of DII had significantly higher global PSQI scores than those in the lowest quartile. Adjustments were made for demographic factors and physical activity levels, but not for any other health-related factors that might impact diet and sleep.

Finally, for this section, Setayesh and colleagues (2021) studied *N* = 219 overweight and obese Iranian females, reporting that higher DII scores were associated with poorer sleep quality (PSQI scores > 5). Adjustments were made for age, physical activity and BMI, but as before, not for any other health-related factors that might impact diet and sleep.

Of the seven studies, none adjusted for both chronic disease (including cardiovascular disease) and mood (i.e., anxiety and depression). However, as discussed earlier in the chapter, a number of meta-analyses showed that DII predicts cardiovascular disease (Shivappa et al., 2018; Okada et al., 2019; Ji et al., 2020; Aslani et al., 2020), anxiety and depression (Chen et al., 2021).

3.3 SUMMARY

A close relationship connects diet, mood and sleep, and the current chapter explored some of the mechanisms that are thought to drive these interactions. Diet was described as a major immunomodulator with the potential to induce a state of chronic, asymptomatic/silent inflammation. Substantial research indicates that inflammation is one of the mechanisms connecting diet to mood, with poor quality, pro-inflammatory diets predicting poor mood. Evidence emerging over the past three years also suggests that diet-derived inflammation connects diet to sleep, and that pro-inflammatory diets are associated with poor quality sleep. However, to date, only a handful of studies have investigated this relationship, so more research is needed. The principal hypothesis of this thesis was that Dietary Inflammatory Index mediates the relationship that connects diet to both mood and sleep, and the following chapters will examine this in three different samples. It is an important hypothesis to test, because diet-derived inflammation, per se, is asymptomatic, but diet is a modifiable behaviour. Thus, if dietary inflammation is a risk factor for disordered mood and sleep, reducing it through dietary modification will improve risk profiles in asymptomatic, but at-risk individuals with poor dietary habits, before clinical disease manifests. Further, mood disorders and poor sleep are highly comorbid, so reducing the dietary inflammatory burden of patients already suffering from these conditions might help to alleviate both.

4 STUDY 1: DIET, MOOD AND SLEEP IN A SAMPLE OF UNIVERSITY STAFF

4.1 INTRODUCTION

A vast body of literature has examined diet quality, mood and sleep quality in general population samples rather than specific focus groups such as night shift workers, or patients with clinically diagnosed mood or sleep disorders. A recent study provides a synthesis of systematic reviews of prospective observational studies, in an umbrella review of dietary indices in relation to selected health endpoints, including cardio-metabolic disease incidence and mortality and all-cause mortality in general population samples (Brlek and Gregorič, 2023). In terms of mood, normative HADS data from the largest UK population-based study of over 6,000 adults, approximately 16% scored above the clinical threshold for depressive symptoms (HADS-D scores $\geq$ 8) and around 30% reached the clinical cut-off for anxiety (HADS-A scores $\geq$ 8) (Breeman et al., 2015).

Regarding nocturnal sleep quality, normative studies have reported approximately 35% of adults scoring on or above clinical thresholds for unsatisfactory sleep quality (e.g., global PSQI scores > 5) (Zeitlhofer et al., 2000; Wong & Fielding, 2011; Rahe et al., 2015; Hinz et al., 2017; Schwarz et al., 2017). In a community sample of 10,000 German adults, 23% of respondents

reported excessive daytime sleepiness according to the Epworth Sleepiness Scale (Sander et al., 2016).

The current study investigated diet quality, mood and sleep quality in a cohort of university staff working standard daytime hours (approximately 9am to 5 pm, Monday to Friday). Given that the majority of adults in the UK work standard daytime hours, university staff are considered to be representative of the population at large.

There are currently over 400,000 academic and non-academic staff working standard daytime hours in tertiary education settings across the UK, and numbers are increasing (Higher Education Staff Statistics, 2021). However, research into the health and wellbeing of this workforce is lacking. The first section of this chapter provides a summary and evaluation of the status of knowledge of diet, mood and sleep in university staff. This provides the relevant background information and builds a rationale towards the aims and objectives of Study 1.

4.1.1 DIET IN UNIVERSITY STAFF

A large body of research has investigated dietary knowledge, attitudes and habits among university students (e.g., Barzegari et al., 2011; Pop et al., 2021). Comparatively, research into the diets of higher education staff is scarce. In 2012, Aldana and colleagues reported that there were no studies published on the subject (Aldana et al., 2012). Since then, a small number have reported high rates of alcohol misuse among university staff (e.g., Awoliyi et al.,

2014; Noel et al., 2021) and some studies have now assessed diet in this workforce (e.g., Caparello et al., 2020; Al-Sayegh et al., 2020).

Of the few studies that investigated diet in the tertiary education setting, Caparello and colleagues assessed adherence to a Mediterranean-style dietary pattern in a cross-sectional study of *N* = 340 university staff in Southern Italy (Caparello et al., 2020). As discussed in Chapter 1, adherence to a Mediterranean-style diet is based on traditional dietary practices in rural Southern Italy. However, despite the Southern Italian demographic of the sample, all staff groups (academic, technical and administrative) consumed below the recommended intakes of fish, nuts and fruit, and adherence was significantly lower in younger (< 45 years) compared to older (> 45 years) age groups.

Al-Sayegh and colleagues analysed diet quality in a cross-sectional study of *N* = 231 academic and non-academic staff working in health sciences at Kuwait University (Al-Sayegh et al., 2020). Approximately 88% of the sample reported consuming below the recommended daily intakes of fruit and vegetables, and around 60% ate fewer than the recommended servings of fish per week. Around 79% ate fast food at least once a week and almost 70% were overweight or obese. The authors noted that participants had dietary habits similar to, rather than superior to the general population, despite working in health education.

Despite the paucity of data on diet in university staff, some studies have assessed interventions to improve diet quality in this workforce (Abood et al., 2003; Byrne et al., 2016; Joy et al., 2018; Mouttapa et al., 2011; reviewed by Plotnikoff et al., 2015). Dooris and colleagues proposed a “National Healthy Higher Education Programme” (Dooris et al., 2010;

Dooris & Doherty, 2010), similar to the UK-wide government-backed initiatives already well established in schools and colleges of further education ("Healthy Schools" and "Healthy Further Education Programme"). However, despite the success of the school and college initiatives, "Healthy Universities" has not been widely embraced (Newton et al., 2016).

4.1.2 MOOD IN UNIVERSITY STAFF

The mental health needs of university students has become a key priority across the UK higher education sector in recent years, with welfare and counselling services now widely available to students. In contrast, the mental health needs of university staff remain relatively neglected (Spalek, 2021).

Over the past decade, studies assessing occupational stress and wellbeing in higher education employees have emerged, and poor mental health has become a serious concern in this workforce. Universities have been labelled "anxiety machines" (Hall & Bowles, 2016, p. 33), and described as environments in which "excessive pressure to perform has been normalised" (Morrish, 2019, p. 51). Increasing work demands and bureaucracy, including regulatory requirements, league tables and targets, metric-driven performance surveillance and audits such as the Teaching Excellence Framework and Research Excellence Framework have seen almost a third of staff across both academic and professional service/support roles report unmanageable workloads "all of the time" and over two-thirds for "half the time" (University and College Union Workload Survey, 2016). Reports also suggest that problematic work-life

balance, a lack of job security and precarious short-term contracts have been normalised (Bothwell, 2018).

There has been a dramatic rise in staff referrals to university occupational health and counselling services for work-related stress and mental health issues over the past few years, as high as 400% increases in some (Morrish, 2019). In one study, 43% of academics had symptoms of mental illness (Gorczynski, 2018), and in another, over 60% had "caseness" levels of psychological distress (Wray & Kinman, 2021). This is more than twice the rate in the UK general population (Stansfeld et al., 2016). A stark report by an occupational health psychologist stated that university workers suffer from higher levels of stress-related mental health problems than those working in the medical profession or police force (Kinman, 2018, reported by Grove, 2018). Some 55% experienced symptoms including cognitive impairment, sleep disturbances and depression (Grove, 2018). Suicides have also been reported, although there are no official statistics for suicide rates in this workforce (Haf Jones, 2019). One report claimed that middle-aged academic staff in senior lecturer roles are at higher risk of suicide than university students (Oswald, 2018).

4.1.3 SLEEP IN UNIVERSITY STAFF

Despite the high levels of mental illness in university staff, there is very little research into sleep in this population. This is perhaps surprising, given that sleep disturbance is a characteristic feature of mood disorders (Asarnow et al., 2014) and poor mood is now recognised in this workforce. Goodyer and colleagues reported that 92% of individuals with

symptoms of depression also complained of sleeping problems (Goodyer et al., 2017). The lack of research on sleep in university staff mirrors the paucity of data on diet in this workforce. In Al-Sayegh and colleagues' study of health science staff at Kuwait University (discussed earlier), only 25.1% reported habitually sleeping the recommended eight or more hours per night (Al-Sayegh et al., 2020). However, that study did not focus specifically on sleep, or measure any sleep quality indices other than duration. In Kinman's research (above), one of the problems reported was "sleeping difficulties" (reported by Grove, 2018), but again, this work did not focus specifically on the sleep, so further research is required to investigate which aspects of sleep (e.g., duration, quality etc.) are compromised in university staff. Several studies have investigated occupational stress and burnout in university workers, and although sleep impairment can be a symptom of both (Grossi et al., 2003; Wu et al., 2020), very few studies focused specifically on sleep. In one of the few studies that did, Wu and colleagues investigated sleep quality in a Chinese university faculty, and reported a mean global PSQI score of 4.71 (*SD* = 3.00) (Wu et al., 2020). This is slightly lower than the widely used clinical cut-off score for poor sleep (global PSQI score > 5). All seven component scores were also lower, suggesting that sleep quality in university staff is, in fact, better than that suggested by studies not focussing specifically on sleep or using validated tools to assess it. However, the paucity of research and lack of consistency leaves findings inconclusive.

4.2 AIMS AND OBJECTIVES

The overarching aim of the research was to investigate potential mechanisms linking diet, mood and sleep. The primary hypothesis of Study 1 was that in this cohort of university staff working standard daytime hours, diet-derived inflammation is one of the mechanisms that connects diet quality to both mood and sleep quality.

A secondary aim was to test the consistency of the current data against known binary relationships. The purpose of this was to establish whether the sample under study shared similar bivariate characteristics as those observed in the published literature, as a measure of the reliability of the current data. Thus, it was hypothesised that in line with robust published evidence from general population samples, mood would be strongly associated with sleep quality in this cohort.

Research into the diets and sleeping patterns of higher education workers is sparse. Regarding mood, however, evidence is accumulating that university workers may suffer from poorer mood and higher levels of stress than many other sectors and the population at large (Wray & Kinman, 2021), and the current research may add weight to this.

4.3 MATERIALS AND METHODS

4.3.1 STUDY SAMPLE

Participants were over the age of 18 and employed as members of staff at Nottingham Trent University, UK. Only those working standard daytime hours (approximately 9 am to 5 pm) were eligible. No other selection criteria were applied, such as work role, sleep complaints, diagnosed sleep disorders, mood disorders or other mental or physical illnesses. Similarly, there were no requirements regarding diet.

4.3.2 STUDY DESIGN AND DATA COLLECTION

The study was a cross-sectional, retrospective analysis of diet quality, mood and sleep quality. It consisted of a self-administered survey, hosted via the online survey platform Qualtrics (Provo, Utah, USA). Participation was voluntary and anonymous, and staff were invited by email. An additional questionnaire of 35 items was devised specifically for the study, and included demographics (e.g., sex, age, ethnicity, educational attainment etc.), lifestyle (e.g., smoking status, alcohol intake etc.) and health. Health questions included current and past medical history of physical and mental illnesses and prescribed/over-the-counter medications. The study was approved by Nottingham Trent University Research Ethics Committee and all participants provided written, informed consent.

4.3.2.1 DIET AND DIET QUALITY

Dietary data were collected using a semi-quantitative food frequency questionnaire (FFQ). Originally developed in 1988 for the European Prospective Investigation into Cancer (EPIC) and Nutrition, Norfolk study (Bingham et al., 2001), it examines the habitual eating habits of adults consuming a traditional UK diet, in other words, food and drink items commonly and less commonly consumed in the UK. Nutrient estimations are based on "The Composition of Foods" by McCance and Widdowson (see Roe et al., 2015 for latest edition). The EPIC-Norfolk instrument (Version 6) was selected for two reasons: (1) it is a UK-specific questionnaire, so it includes foods and beverage items known to be consumed in the UK, and (2) it was validated in a UK population. It was initially validated against a computer-assisted face-to-face 24-hour dietary recall in a subsample of the EPIC-Norfolk study population, and then against sixteen days of weighed food records, a seven-day diet diary, and urinary and plasma/serum biomarkers (Bingham et al., 1997, 2001; McKeown et al., 2001).

The Epic-Norfolk questionnaire consists of a list of 130 food and beverage items to assess habitual intake over the previous year. Participants are required to select their usual intake of each item from one of nine frequency categories ranging from "6+ times per day" to "never or less than once per month". Serving sizes are estimated from standard household measures (e.g., one teaspoon, one glass) or typical portions (e.g., one banana, one bread roll), and an average adult portion size is assigned to each. An additional free text section allows participants to report any other items consumed regularly that are not on the list, and also asks about the quantity and type of milk used (e.g., semi-skimmed, soya milk etc.), the type of fat used for cooking and the brand of breakfast cereal most commonly consumed.

Response data are processed using the "FFQ EPIC Tool for Analysis" (FETA). This is an open-source software tool based on version 6 of the EPIC-Norfolk FFQ (Mulligan et al., 2014). FETA computes an average daily intake weight for each of the 130 items by multiplying the reported frequency of intake (e.g., twice a week [2/7] = 0.29) by the average portion size of the food, and then multiplying this weight by the nutrient composition, to compute the total amount consumed. Each nutrient is summed to yield individual-level average daily intakes of macronutrients (e.g., protein, grams/day), micronutrients (e.g., iron, milligrams/day, folic acid, micrograms/day), alcohol (grams/day), energy (kcal/day), and fourteen food groups (e.g., meat and meat products, eggs and egg dishes, grams/day).

Of the 74 individual food parameters generated from the FFQ, the current study focussed on seven macronutrient variables (grams/day): total *Carbohydrates,* total *Sugars* (i.e., glucose, galactose, fructose, lactose and maltose), *Fibre* (i.e., non-starch polysaccharides), *Monounsaturated Fatty Acids (MUFA), Polyunsaturated Fatty Acids (PUFA), Saturated Fatty Acids (SFA)* and *Cholesterol;* four food groups*: Fruit, Vegetables, Fish and Fish Products, Meat and Meat Products,* and total *Energy* (kcal/day). These variables cover all the major dietary constituents, and rather than including protein as a macronutrient variable, the food groups *Meat and Meat Products and Fish and Fish Products* were selected because meat products may contain saturated fats as well as protein, and oily fish contains polyunsaturated fat (i.e., omega-3 PUFA) as well as protein. A further, dichotomous variable, *Fast Food* (once a week or more: yes/no) was created from the free-text section of the FFQ, to capture intake of fast food (e.g., mass produced pizzas, burgers, chips, kebabs etc.) and takeaways (e.g., Chinese, Indian etc.). As discussed in Chapter 1, these convenience foods are a common component of the Western-style diet, and may be very high in fat. They are also typically lacking in fresh

ingredients, micronutrients and dietary fibre, and regular intake may be indicative of a poor overall dietary pattern.

4.3.2.1.1 DIETARY INFLAMMATORY INDEX

The FFQ data were also used to generate Dietary Inflammatory Index (DII) scores as a measure of diet quality in terms of its inflammatory potential. Ranging from + 7.98 to - 8.87, positive DII scores indicate a higher level of diet-derived inflammation and negative scores a more anti-inflammatory diet. Development of the DII has been described in detail elsewhere (Shivappa et al., 2014a) and more information is also provided in Chapter 3. Briefly, it is a literature-based score calculated from individual-level food parameter intakes obtained from standard dietary assessment tools (e.g., diet diaries, FFQs etc.), which are standardised to global intakes using worldwide reference data (mean $\pm$ *SD* in grams or micrograms etc.) for each parameter. The resulting standardised scores (*z*-scores) are converted to proportions/percentiles and centred, and then multiplied by an inflammatory effect score for each food parameter. Inflammatory effect scores were derived from a literature review of the inflammatory properties of 45 different food parameters, including micronutrients, macronutrients and whole foods (see Chapter 3 for table of the 45 food parameters and their inflammatory effect scores). All values are then summed to give an overall estimate of the inflammatory potential of the diet on an individual level. The index has been validated against plasma and cellular markers of inflammation (e.g., Shivappa et al., 2014b).

At least twenty food parameters are required to calculate DII scores, and for the current study, twenty-five variables from the EPIC-Norfolk FFQ were used, including fifteen micronutrients (vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, beta carotene, folic acid, iron, magnesium, niacin, selenium and zinc); eight macronutrients (cholesterol, total carbohydrate, total fat, fibre, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids and protein), alcohol and total energy.

4.3.2.2 MOOD

Mood was assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). This is a well validated measure of psychological distress, consisting of seven items relating to symptoms of anxiety (HADS-A) and seven to depressive symptoms (HADS-D) experienced over the previous week. The depression items focus mainly on anhedonic symptoms (Fiske et al., 2020). Responses are based on a four-point Likert-type scale with scores ranging from 0 to 3 for each item. Scores are summed separately for anxiety and depression to yield two global scores ranging from 0 to 21. Scores below eight indicate non-cases, 8 to 10 mild, 11 to 14 moderate, and 15 or more are indicative of severe cases. In terms of internal consistency, Cronbach's alpha is high, with .81 for HADS-D and .82 for HADS-A (Jack et al., 1987).

4.3.2.3 SLEEP QUALITY

Sleep quality was assessed using two well-validated scales: the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and the Epworth Sleepiness Scale (ESS; Johns, 1991). PSQI consists of nineteen questions about nocturnal sleep habits and sleep difficulties experienced over the previous month. Each item is rated on a four-point scale (0 – 3) ranging from "not during the past month" to "three or more times a week", and scored according to a protocol to yield seven subcomponent scores: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction. The seven subcomponent scores are summed to yield a global score ranging from 0 to 21, in which higher scores reflect poorer sleep quality; global scores greater than five indicate that sleep quality is inadequate. Global PSQI scores greater than five yielded a sensitivity of 89.6% and specificity of 86.5% for distinguishing adequate from inadequate sleep quality in the authors' original article (Buysse et al., 1989). Several studies have since assessed its reliability in different populations, and a relatively recent systematic review and meta-analysis reported Cronbach's alphas ranging from .70 to .83 (Mollayeva et al., 2016).

The Epworth Sleepiness Scale (Johns, 1991) is a well validated measure of daytime sleepiness/ sleep propensity. It consists of eight common daytime activities and scenarios (e.g., sitting and reading; in a car or bus while stopped for a few minutes in traffic) in which respondents rate their chance of "dozing off" under normal circumstances, "in recent times". Each item is scored on a four-point scale (0 – 3), ranging from "would never doze" to "high chance of dozing". Global scores range from 0 to 24, with scores over ten indicating excessive daytime sleepiness, and scores over twelve suggesting severe excessive daytime sleepiness. In terms

of internal consistency, a systematic review reported Cronbach's alphas ranging from .73 to .86 (Kendzerska et al., 2014).

4.3.2.4 PHYSICAL ACTIVITY

Physical activity levels were assessed using the International Physical Activity Questionnaire, long form (IPAQ; Craig et al., 2003; Hagströmer et al., 2006). This is a validated scale that measures physical activity and sedentary behaviour over the previous seven days. It consists of twenty-seven questions across five domains of activity: (1) job-related physical activity, (2) travel-related physical activity, (3) housework, house maintenance and caring for family, (4) recreation, sport and leisure-time physical activity and (5) time spent sitting. Responses are scored using a standardised protocol that categorises activity levels as either low, moderate, or high (The IPAQ Group, 2015. "Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire", www.ipaq.ki.se). Craig and colleagues investigated its reliability and validity across twelve countries, and reported that IPAQ had acceptable measurement properties, with Spearman's rho of .8 for repeatability and criterion validity, and a median rho of .3 (Craig et al., 2003).

4.3.3 DATA MANAGEMENT/STATISTICAL ANALYSES

The IBM SPSS Data Analysis version 28 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. An alpha level of .05 was set as the significance criterion for all statistical tests and reported *p* values are all 2-tailed.

The EPIC-Norfolk FFQ data were adjusted using the "residual method" (Willett & Stampfer, 1986) to generate intakes that are independent of total caloric intake. This allows estimation of intake without the potential confound of variations in total energy intake. Briefly, food parameter intakes (dependent variable) are regressed onto total calorie intake (independent variable), and the residuals form the energy-adjusted values (see Willett and Stampfer, 1986 for further details). Although the energy-adjusted residuals were used in all statistical tests involving FFQ data, the raw values (in grams) were quoted for mean/median intakes, to better illustrate actual food intakes.

The Dietary Inflammatory Index scores were also energy adjusted, via the "density method". This uses a global reference database, similar to the one used to calculate unadjusted DII, but in which the food parameters are expressed per 1,000 calories consumed. Thus, the energy adjusted ("E-DII") scores were calculated from twenty-four of the FFQ variables, i.e., all twenty-five listed in the previous section, but excluding energy.

Preliminary analyses consisted of an examination of the distributions; if non-normal distributions were observed, non-parametric tests were used to assess bivariate relationships. Data were also checked for outliers and missing values. Graham (2009)

suggested that if mean item scores are used to replace missing values in a scale, at least 50% of its components should be complete for it to remain valid. A more stringent approach was applied in the current study, due to the relatively large sample size. Thus, if fewer than 10% of values were missing from individual responses, these items were replaced by the mean score for that variable, or in the case of sleep duration, the mode was used. FFQ and DII data were excluded if participants reported extreme energy intakes (< 500 or > 4000 kcal/day), in line with widely used criteria (e.g., Katagiri et al., 2014). Descriptive statistics enabled the demographic, lifestyle and health characteristics of the sample to be described. Pearson's chi-square tests of independence and Fisher's exact tests were used to examine the relationship between dichotomous categorical variables such as sex and smoking status. Independent samples *t*-tests or Mann-Whitney U tests (where a non-parametric approach was indicated) tested for sex differences in continuous variables such as age, mood, sleep quality and diet quality, including E-DII scores.

To reduce the number of independent variables and identify mutually independent dietary patterns, principal components analysis (PCA) was carried out on the energy-adjusted EPIC-Norfolk FFQ variables (i.e., *Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products*, and *Meat and Meat Products*). The relationship between the dietary patterns that emerged as components, and the E-DII, mood and sleep variables, was then examined using multiple linear regression, with the dietary components as predictors. Where these tests of direct effects indicated the possibility of an indirect pathway between a dietary pattern and a mood or sleep variable via E-DII, Hayes' PROCESS procedure (version 4, http://www.afhayes.com) was used to test whether the indirect effect was significant. Together, the PCA and mediation analyses enabled evaluation of the impact of

emergent dietary patterns and other dietary behaviours (i.e., regular fast food intake), and their associated inflammatory potential, on the mood and sleep measures.

4.4 RESULTS

4.4.1 PARTICIPANT CHARACTERISTICS

4.4.1.1 DEMOGRAPHICS

A total of *N* = 180 complete survey responses were received. Demographic, lifestyle and health characteristics of the sample are summarised in Table 4.1

Table 4.1. Demographic, lifestyle and health characteristics of university staff [*N* = 180 unless stated].

Sex (%)	
Male	66 (36.7)
Female	114 (63.3)
Age (y)	
Range	23 - 66
Median	41
Education (%)	
Degree level or above	157 (87.22)
A/AS level	16 (8.89)
BTEC/GNVQ or equivalent	4 (2.22)
Other qualification(s)	3 (1.67)
Working status (%)	
Full time	147 (81.67)
Part time	33 (18.33)
Work role (%)	
Academic	44 (24.44)
Support	78 (43.33)
Administrative/Management	58 (32.22)
Smoking status (%)	
Smokers	15 (8.33)
Non-smokers	165 (91.67)
Withheld	2 (1.11)

Median cigarettes/day	5
Range	1 – 20
Alcohol consumption at least weekly (%)	
Yes	148 (82)
No	31 (17.22)
Withheld	1 (0.56)
Median units/week	12
Range	1 – 65
Physical activity (%) [*n* = 121]	
Low	6 (4.96)
Moderate	30 (24.79)
High	85 (70.25)
General health (%)	
Chronic illness (total)	40 (22.22)
Physical illness	29 (16.11)
Anxiety and/or depression	12 (6.67)
Withheld	6 (3.33)
Regular prescription medication	69 (38.33)

Preliminary analyses included Shaprio-Wilk and Kolmogorov-Smirnov tests of normality in conjunction with inspection of Q-Q plots. Only *E-DII* had an approximately normal distribution and a non-significant Kolmogorov-Smirnov test. Based on this, median rather than mean descriptive statistics are reported, and non-parametric tests (Spearman's rho) were used to examine bivariate relationships between variables.

Participants ranged from 23 to 66 years of age (*Mdn* = 41) and over half (63.3%) were female. The majority (92.22%) described themselves as White, so no further analysis of ethnicity was undertaken. Males were older (*Mdn* = 47) than females (*Mdn* = 39) and an independent samples Mann-Whitney U test revealed that this difference was statistically significant $U(N_{male} = 66, N_{female} = 114) = 4481$, $z = 2.14$, $p = .03$. The majority were educated to degree level or above (87.22%), and most worked full time (81.67%), describing their role as "support" (43.33%), "administrative/management" (32.32%) or "academic" (24.44%).

4.4.1.2 LIFESTYLE

8.33% of the sample were current tobacco smokers (*Mdn* = 5 cigarettes/day, range 1 – 20), which was below the national average figure of 13.8%, according to the latest (2020) official UK government figures for England (ons.gov.uk, 2021). A Pearson's chi-square test of independence revealed that males were more likely to be smokers than females, but with marginal significance, X^2 (1, N = 180) = 3.84, p = .05.

82% of the sample reported drinking alcohol at least weekly (*Mdn* = 20 units/week, range 1 – 65). 20.31% of drinkers consumed more than the UK government's recommended limit of 14 units per week. This is lower than the latest national figure of 24% (UK government National Statistics, 2020). A Pearson's chi-square test of independence revealed that the relationship between sex and alcohol intake was significant, and that males were more likely to consume above the recommended limit (X^2 (1, N = 180) = 7.85, p = .005).

Regarding physical activity, almost one third of the sample (32.78%) had a substantial amount of missing data. This meant that a total physical activity score could not be calculated for these individuals. Of the remainder, 70.25% had high weekly physical activity levels, 24.79% had moderate levels and only 4.96% had low levels of physical activity, according to the IPAQ scoring criteria. Given that academic work is primarily a sedentary activity, and over 80% of the sample worked full time, the high levels of physical activity in the current sample may be an overestimate. This, plus the substantial amount of missing data, meant that a decision was taken not to use the physical activity data in subsequent analyses.

4.4.1.3 GENERAL HEALTH

Healthwise, 22.22% of respondents were suffering from at least one diagnosed chronic illness (physical and/or mental) and 38.33% took regular prescription medications. The commonest class of drug was antidepressants, which 11.11% of the sample were taking. 16.11% declared chronic physical illnesses, of which asthma and osteoarthritis were commonest, followed by "back pain," then diabetes. There were no significant differences between males and females in terms of numbers suffering from chronic illnesses or taking regular medications. Two participants (1.15%) were suffering from diagnosed sleep disorders, namely obstructive sleep apnoea. The estimated prevalence of sleep apnoea in the UK is around 2.5 to 3% but remains uncertain because the majority of cases (up to 85%) are thought to be undiagnosed (Rejon-Parrilla et al., 2014). It is therefore likely that the case rate in the sample was higher than 1.15%, but that other cases were undiagnosed.

6.67% of respondents were suffering from diagnosed anxiety and/or depressive disorders. This is slightly lower than the latest national figures reported in the seven-yearly survey of mental health in England (Stansfeld et al., 2016), in which 7.8% of the general adult population had diagnosed mixed anxiety and depressive disorders, with higher rates in females. Contrary to the national figures, males in the current sample had higher rates of diagnosed anxiety and depression (58.33%) than females, but a Fisher's exact test revealed that this sex difference was not significant.

4.4.2 DIET AND DIET QUALITY

Independent samples Mann-Whitney U tests revealed that males consumed significantly more *Energy* (*Mdn* = 1684.69 kcal/day) than females (*Mdn* = 1525.97 kcal/day), $U(N_{male}= 66, N_{female} = 114) = 4603.00$, $z = 2.50$, $p = .01$. Following energy adjustment, males consumed significantly more *Meat and Meat Products*, (*Mdn* = 126.50 grams/day) than females (*Mdn* = 88.43 grams), $U(N_{male}= 66, N_{female} = 114) = 4724.00$, $z = 2.86$, $p = .004$). They also consumed significantly more *Carbohydrates* (*Mdn* = 194.04 grams/day) than females (*Mdn* = 174.46 grams/day), $U(N_{male}= 66, N_{female} = 114) = 3012.00$, $z = -2.23$, $p = .03$, and significantly more *Sugars* (*Mdn* = 89.28 grams/day) than females (*Mdn* = 82.55 grams/day), $U(N_{male}= 66, N_{female} = 114) = 3032.00$, $z = -2.17$, $p = .03$.

Diet quality was also assessed in terms of its inflammatory potential (*E-DII* scores), which was calculated from twenty-five of the Epic-Norfolk FFQ variables. If calculated from twenty-five to thirty food parameters, scores range from around -5.5 to +5.5 (Hébert et al., 2019). As stated above, scores were normally distributed and ranged from -4.73 (most anti-inflammatory) to +3.63 (most pro-inflammatory) with a mean of -0.62 (*SD* = 2.03). This range is in line with Hébert and colleagues' findings from over 160 published studies over four years, in which E-DII ranges rarely exceeded eleven (Hébert et al., 2019). Scores less than -3.0 are considered very anti-inflammatory, -3.0 to -1.01 are moderately inflammatory, scores of -1 to 0.99 are neutral, 1 to 3 are moderately pro-inflammatory and scores over 3 are very pro-inflammatory (Wirth et al., 2021). Hence, in the current sample, scores ranged from very anti-inflammatory to very pro-inflammatory, and the mean score was neutral. Scores were

not significantly associated with age and did not differ between males and females, so data were not stratified by sex.

4.4.3 MOOD

HADS-A scores ranged from 0 to 19 (possible range 0 – 21) with a median score of 8. Over half (55.56%) the sample scored on or above the clinical cut-off for anxiety (HADS-A scores $\geq$ 8). This is substantially higher than Breeman and colleagues' normative data, in which around 32% of a general population sample had clinically significant levels of anxiety (Breeman et al., 2015). *HADS-D* scores ranged from 0 to 18 (possible range 0 – 21) with a median score of 5. One quarter (25%) of respondents scored on or above the clinical cut-off for depressive symptoms (HADS-D scores $\geq$ 8). This is notably higher than normative HADS data from the largest UK population-based study of over 6,000 adults, in which approximately 16% scored above the clinical cut-off (Breeman et al., 2015).

Spearman's correlations indicated that *HADS-A* and *HADS-D* scores were strongly correlated (r_s = .65, p < .001, N = 180; see Table 4.2). As discussed in Chapter 1, anxiety and depression are often comorbid, (Kessler et al., 1996) so this was expected. HADS scores were not significantly associated with age, and independent samples Mann-Whitney U tests revealed that neither anxiety nor depression scores differed significantly between males and females, although rates are typically higher in women (Breeman et al., 2015; Stansfeld et al., 2016).

4.4.4 SLEEP QUALITY

PSQI-global scores ranged from 0 to 18 (possible range 0 – 21), with a median score of 6. Over half (58.33%) reported unsatisfactory sleep quality according to the clinical cut-off (global PSQI scores > 5). This is substantially higher than normative data from general population samples, including Austria (Zeitlhofer et al., 2000), Hong Kong (Wong & Fielding, 2011) and Germany (Hinz et al., 2017; Rahe et al., 2015), in which rates of unsatisfactory sleep (global PSQI scores > 5) were 32.1%, 39.4%, 35.9% and 34.7% respectively. The mean *PSQI-global* score (6.43, *SD* = 3.5) was also higher in the current sample compared to the four studies quoted above, which had mean global scores of 4.51, 5.3, 5 and 5.2 respectively. Regarding *Sleep Duration* specifically, only 32.22% of the current sample reported sleeping more than seven hours per night. Only 13.33% slept for eight or more hours, and although this is lower than Al-Sayegh and colleagues' previously reported figure of 25.1% in Kuwaiti university staff (Al-Sayegh et al., 2020), as discussed in Chapter 1, the recommended sleep duration for adults is 7 to 9 hours (Chaput et al., 2018).

Females typically report more problematic sleep than males (Hinz et al., 2017; Mong & Cusmano, 2016; Sander et al., 2016), but a Pearson's chi-square test of independence indicated that there were no significant differences in clinically significant symptoms in categorical data (PSQI scores > 5) between males and females in the current sample. Similarly, an independent samples Mann-Whitney U test revealed that there were no significant differences in *PSQI-global* scores between males and females in continuous data, and sleep quality was not significantly associated with age.

ESS scores ranged from 0 to 19 (possible range 0 – 24) with a median score of 6. 13.89% of the sample reported excessive daytime sleepiness according to the clinical threshold (scores >10). This is lower than some normative studies that used ESS, for example a community-based sample of circa 10,000 Germans, in which 23% of respondents reported excessive daytime sleepiness (Sander et al., 2016). According to a Pearson's chi-square test of independence, there were no significant differences in clinically relevant daytime sleepiness (scores > 10) between males and females in the current sample. Similarly, an independent samples Mann-Whitney U test indicated that levels of excessive daytime sleepiness did not differ significantly between males and females in continuous data. In line with the nocturnal sleep quality data, Spearman's correlations did not reveal any significant associations between daytime sleepiness and age. Nocturnal sleep quality (*PSQI-global* scores) and daytime sleepiness (*ESS* scores) were moderately correlated (r_s = .42, p < .001, N = 180). This was expected, as individuals reporting poor sleep quality are also likely to complain of daytime sleepiness, as a symptom of poor nocturnal sleep quality.

4.4.5 RELATIONSHIPS BETWEEN DIET QUALITY, MOOD AND SLEEP QUALITY

Non-parametric tests (Spearman's rho) were used to examine bivariate relationships between E-DII, mood and sleep quality variables, as illustrated in Table 4.2.

Table 4.2. Spearman's correlations between diet quality, mood and sleep quality in university staff (*N* = 180).

Correlations

			HADS-A	HADS-D	ESS	PSQI-global	E-DII	FAST FOOD
Spearman's rho	HADS-A	Correlation Coefficient	--					
		Sig. (2-tailed)	.					
		N	180					
	HADS-D	Correlation Coefficient	.645**	--				
		Sig. (2-tailed)	<.001	.				
		N	180	180				
	ESS	Correlation Coefficient	.353**	.360**	--			
		Sig. (2-tailed)	<.001	<.001	.			
		N	180	180	180			
	PSQI-global	Correlation Coefficient	.460**	.522**	.417**	--		
		Sig. (2-tailed)	<.001	<.001	<.001	.		
		N	180	180	180	180		
	E-DII	Correlation Coefficient	.161*	.236**	.103	.101	--	
		Sig. (2-tailed)	.031	.001	.168	.178	.	
		N	180	180	180	180	180	
	FAST FOOD	Correlation Coefficient	.199**	.174*	.135	.092	.191*	--
		Sig. (2-tailed)	.007	.020	.070	.219	.010	.
		N	180	180	180	180	180	180

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4.2 indicates that both mood variables were related to sleep quality. Individuals with higher levels of anxiety (*HADS-A* scores) and depression (*HADS-D* scores) had significantly higher levels of daytime sleepiness (*ESS* scores) and poorer sleep quality (*PSQI-global* scores). These results reflect well-established published evidence highlighting a bidirectional relationship between mood and sleep, as discussed in Chapter 2.

E-DII scores were positively correlated with both HADS scores. Thus, respondents with higher levels of diet-derived inflammation had significantly higher levels of anxiety and depression.

This is in line with recent systematic reviews and meta-analyses demonstrating a robust relationship between dietary inflammation and mood (Chen et al., 2021; Wang et al., 2019), as discussed in Chapter 3.

E-DII scores did not correlate significantly with either sleep quality measure (*ESS* or *PSQI-global*), or with PSQI subcomponent scores in continuous data (subcomponent data not shown). In terms of the clinical thresholds for daytime sleepiness (*ESS* > 10) and nocturnal sleep quality (*PSQI-global* > 5), these were not significantly related to continuous *E-DII* scores (data not shown). Similarly, in categorical data, individuals in the highest quartile of dietary inflammation (*E-DII* scores > 0.91) compared to those in the lowest (*E-DII* scores $\leq$ -2.36), did not differ significantly in terms of sleep quality indices (data not shown).

Fast Food correlated positively with *E-DII* scores, indicating that consuming this type of food on a regular basis was a pro-inflammatory dietary behaviour. *Fast Food* also correlated positively with both HADS scores, demonstrating that regular consumption was associated with significantly worse mood, in terms of both depressive and anxiety symptoms.

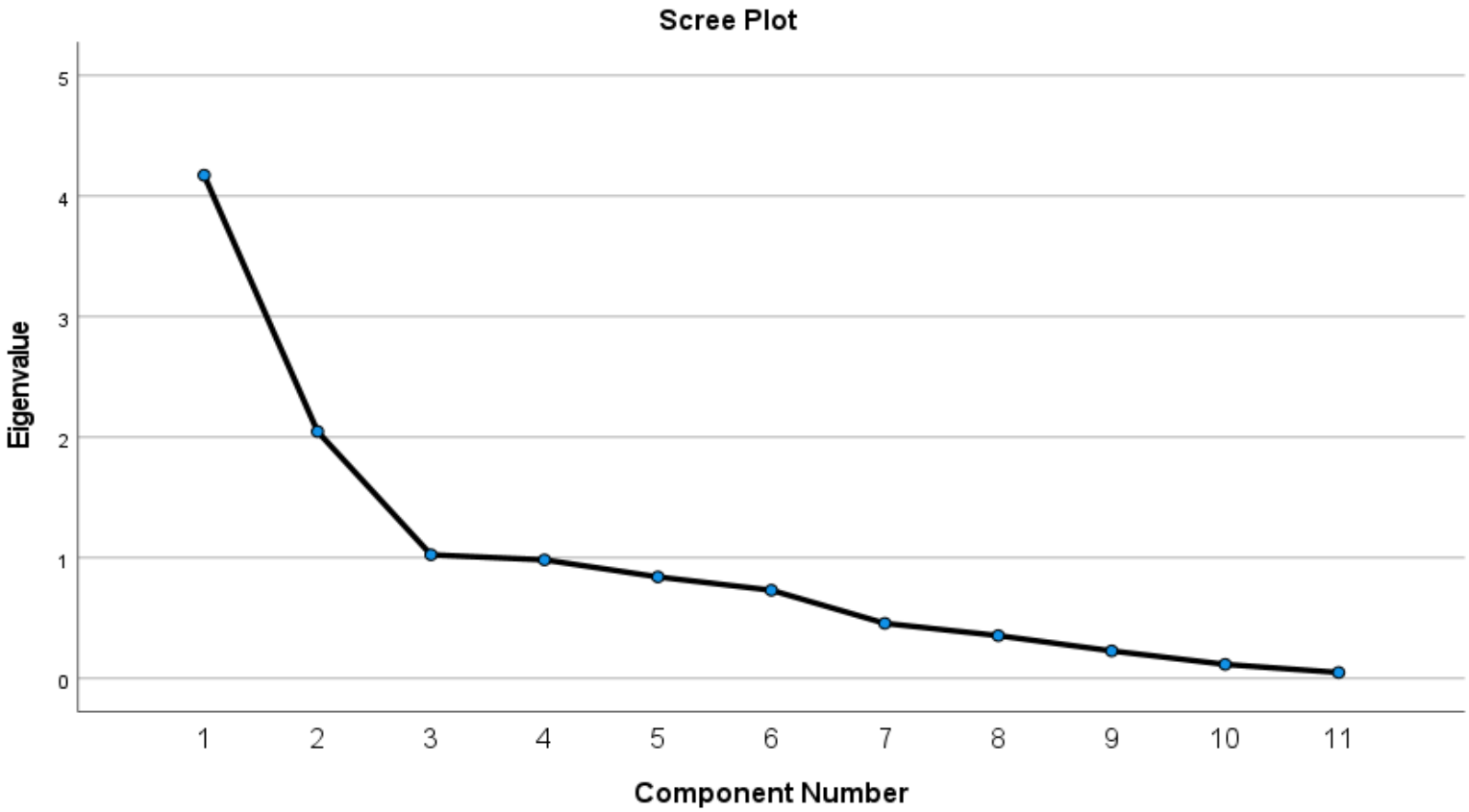
Given that regular intake of *Fast Food* was a pro-inflammatory dietary behaviour and both *Fast Food* and *E-DII* scores correlated positively with HADS scores, it was possible that the association between regular *Fast Food* intake and poor mood was driven by the pro-inflammatory properties of fast food. To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) model 4, with 5000 bootstrap samples, with *Fast Food* as the predictor, *E-DII* as mediator, and either *HADS-A* or *HADS-D* as the outcome variable. Mediation analysis confirmed the direct relationship between *Fast*

Food and *HADS-D* (direct effect = 2.45, 95% CI [0.42, 4.49]), and between *Fast Food* and *HADS-A* (direct effect = 2.71, 95% CI [0.43, 4.99]). Moreover, the indirect pathway, via *E-DII*, was also significant between *Fast Food* and *HADS-D* (indirect effect = 0.45, 95% CI [0.02, 1.04]), but there was no indirect pathway between *Fast Food* and *HADS-A*. Thus, the association between regular fast food intake and depressive (but not anxiety) symptoms was partially mediated by the pro-inflammatory properties of this dietary behaviour.

4.4.6 EXTRACTION OF DIETARY PATTERNS

To identify mutually independent patterns in the FFQ data, principal components analysis with Varimax rotation was conducted on the energy-adjusted variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products* and *Meat and Meat products*). Bartlett's test of sphericity assessed the significance of all the correlations within the correlation matrix, and indicated that the data were suitable for PCA (approx. chi-square$_{(55)}$ = 1184.52, $p < .001$). The Kaiser-Meyer-Olkin (KMO) test returned a value of 0.59, which met the minimum acceptable value for adequate sampling.

Figure 4.1. Scree plot showing eigenvalues of principal components (*N* = 180).



A criterion of eigenvalues > 1 suggested a three-component model, which was also indicated graphically. The rotated component matrix is shown in Table 4.3.

Table 4.3. Rotated component matrix[a] with dietary loadings (*N* = 180).

	Component		
	1	**2**	**3**
Dietary variables[b]	***HI-FRUIT-LO-FATS***	***MEDITERRANEAN***	***HI-MEATS-LO-CARBS***
Carbohydrates (total)	**.690**	-.229	**-.571**
Cholesterol	-.079	.153	**.748**
Fibre	**.634**	**.601**	**-.338**
Sugars (total)	**.626**	**-.349**	**-.338**
MUFA	**-.872**	.040	.040
PUFA	-.279	**.711**	.157
SFA	**-.722**	**-.318**	-.025
Fish and Fish Products	.035	**.456**	.370
Fruit	**.698**	.087	-.210
Meat and Meat Products	-.241	-.195	**.770**
Vegetables	.385	**.736**	-.189

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids
a. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 7 iterations.
b. All EPIC-Norfolk FFQ variables adjusted for total energy intake (residual method).

The three components extracted explained 65.86% of the total variance in the model, and were labelled according to the salient features of their loadings. In Component 1, *Fruit* was the highest positively-loading variable, followed by *Carbohydrates*, *Fibre* and then *Sugars*; the fats (especially *MUFA* and *SFA*) loaded negatively onto Component 1. Thus, this component/dietary pattern was labelled *HI-FRUIT-LO-FATS*. *Vegetables, PUFA, Fibre* and *Fish* loaded positively, while *Sugars* and *SFA* loaded negatively onto Component 2, so this component/dietary pattern was labelled *MEDITERRANEAN,* given its similarities to a Mediterranean-style dietary pattern. Component 3 was named *HI-MEATS-LO-CARBS*, along similar lines.

4.4.6.1 DIETARY PATTERNS AND THEIR INFLAMMATORY POTENTIAL

To test the possibility that the dietary patterns were directly related to *E-DII,* a multiple linear regression analysis was conducted, with the three principal dietary components as predictors and *E-DII* as the outcome variable. The *HI-FRUIT-LO-FATS* (β = -.54, $p < .001$) and *MEDITERRANEAN* (β = -.61, $p < .001$) components were strongly associated with *E-DII* scores, accounting for 66% of the variance in the model (adjusted $R^2 = .66$, $F_{(3,176)} = 159.76$, $p < .001$). High scores on both components were associated with significantly lower *E-DII* scores, indicating that they were both anti-inflammatory dietary patterns. The *HI-MEATS-LO-CARBS* component was not significantly associated with *E-DII,* so this component was neither a pro- nor anti-inflammatory dietary pattern in this model.

4.4.6.2 DIETARY PATTERNS AND MOOD

To test the possibility that the dietary patterns were directly related to mood, separate multiple linear regressions were conducted with the three principal dietary components as predictors and either *HADS-A* or *HADS-D* as the outcome variable. None of the models were significant, indicating that there were no direct relationships between dietary patterns and mood in this sample. However, given that *HI-FRUIT-LO-FATS* and *MEDITERRANEAN* were anti-inflammatory dietary patterns, and *E-DII* scores correlated positively with *HADS-A* and *HADS-D* scores, it was possible that these two dietary patterns were indirectly related to mood, via their anti-inflammatory properties.

To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) model 4, with 5000 bootstrap samples as before, with either *HI-FRUIT-LO-FATS* or *MEDITERRANEAN* as the predictor, *E-DII* as mediator, and either *HADS-A* or *HADS-D* as the outcome variable. As indicated by the regression analysis, there was no direct relationship between *HI-FRUIT-LO-FATS* and *HADS-D*, but the indirect pathway, via *E-DII*, was significant (indirect effect = -0.43, 95% CI [-0.88, -0.03]). There was no direct or indirect pathway between *HI-FRUT-LO-FATS* and *HADS-A*, or between *MEDITERRANEAN* and *HADS-A*. As illustrated by the regression, there was no direct effect of *MEDITERRANEAN* on *HADS-D*, but the indirect pathway, via *E-DII*, was significant (indirect effect = -0.6, 95% CI [-1.12, -0.09]). Thus, both dietary patterns protected against depression, which in this model, was driven entirely by their anti-inflammatory properties.

4.4.6.3 DIETARY PATTERNS AND SLEEP

To test the possibility that the dietary patterns were directly related to sleep quality, separate multiple linear regressions were conducted, with the three principal dietary components as predictors and sleep quality indices as outcome variables. None of the models with *PSQ-global* or its subcomponents were significant. However, with *ESS* as the outcome variable, the model was significant. *HI-FRUIT-LO-FATS* was associated with significantly lower *ESS* scores (β = -.20, p = .01) and accounted for 3.40% of the total variance in the model (adjusted R^2 = .034, $F_{(3,176)}$ = 3.09, p = .03). Potential mediation via *E-DII* was not tested, because *E-DII* was not directly related to *ESS* (see Table 4.2). Thus, the *HI-FRUIT-LO-FATS* was protective

against daytime sleepiness, but not via the anti-inflammatory properties of this dietary pattern.

4.4.7 ADJUSTMENTS FOR POTENTIAL COVARIATES AND CONFOUNDERS

Several factors, including age, sex and health status, could be related to the diet, mood and sleep variables and therefore potentially confound the observed relationships. Spearman's correlations revealed that there were no statistically significant relationships between age and the dietary (i.e., E-DII, principal components), mood and sleep quality variables in continuous data.

In terms of health status, cardiovascular disease, and chronic diseases associated with pain, such as musculoskeletal conditions (osteoarthritis, chronic "back pain" etc.) could covary with mood and sleep. No participants declared that they were suffering from cardiovascular disease, but eight were taking cardiovascular system drugs (e.g., anti-hypertensives, statins), presumably for primary prevention in the presence of risk factors such as hypertension and hypercholesterolaemia. Therefore, a categorical variable, *Cardiovascular System Drugs* (yes/no) was created. Similarly, a categorical variable *Chronic Musculoskeletal Disorders* (yes/no) was created.

Independent samples Mann-Whitney U tests examined relationships between categorical variables (e.g., sex, health status variables) and the continuous diet quality (i.e., E-DII, principal components), mood and sleep quality scores. Sex was not significantly associated

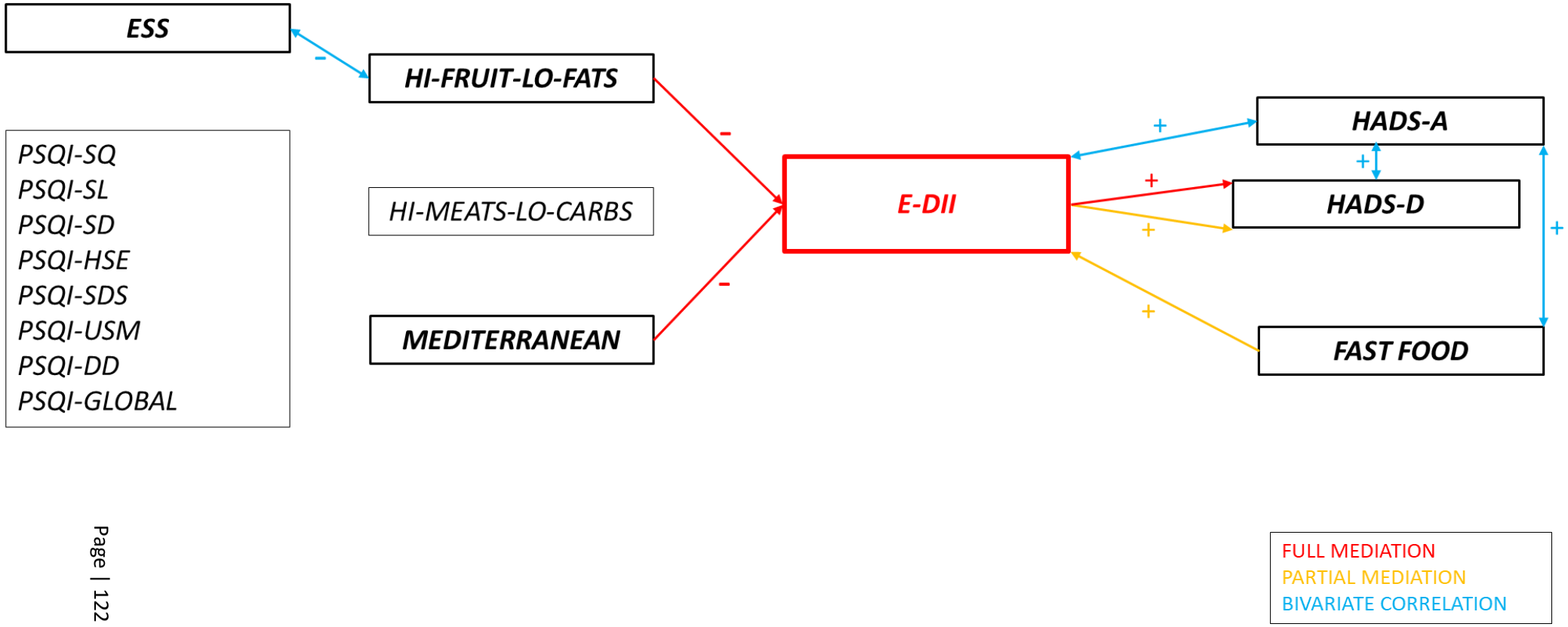
with the continuous variables. Both health status variables were associated with increasing age, but they were not related to the mood and diet quality variables. Neither were they associated with ESS or PSQI-global scores, but of the PSQI subcomponents, those who took cardiovascular system drugs had significantly shorter sleep duration than individuals not taking these drugs. Further, those declaring chronic musculoskeletal conditions had significantly more sleep disturbance than those without musculoskeletal conditions. However, none of the continuous independent dietary variables (i.e., E-DII scores, principal components) were related to *Sleep Duration* or *Sleep Disturbance,* so no statistical adjustments were made for health status.

Pearson's chi-square tests of independence revelated that there were no significant differences between the categorical diet quality variable *Fast Food* and the two health status variables, or sex, and an independent samples Mann-Whitney U test indicated that there was not a significant association between fast food intake and age.

Although physical activity levels could also be related to diet quality, mood and sleep quality, as discussed above, significant problems with the IPAQ data meant that these relationships could not be examined.

Results of Study 1 analyses are summarised in Figure 4.2.

Figure 4.2. Schematic showing significant pathways linking diet quality, mood and sleep quality variables in day and night shift workers (for clarity expected sleep-sleep and sleep-mood relationships not shown).



SQ = Sleep Quality; SL = Sleep Latency; SD = Sleep Duration; HSE = Habitual Sleep Efficiency; SDS = Sleep Disturbances; USM = Use of Sleeping Medication; DD = Daytime Dysfunction.

4.5 DISCUSSION

The aim of Study 1 was to investigate potential mechanisms linking diet, mood and sleep, in a sample of *N* = 180 university employees working standard daytime hours. The primary hypothesis was that diet-derived inflammation is one of the mechanisms that connects diet quality to both mood and sleep quality.

Principal components analysis was used to extract mutually independent dietary patterns from eleven individual macronutrients/food groups that were selected to cover the major dietary constituents. This approach identified three different dietary patterns in the data, two of which had significant anti-inflammatory properties, evidenced by strong negative associations with *E-DII* scores. Conversely, regular intake of fast food was shown to be a pro-inflammatory dietary behaviour, via a significant positive association with *E-DII* scores.

The three principal components of diet were not directly related to mood. However, in support of the main hypothesis, higher intakes of two of the three (*HI-FRUIT-LO-FATS* and *MEDITERRANEAN*) were indirectly related to better mood (less depression), and in the current model this relationship was mediated entirely by the anti-inflammatory properties of these two dietary patterns.

The dietary components that appeared to be protective of mood via their anti-inflammatory properties loaded positively towards fruit, vegetables, carbohydrates, fibre, fish and

polyunsaturated fats, and negatively towards saturated and monounsaturated fats. As well as its high positive loading towards *Fruit*, the *HI-FRUIT-LO-FATS* component also loaded positively towards *Sugars,* suggesting that diets **high** in *Sugars* are anti-inflammatory, yet the *MEDITERRANEAN* pattern loaded negatively towards *Sugars,* suggesting that diets **low** in *Sugars* are anti-inflammatory. This appears to be contradictory, but it may simply reflect the high sugar content of fruit. The highest loading in the *HI-FRUIT-LO-FATS* pattern came from *Fruit*, so it is not surprising that this component also loaded highly towards *Sugar*, because fruit contains relatively high levels of sugar. Conversely, the *MEDITERRANEAN* pattern did not feature *Fruit* all – the highest loading came from *Vegetables*, which contain relatively low levels of sugar – and this dietary pattern loaded negatively towards sugar. This indicates that it is fruit and vegetables, rather than sugar, that protect mood via their anti-inflammatory properties. As discussed in Chapter 3, fruit and vegetables contain high levels of vitamins, minerals and antioxidants (e.g., flavonoids and polyphenols) which may contribute towards the anti-inflammatory properties of the two dietary patterns (Crispo et al., 2021; de Mello et al., Harms et al., 2020; Huang et al., 2019).

Both the *HI-FRUIT-LOW-FATS* and *MEDITERRANEAN* dietary patterns loaded positively towards *Fibre.* Fruit (in *HI-FRUIT-LOW-FATS)* and vegetables (in *MEDITERRANEAN*) both contain high levels of dietary fibre. As discussed in Chapter 3, fibre may exert anti-inflammatory effects by promoting eubiosis of the intestinal microbiota, favouring microbial species with anti-inflammatory actions (Berk et al., 2013; Young et al., 2021).

The *MEDITERRANEAN* dietary pattern loaded highly towards *PUFA* and *Fish and Fish Products*. As discussed, oily fish is high in omega-3 PUFA which also has anti-inflammatory properties

(de Mello et al., 2011) via down-regulation of the NF-kappaB pathway (Balta et al., 2021; Li et al., 2020; Rogero & Calder, 2018) and production of anti-inflammatory and inflammation-resolving eicosanoids (e.g., resolvins and protectins) (Balta et al., 2021; Souza et al., 2020).

In contrast to the positive *PUFA* loading, *HI-FRUIT-LOW-FATS* loaded negatively towards *MUFA* and *SFA,* and *MEDITERRANEAN* also loaded negatively towards *SFA*. These dietary patterns were therefore relatively low in pro-inflammatory saturated fats. As discussed, saturated fats exert their pro-inflammatory effects by upregulating the NF-kB pathway, which switches on the expression of a wide range of pro-inflammatory cytokines (Fritsche, 2015).

In contrast to the apparent protective effects of the *HI-FRUIT-LOW-FATS* and *MEDITERRANEAN* dietary patterns*, Fast Food* was associated with higher levels of depression in the current sample. Consumption of one or more fast food or takeaway meals per week was a pro-inflammatory dietary behaviour, and its relationship with mood was partially mediated by *E-DII.* As discussed in Chapter 1, fast food may be high in saturated and *trans* fats, both of which have highly pro-inflammatory DII effect scores (Shivappa et al., 2014a). In the current sample, fast food intake correlated positively with energy-adjusted saturated fat intake (r_s = .15, p < .04, N = 180), but not with any of the healthier unsaturated fats. Unfortunately, it was not possible to test whether fast food intake was associated with *trans* fat intake, because the EPIC-Norfolk FFQ does not provide data on *trans* fat intake.

In terms of diet/sleep relations, higher intakes of *HI-FRUIT-LO-FATS* was associated with significantly less daytime sleepiness (*ESS*), although this relationship was not mediated by *E-DII*. Thus, the apparent protective effect of *HI-FRUIT-LO-FATS* over daytime sleepiness was

driven by something other than the anti-inflammatory properties of this dietary pattern, so a discussion of alternative mechanisms is warranted.

HI-FRUIT-LO-FATS loaded positively towards *Carbohydrates*. Carbohydrate has a positive DII effect score (+0.097), which supports the fact that the association between *HI-FRUIT-LO-FATS* and *ESS* was not driven via the anti-inflammatory properties of this dietary pattern. However, carbohydrate may increase tryptophan availability (Doherty et al., 2019). Tryptophan is an essential amino acid and precursor of the neurotransmitter serotonin and the neurohormone melatonin, both of which are involved in regulating the sleep-wake cycle, so increasing tryptophan availability may help to regulate sleep patterns and to enhance the synthesis of endogenous sleep-promoting substances such as melatonin. This, in turn, may contribute towards the lower levels of daytime sleepiness observed with higher intakes of *HI-FRUIT-LO-FATS.*

HI-FRUIT-LO-FATS also loaded positively towards *Fibre*. High fibre diets promote gut health and modulate the composition of the gut microbiome. Some microbial species synthesise acetylcholine, gamma-amino butyrate (GABA), noradrenaline, dopamine and serotonin (Cryan & Dinan, 2012; Kaur et al., 2019), all of which are involved in regulation of the sleep-wake cycle (Kesner & Lovinger, 2021; Watson et al., 2010). Gut microbes act as sources of these essential neurotransmitters in the central nervous system (Kaur et al., 2019), although the exact mechanisms underlying their interaction with the brain are still under investigation (Kaur et al., 2019). Further, certain gut microbial metabolites (e.g., the short chain fatty acid butyrate) have been found impact serotonin secretion from intestinal cells (Reigstad et al., 2015).

The secondary aim of Study 1 was to test the consistency of the current data against known two-way relationships, as a measure of the reliability of the data. Thus, it was hypothesised that sleep quality would be strongly associated with mood, on the basis of robust published evidence. In support of this, poorer nocturnal sleep quality was strongly correlated with depressive symptoms and moderately correlated with symptoms of anxiety in the current sample; daytime sleepiness was also moderately correlated with both depression and anxiety. Further, as expected, shorter sleep duration was significantly associated with poorer mood. This is important in the context of the current sample, in which the vast majority of participants slept for less than the recommended eight hours per night. These findings suggest that the current data are reliable, as they are consistent with a robust evidence base of published work.

Neither daytime sleepiness nor nocturnal sleep quality were significantly associated with age in the current sample. Self-reported sleep quality typically changes with age, with older individuals reporting poorer sleep (Schwarz et al., 2017), although not in all studies (Hinz et al., 2017). In the current sample, participants were predominantly in their forties, as they were all working age. The mean age was 42.17 (*SD* = 12.57), so the data were also relatively narrowly dispersed. This demographic may explain why age-related differences in sleep quality were not observed in this exclusively working-age sample.

To my knowledge, this is the first study to investigate Dietary Inflammatory Index in university staff. The absence of research published in this workforce, and paucity of DII studies in the UK population as a whole makes it difficult to consider the current results in a broader context and to compare them with population norms. In one of the few studies to be conducted in a

non-shift working UK workforce, Akbaraly and colleagues (2016) used data from the Whitehall II study to assess DII and recurrent depressive symptoms in *N* = 4246 office workers. Whitehall II is a longitudinal study of desk-based civil servants working in Whitehall, London, aged 35 to 55 years at baseline (Marmot & Brunner, 2005). Akbaraly reported mean DII scores of -0.03 (*SD* = 1.3), range -3.35 to +4.23 in men, and -0.002 (*SD* = 1.4), range -3.35 to +3.98 in women. Thus, overall DII scores in the current sample are slightly more anti-inflammatory than the Whitehall II study, suggesting that university staff may have healthier dietary habits than other office-based workers of a similar age range. This may be attributable to the high levels of education in the university sample, in which 87% were educated to degree level or above.

The final hypothesis of Study 1 was that due to the demands of their work, university workers would report poorer mood than that observed in the general population. With 55.56% of respondents scoring on or above the clinical cut-off for anxiety (HADS-A $\geq$ 8), this is substantially higher than Breeman and colleagues' general population sample, in which 32% scored above the clinical threshold for anxiety (Breeman et al., 2015). However, they had almost exactly the same levels as Kinman's poll of over 6000 UK academics, in which around 55% suffered from symptoms of poor mental health (Grove, 2018). One-quarter of the current sample scored on or above the clinical cut-off for depression (HADS-D $\geq$ 8), which is also notably higher than Breeman's general population sample, in which 16% reported depressive symptoms above the clinical threshold (Breeman et al., 2015). Thus, the current findings support the hypothesis that symptoms of anxiety and depression in university employees are well in excess of general population rates.

Despite the high rates of clinically significant symptoms identified by HADS (mean 40.28% anxiety and depression combined), the rate of *diagnosed* anxiety and/or depressive disorders was only 6.67% in the current sample. The large discrepancy between the two suggests that there were substantial numbers of undiagnosed, but clinically significant cases of anxiety and depression in the sample. Furthermore, circa 11% of respondents reported taking prescribed antidepressants, which is at odds with the 6.67% who declared having diagnosed anxiety and/or depressive disorders. This discrepancy may be because patients on established antidepressant therapy may have remission of their symptoms and therefore not report that they are "currently" suffering from an anxiety or depressive disorder. An alternative explanation is that some of the antidepressants declared (amitriptyline in particular, an older generation tricyclic antidepressant), were prescribed off-licence for indications other than mood disorders, for example neuropathic pain syndromes, migraine or fibromyalgia.

Results should be interpreted with methodological limitations in mind, and those that applied across all three studies will be discussed in the final chapter. With regard to Study 1 specifically, it was assumed that the university staff worked standard (9 – 5) daytime hours. However, a growing student population and ever-increasing workload may force some, particularly those in academic roles, to work longer than a standard eight-hour day (personal observation!). That said, they do not work 12-hour shifts, or the night shift – this workforce will be the focus of Study 2.

5 STUDY 2: DIET, MOOD AND SLEEP IN A SAMPLE OF SHIFT WORKERS

5.1 INTRODUTION

Almost 20% of the UK workforce is employed in regular night shift work (Reynolds et al., 2017), which is defined as regularly working "outside the hours of 7 am to 7 pm in your (main) job" (Weston, 2013). According to the Trades Union Congress, the number of people working night shifts has increased by 5% since 2013, and night work now accounts for one in nine (11.5%) of the total UK workforce (Trades Union Congress, 2018). Shift workers are exposed to numerous challenges, including but not limited to, psychological stress, fatigue, sleep disturbance, chronic sleep loss and social and circadian misalignment. Strong evidence links long-term night work with the vast majority of non-transmissible, chronic inflammatory conditions, including obesity (Liu et al., 2018), metabolic disease (Wang et al., 2014; Wirth et al., 2014b) cardiovascular (Knutsson, 2003; Sookoian et al., 2007; Zhao et al., 2012; Barbadoro et al., 2013 Vyas et al., 2012) and gastrointestinal disease (Knutsson & Bøggild, 2010), some cancers (e.g., breast cancer: Szkiela et al., 2020), and depression (Brown et al., 2020; Lee et al., 2017). However, the increased risk, and relative contribution of diet to these inflammatory outcomes is poorly understood (Szkiela et al., 2020; Wirth et al., 2014b). Night work is associated with poor diet, higher rates of depression, poor quality sleep, and increased risk of inflammatory disease. Thus, this workforce is particularly relevant to the current research,

and Study 2 focusses on a sample of shift workers, including night workers. The following section summarises what is known about diet, mood and sleep in this group. This provides the relevant background information and builds a rationale towards the hypotheses, aims and objectives of Study 2.

5.1.1 DIET IN SHIFT WORKERS

Overweight and obesity is a consistent finding among regular night workers (Buchvold et al., 2015; Liu et al., 2018; Ramin et al., 2015). In contrast, research into dietary behaviours and overall diet quality in shift workers is conflicted (Shan et al., 2018). Some studies report poorer eating habits (Ferri et al., 2017; The PLoS Medicine Editors, 2011) such as higher saturated fat intakes (e.g., +10%) (Esquirol et al., 2009) and lower fruit and vegetable consumption in night workers compared to fixed day workers (e.g., Weston, 2013). Others report overeating (Lowden et al., 2010) and increased snacking in shift workers (Waterhouse et al., 2003). However, a systematic review and meta-analysis found significant heterogeneity in dietary methods across studies, and concluded that there were no differences in energy intake between night shift workers and fixed day workers (Bonham et al., 2016). A review of studies in nurses found poorer quality diets and higher snack intakes in night shift workers compared to day workers, but again, heterogeneity in dietary assessment methods made studies difficult to compare (Pepłońska et al., 2019). As well as the obvious differences in meal timings when working nights, the availability of freshly cooked meals is likely to limited, because workplace canteens and other vendors of fresh foods tend not to operate at night

(Antunes et al., 2010). This may explain, at least partly, the increased rates of snacking observed in night shift workers (Waterhouse et al., 2003).

Regarding the inflammatory potential of shift workers' diets, in one of the first studies to use the (then novel) Dietary Inflammatory Index, Wirth and colleagues examined the relationship between DII and metabolic syndrome in police officers working day shifts (*n* = 6198), evening/nights, and rotating shifts (*n* = 1445) (Wirth et al., 2014b). After adjusting for demographic factors, perceived health status and physical activity, all police shift workers, especially those with rotating shift patterns, had significantly higher (i.e., more pro-inflammatory) DII scores than non-shift working day workers. The authors reasoned that the pro-inflammatory diets of shift workers are likely to contribute to the increased risk of chronic inflammatory disease they face compared to non-shift workers. However, no adjustments were made for other inflammation-related outcomes, such as obesity and cardiovascular disease. In a subsequent study by the same group, this time assessing depressive symptoms, average DII scores were approximately 32% higher in shift workers compared to non-shift working day workers (Wirth et al., 2017). As well as adjusting for demographic, perceived health and physical activity, in line with the 2014 study, the 2017 study adjusted for a range of inflammation-related confounders, including smoking status, family history of smoking, average sleep duration, current infection status, arthritis and past medical history of cancer, although no adjustments were made for cardiovascular disease. In a recent longitudinal study of police officers by the same group (Wirth et al., 2021), higher DII scores at baseline were associated with more actigraphic wake-after-sleep-onset (i.e., poorer objective sleep quality) but lower global PSQI scores (i.e., better subjective sleep quality). Similarly, at follow up (15 years), increasing DII scores were associated with more actigraphic wake-after-sleep-onset,

but lower global PSQI scores, as before. These apparent contradictions are consistent with other studies reporting that objective and subjective measures of sleep quality do not always coincide (e.g., Baker et al., 1999; Lauderdale, 2008). The study controlled for variables identified as confounders, including depression, anxiety and cardiovascular disease risk factors. In summary, it appears that shift work (day and night shifts) is associated with poorer diet quality and higher DII scores than non-shift working schedules, but more research is needed, especially studies investigating the inflammatory potential of shift workers' diets.

5.1.2 MOOD IN SHIFT WORKERS

Some studies report that night shift workers have poorer mental health and higher rates of anxiety and depression than their day working colleagues (e.g., Bara & Arber, 2009; Weston, 2013). In contrast, some reviews claim that evidence linking night work to the development of mental illnesses is limited (Amlinger-Chatterjee, 2016; Angerer et al., 2017). However, a meta-analysis of five prospective studies found a 42% increased risk of depression in night shift workers (Angerer et al., 2017). This may in part be due to psychosocial stress (e.g., social isolation and disrupted family life) and acute and chronic exhaustion (Amlinger-Chatterjee 2016; Angerer et al., 2017) experienced by night shift workers. Of particular interest is Wirth and colleagues' investigation of depression and DII in shift workers (reported above). Those engaged in any form of shift work were at higher risk of mild depression than non-shift working day workers, and this relationship was partly mediated by DII (Wirth et al, 2017).

5.1.3 SLEEP IN NIGHT SHIFT WORKERS

Shift workers with non-daytime schedules tend to report significantly shorter sleep duration than non-shift working day workers (Wirth et al., 2014a; Brown et al., 2020). Achieving adequate sleep during the day rather than at night, is a significant challenge, both physically and psychologically. The circadian system, synchronised with exogenous environmental cues such as the light-dark cycle, promotes activity during daylight hours and rest/sleep at night (Boivin & Boudreau, 2014; Richardson, 2005). Inverting this natural rhythmicity by working at night and trying to rest/sleep during the day is a significant risk factor for genetic dysregulation and desynchronisation of the circadian system (Ferri et al., 2017; Sookoian et al., 2007). Chronobiological adaption of the sleep-wake cycle is usually inadequate because the environmental influencers are dominant (Knauth, 2007; Tucker et al., 2010).

Studies of subjective sleep quality in night shift workers report poorer sleep quality (PSQI), more sleep disturbance, shorter sleep duration, longer sleep latency and more daytime dysfunction compared to day workers (Lim et al., 2020). A recent review and meta-analysis of studies of objective (actigraphic) measures of sleep quality found that night workers had longer sleep latencies and more episodes of wake-after-sleep-onset than day shift workers (Chang & Peng, 2021). This could in part be due to more noise (e.g., telephones, doorbells, family) in the home whilst trying to sleep during the day. In contrast to Lim and colleagues' findings of shorter sleep duration (above), night workers had longer total actigraphic sleep time than day workers, suggesting that they were able to adapt their sleep, at least partially (Chang & Peng, 2021).

5.2 AIMS AND OBJECTIVES

The overarching aim of the thesis was to investigate potential mechanisms linking diet, mood and sleep. As discussed, night shift work is associated with increased risk of chronic inflammatory disease, but how shift work, and diet in shift workers, contributes towards this is poorly understood (Szkiela et al., 2020). The current study hypothesised that in a sample of day and night shift workers, diet-derived inflammation is one of the mechanisms that connects diet quality to both mood and sleep quality.

Further analyses relate to hypothesised differences between day and night shift workers. Given the dietary challenges faced by night workers, it is predicted that there will be significant differences in diet quality between regular day workers and their night working counterparts. Dietary Inflammatory Index, as a measure of diet quality, is hypothesised to be significantly higher (more pro-inflammatory) in night shift workers compared to day staff. Given the increased rates of obesity (Proper et al., 2016) and other chronic inflammatory conditions in shift workers (Szkiela et al., 2020), it is also hypothesised that regular night workers will have significantly higher rates of obesity and diagnosed chronic inflammatory disease than regular day workers. Similarly, given that sleeping during the day presents significant physical and psychosocial challenges, a further hypothesis is that sleep quality and mood will be significantly poorer in night workers compared to those working the day shift.

5.3 MATERIALS AND METHODS

5.3.1 STUDY SAMPLE

Participants were over the age of 18 and employed by Derbyshire Police Constabulary, UK. No other eligibility criteria were applied, such as work role or shift work status, sleep complaints or diagnosed sleep disorders, mood disorders or other mental or physical illnesses. Similarly, there were no requirements regarding diet.

5.3.2 STUDY DESIGN AND DATA COLLECTION

The overall design was the same as Study 1, i.e., a cross-sectional, retrospective analysis of diet quality, mood and sleep quality. It was approved by Nottingham Trent University Research Ethics Committee and all participants provided written, informed consent. Participation was voluntary and anonymous, and staff were invited to take part by email. As before, the study consisted of a self-administered survey, hosted via the online survey platform Qualtrics (Provo, Utah, USA), and included a battery of validated self-report instruments. The 35-item demographics/lifestyle/health questionnaire that was devised for Study 1 was also included, but questions about height and weight were added (for BMI calculation). In addition, shift work status was ascertained with a question relating to the

frequency of night shift work (i.e., “most or all of the time”, “frequently”, “occasionally” or “never”).

5.3.2.1 DIET AND DIET QUALITY

Dietary data were collected using the semi-quantitative food frequency questionnaire (FFQ) developed for the European Prospective Investigation into Cancer and Nutrition Norfolk (EPIC-Norfolk) study (Bingham et al., 2001). This was also used in Study 1, and further details were provided in Chapter 4. As before, the current study focussed on the following seven macronutrient variables (grams/day): total *Carbohydrates*, total *Sugars*, *Fibre*, *MUFA*, *PUFA*, *SFA* and *Cholesterol*, four food groups: *Fish and Fish Products*, *Fruit, Vegetables, Meat and Meat Products* and *Energy* (kcal/day). In line with Study 1, a further, dichotomous variable, *Fast Food* (once a week or more: yes/no) was included.

5.3.2.1.1 DIETARY INFLAMMATORY INDEX

The EPIC-Norfolk FFQ data were also used to generate energy-adjusted Dietary Inflammatory Index (E-DII) scores as a measure of diet quality in terms of its inflammatory burden (Shivappa et al., 2014a). This was also used in Study 1, and detailed information, including a list of the 25 food parameters (from the FFQ) that were used to calculate DII scores, was provided in Chapter 4.

5.3.2.2 MOOD

Mood was assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). This is a well validated measure of psychological distress experienced over the previous week, and as before, further details can be found in Chapter 4.

5.3.2.3 SLEEP QUALITY

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and Epworth Sleepiness Scale (ESS; Johns, 1991). Both validated instruments were used in Study 1, and detailed information was provided in Chapter 4.

5.3.2.4 PHYSICAL ACTIVITY

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ; Booth, 2000; Craig et al., 2003). This is a validated scale assessing physical activity and sedentary behaviour over the previous seven days. The long version was used in Study 1, but the short version was selected for Study 2 to reduce the overall length of the survey slightly. It consists of eight items to assess moderate and vigorous activity and sedentary behaviour (i.e., time spent sitting).

5.3.3 DATA MANAGEMENT/STATISTICAL ANALYSES

The IBM SPSS Data Analysis version 28 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. An alpha level of .05 was set as the significance criterion for all statistical tests and reported *p* values are all 2-tailed.

Participants who reported working night shifts "most or all of the time" and "frequently" were grouped together as regular night shift workers and those who only worked nights "occasionally" or "never" were categorised as regular day shift workers. Thus, shift work status was re-categorized into a dichotomous variable.

As per Study 1, EPIC-Norfolk food frequency questionnaire data were energy adjusted using the "residual method" (Willett and Stampfer, 1986). This generates dietary data that are independent of total calorie consumption, allowing for estimation of nutrient intake without the potential confound of variations in total daily energy intake. The residual method was described in Chapter 4. DII scores were also energy adjusted (E-DII), using the "density method" (see Chapter 4 for further details).

Preliminary analyses consisted of an examination of the distributions; if non-normal distributions were observed, non-parametric tests were used to assess bivariate relationships. Data were checked for outliers and missing values. As before, if fewer than 10% of values were missing from a questionnaire, these items were replaced by the mean score for that variable, or in the case of *Sleep Duration*, the mode was used. FFQ and DII data were excluded if participants reported extreme energy intakes (< 500 or > 4000 kcal/day).

Descriptive statistics enabled the demographic, lifestyle and health characteristics of the sample to be described. Pearson's chi-square tests of independence and Fisher's exact tests were used to examine the relationship between dichotomous categorical variables, such as sex and smoking status. Independent samples *t*-tests or Mann-Whitney U tests (where a non-parametric approach was indicated) tested for sex differences in continuous variables such as age, mood, sleep quality and diet quality, including E-DII scores.

To reduce the number of independent variables and identify mutually independent patterns in the dietary data, principal components analysis was carried out on the energy-adjusted FFQ variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products* and *Meat and Meat Products*). The relationship between the dietary patterns that emerged as components, and E-DII, mood and sleep variables, was then examined with multiple linear regression, with the dietary components as predictors. As before, where these tests of direct effects indicated the possibility of an indirect pathway between a dietary pattern and mood or sleep variable via E-DII, Hayes' PROCESS procedure (v4, http://www.afhayes.com), was used to test whether the indirect effect was significant. Together, these analyses enabled evaluation of the impact of dietary patterns and other dietary behaviours (i.e., regular fast food intake), and their inflammatory potential, on the mood and sleep measures.

5.4 RESULTS

5.4.1 PARTICIPANT CHARACTERISTICS

5.4.1.1 DEMOGRAPHICS

A total of *N* = 410 complete survey responses were received. Demographic, lifestyle and health characteristics of the sample are presented in Table 5.1.

Table 5.1. Demographic, lifestyle and health characteristics of police shift workers [*N* = 410 unless otherwise stated].

Sex (%)	
Male	153 (37.32)
Female	256 (62.44)
Withheld	1 (0.24)
Age (y)	
Range	18 - 65
Median	44
Educational attainment (%)	
Degree level or above	128 (31.22)
A/AS level	76 (18.54)
BTEC/GNVQ or equivalent	61 (14.88)
Other qualification(s)	26 (6.34)
Withheld	1 (0.24)
Working status (%)	
Full time	332 (80.96)
Part time	78 (19.02)
Night shift work (%)	
Most/all of the time	59 (14.39)
Frequently	56 (13.66)
Occasionally	40 (9.76)
Never	255 (62.2)
Smoking status (%)	

Smokers	37 (9.02)
Non-smokers	367 (89.51)
Withheld	6 (1.46)
Median cigarettes/day	8
Range	1 – 30
Alcohol consumption at least weekly (%)	
Yes	353 (86.1)
No	57 (18)
Median units/week	6
Range	1 – 60
BMI (%) [*n* = 401]	
Under weight	1 (0.24)
Normal	158 (38.54)
Over-weight	134 (32.68)
Obese	98 (23.9)
Morbidly obese	10 (2.44)
Physical activity (%) [*n* = 400]	
Low	27 (6.75)
Moderate	129 (32.25)
High	244 (61)
General health (%)	
Chronic illness (total)	133 (32.44)
Physical illness	79 (19.27)
Anxiety and/or depression	54 (13.17)
Withheld	7 (1.71)
Regular prescription medication	224 (54.63)

Preliminary analyses included Shaprio-Wilk and Kolmogorov-Smirnov tests of normality in conjunction with inspection of Q-Q plots. Only *E-DII* had an approximately normal distribution and a non-significant Kolmogorov-Smirnov test. Based on this, median rather than mean descriptive statistics are reported, and non-parametric tests (Spearman's rho) were used to examine bivariate relationships between variables.

Participants ranged from 18 to 65 years of age (*Mdn* = 44), and over half (62.44%) were female. An independent samples Mann-Whitney U test revealed that males and females did not differ significantly in age. In total, 84.84% described themselves as White, with very low numbers across a range of other ethnic groups, so no further analysis of ethnicity was

undertaken. 31.22% were educated to degree level or above. The majority (80.96%) of employees worked full time, 14.39% worked night shifts most or all of the time, 13.66% worked nights frequently, 9.76% worked nights occasionally, and 62.2% never worked night shifts.

5.4.1.2 LIFESTYLE

9.02% of the sample declared themselves tobacco smokers (*Mdn* = 8 cigarettes/day, range 1 - 30). This is below the national average of 13.8% according to the latest (2020) official UK government figures for England (ons.gov.uk, 2021). A Pearson's chi-square test of independence revealed that the relationship between sex and smoking status was not significant, so males were no more likely to smoke than females. A Pearson's chi-square test of independence revealed that smoking status was not significantly associated with shift work status. Thus, night shift workers were no more likely to smoke than day shift workers. This contrasts with some published reports showing higher smoking rates in night shift workers compared to day workers (van Amelsvoort et al., 2006; Weston, 2013).

The majority of employees (86.1%) reported drinking alcohol once a week or more (*Mdn* = 6 units/week). Weekly intakes ranged widely, from 1 to 60 units, and 15.49% of drinkers admitted consuming above the UK government's recommended limit of 14 units per week. This is lower than the latest national figure of 24% (UK government National Statistics, 2020). A Mann-Whitney U test indicated that alcohol intake did not differ significantly between night workers and day workers.

With regard to body mass index (BMI), *n* = 9 participants had missing data, so their BMI could not be calculated. Less than 40% of the total sample (38.54%) were classed as normal weight (BMI 18.50 – 24.99), almost one-third (32.68%) were over-weight (BMI 25 – 29.99), nearly a quarter (23.90%) were obese (BMI 30 – 39.99), and 2.44% were morbidly obese (BMI $\geq$ 40). In line with published evidence, it was hypothesised that night shift workers would have significantly higher BMIs than day shift workers. However, a Mann-Whitney U test indicated that BMI was not significantly different between the two groups.

Regarding physical activity, *n* = 10 participants had missing data so their activity score could not be calculated. Of the remaining 400, over half (61%) declared high levels, 32.25% moderate, and 6.75% reported low levels of physical activity.

5.4.1.3 GENERAL HEALTH

Almost one third (32.93%) of the total sample declared that they were suffering from at least one diagnosed chronic illness (physical and/or mental). A chi-square test revealed that night shift workers reported significantly more diagnosed chronic disease than day shift workers, X^2 (1, N = 410) = 25.96, p = <.001. The most diagnosed conditions were comorbid anxiety and depression, of which 6.34% of the sample declared. Although night shift workers suffered from significantly more diagnosed chronic disease overall than day shift workers, a chi-square test revealed that there were no significant differences in the rates of diagnosed anxiety and depression between the two groups. Three participants (0.73%) suffered from diagnosed sleep disorders: two cases of obstructive sleep apnoea and one case of insomnia. As

explained in Chapter 4, the estimated prevalence of sleep apnoea in the UK is around 2.5 to 3%, but the true prevalence is uncertain because most cases remain undiagnosed (Rejon-Parrilla et al., 2014). It is therefore likely that the rate in the current sample was higher than 0.73%, but that other cases remained undiagnosed.

Over half (54.63%) the sample took regular prescription medications, the commonest being antidepressants. The second commonest was cardiovascular system drugs (i.e., antihypertensives, antiarrhythmics, statins, diuretics), of which 8.78% of participants were taking.

5.4.2 DIET AND DIET QUALITY

An independents samples Mann-Whitney U test revealed that night shift workers consumed significantly more *Energy* (*Mdn* = 1703.41 kcal/day) than day shift workers (*Mdn* = 1505.45 kcal/day), $U(N_{nights}= 115, N_{days} = 295) = 20006$, $z = 2.82$, $p = .01$. Of the seven energy-adjusted macronutrients and four food group variables, night shift workers consumed significantly less *Fibre* (*Mdn* = 13.01 grams/day) than day shift workers (*Mdn* = 13.02 grams/day), $U(N_{nights}= 115, N_{days} = 295) = 14420$, $z = -2.36$, $p = .02$), and significantly more *SFA* (*Mdn* = 26.14 grams/day) than day shift workers (*Mdn* = 21.84 grams/day), $U(N_{nights}= 115, N_{days} = 295) = 1908$, $z = 1.97$, $p = .05$). There was no significant difference in *Fast Food* intake between the two groups. There was a significant positive correlation between *Fast Food* and *E-DII* scores ($r_s = .1$, $p = .04$, $N = 410$), indicating that regular intake of this type of food was a pro-inflammatory dietary behaviour, as was the case in Study 1. However, in contrast to Study 1,

there were no significant associations between *Fast Food* and any of the mood or sleep quality variables, so no further analysis of *Fast Food* was undertaken.

5.4.2.1 DIETARY INFLAMMATORY INDEX

As stated above, *E-DII* was the only dietary variable that was normally distributed. Night workers' *E-DII* scores ranged from -3.81 to +4.93, while day workers' scores ranged from -4.67 to +4.15; scores typically range from -5.5 to +5.5 when calculated from 25 to 30 food parameters (Hébert et al., 2019), as in this case. An independent samples *t*-test revealed that night shift workers had a significantly higher mean *E-DII* score (M = +0.23, SD = 2) than day shift workers (M = -0.6, SD = 1.94), $t_{(408)} = 3.82$, p = <.001. On average, night workers had mildly pro-inflammatory diets (positive mean *E-DII* score), whereas day workers' diets were mildly anti-inflammatory (negative mean *E-DII* score), although both mean scores indicate a neutral inflammatory diet (Wirth et al., 2021).

5.4.3 MOOD

The median *HADS-A* score for the total sample was 9, and the rate of clinically significant depressive symptoms (HADS-A $\geq$ 8) was 37.56%. The median *HADS-D* score was 6, with a clinically significant rate (HADS-D $\geq$ 8) of 59.27%. An independent samples Mann-Whitney U test revealed that night shift workers (Mdn = 7) were significantly more depressed than day

workers (*Mdn* = 6), $U(N_{nights}= 115, N_{days} = 295) = 19880.50$, $z = 2.71$, $p = .01$, but not significantly more anxious.

5.4.4 SLEEP QUALITY

ESS scores for night shift workers ranged from 0 to 19 (possible range 0 - 24), with a median score of 9. Day workers' scores also ranged from 0 to 19, but with a median of 7, and an independent samples Mann-Whitney U test revealed that this difference was significant, $U(N_{nights}= 115, N_{days} = 295) = 19369.5$, $z = 2.24$, $p = .03$. Thus, regular night shift workers suffered from more daytime sleepiness than their day working colleagues.

PSQI-global scores for night shift workers ranged from 3 to 19 (possible range 0 – 21) with a median score of 9; day shift workers' scores ranged from 1 to 20 with a median of 8. Mean global scores were 9.41 (*SD* = 3.04) and 8 (*SD* = 3.35) for night and day shift workers respectively. Thus, all police employees, irrespective of the type of shift worked, had higher mean scores than normative studies in general population samples which report means of around 5 (e.g., Hinz et al., 2017), as discussed previously. An independent samples Mann-Whitney U test revealed that scores were significantly higher in night workers than day workers, $U(N_{nights}= 115, N_{days} = 295) = 21499$, $z = 4.23$, $p < .001$. Regarding *Sleep Duration* specifically, an independent samples Mann-Whitney U test revealed night shift workers had significantly shorter sleep duration (*Mdn* = 6 hours/night) than day shift workers (*Mdn* = 6.5 hours/night), $U(N_{nights}= 115, N_{days} = 295) = 13940$, $z = -2.83$, $p = .01$. The current results are in line with published studies that used PSQI, which report poorer overall sleep quality and

shorter sleep duration in night workers compared to day workers (Lim et al., 2020). As discussed in Chapter 1, the recommended sleep duration for adults is 7 to 9 hours (Chaput et al., 2018). In the current sample, only 9.57% of night workers and 10.85% of day workers reported sleeping an average of 8 hours per night. A Spearman's correlation did not reveal any significant associations between age and sleep quality (*PSQI-global* or *ESS*) when day and night workers were analysed together.

5.4.5 RELATIONSHIPS BETWEEN DIET QUALITY, MOOD AND SLEEP QUALITY (COMBINED DATASET)

First, day shift workers and night shift workers were analysed together as one group. Non-parametric tests (Spearman's rho) were used to examine bivariate relationships between variables, as illustrated in Table 5.2.

Table 5.2. Spearman's correlations between diet quality, mood and sleep quality in day shift workers and night shift workers (*N* = 410).

Correlations

			ESS	PSQI-global	HADS-A	HADS-D	E-DII
Spearman's rho	ESS	Correlation Coefficient	--				
		Sig. (2-tailed)	.				
		N	410				
	PSQI-global	Correlation Coefficient	.329**	--			
		Sig. (2-tailed)	<.001	.			
		N	410	410			
	HADS-A	Correlation Coefficient	.256**	.435**	--		
		Sig. (2-tailed)	<.001	<.001	.		
		N	410	410	410		
	HADS-D	Correlation Coefficient	.322**	.486**	.582**	--	
		Sig. (2-tailed)	<.001	<.001	<.001	.	
		N	410	410	410	410	
	E-DII	Correlation Coefficient	.128**	.010	.088	.177**	--
		Sig. (2-tailed)	.010	.842	.076	<.001	.
		N	410	410	410	410	410

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5.2 indicates that anxiety (*HADS-A*) and depression (*HADS-D*) were strongly correlated, as expected (Kessler et al., 1996). Daytime sleepiness (*ESS*) and nocturnal sleep quality (*PSQI-global*) were moderately correlated, and individuals with higher levels of anxiety and depression had significantly poorer sleep quality (i.e., higher *ESS* and *PSQI-global* scores). Again, these results are in line with well-established evidence highlighting a bidirectional relationship between mood and sleep quality (see Chapter 2).

ESS scores correlated positively with *E-DII*. *PSQI-global* scores did not correlate significantly with *E-DII* scores, but correlated positively with the PSQI subcomponent *Daytime Dysfunction*,

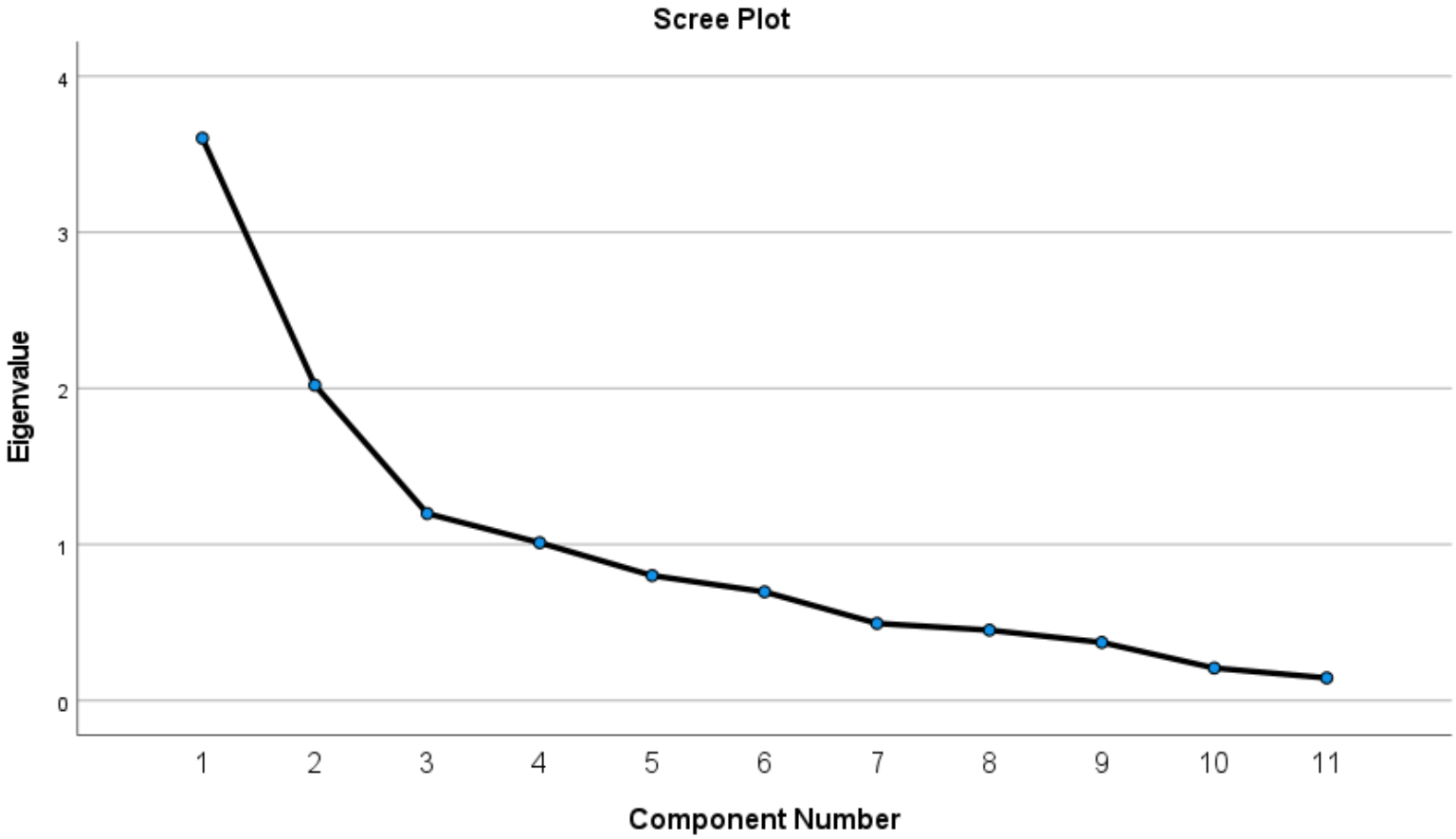
(r_s = .12, p < .01, N = 410; subcomponent data not tabulated for clarity). Thus, higher levels of diet-derived inflammation were associated with significantly more daytime sleepiness and daytime dysfunction. Higher *E-DII* scores were also associated with significantly higher *HADS-D* (but not *HADS-A*) scores, indicating that higher levels of diet-derived inflammation were associated with significantly more depressive symptoms. This is in line with published evidence from recent systematic reviews and meta-analyses (e.g., Chen et al., 2021; Wang et al., 2019), as previously discussed.

5.4.6 EXTRACTION OF DIETARY PATTERNS

As before, to reduce the number of independent variables and identify mutually independent patterns in the dietary data, PCA with Varimax rotation was conducted on the energy-adjusted FFQ variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products* and *Meat and Meat products*).

Bartlett's test of sphericity indicated that the data were suitable for PCA (approx. chi-square$_{(55)}$ = 1780.43, p = .00). The KMO measure of sampling adequacy returned a value of .71, which exceeded the minimum acceptable value.

Figure 5.1. Scree plot showing eigenvalues of principal components (*N* = 410).



Component 4 had an eigenvalue of 1.01, and the scree plot indicated that a three-component model was optimal. The rotated component matrix is shown in Table 5.3.

Table 5.3. Rotated component matrix[a] with dietary loadings (*N* = 410).

	Component		
	1	2	3
Dietary variables[b]	***HI-FATS-LO-CARBS***	***MEDITERRANEAN***	***HI-FIBRE-LO-SFA***
Carbohydrates (total)	**-.892**	.011	.253
Cholesterol	.600	.039	-.150
Fibre	-.167	.224	**.772**
Sugars (total)	**-.843**	.067	.153
MUFA	**.708**	-.048	**-.420**
PUFA	**.793**	.024	.222
SFA	.224	-.055	**-.858**
Fish and Fish Products	.103	**.593**	.129
Fruit	-.164	**.706**	.145
Meat and Meat Products	.149	**-.544**	.260
Vegetables	.181	**.793**	.217

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids
a. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations.
b. All EPIC-Norfolk FFQ variables adjusted for total energy intake (residual method).

The three components explained 62.02% of the total variance in the model, and were labelled according to the salient features of their loadings. *PUFA* and *MUFA* loaded positively (particularly *PUFA*), and the two carbohydrates (total *Carbohydrates* and total *Sugars*) loaded negatively onto Component 1, so this component was labelled *HI-FATS-LO-CARBS*. *Vegetables, Fruit* and *Fish and Fish Products* loaded positively, and *Meat and Meat Products* loaded negatively onto Component 2, so this component was named *MEDITERRANEAN,* due to its similarity to a Mediterranean-style diet (i.e., high in vegetables, fruit, and fish, low in meat products). Component 3 was high in *Fibre*, and low in *SFA* and *MUFA* (particularly *SFA*), so was labelled *HI-FIBRE-LO-SFA.*

5.4.6.1 DIETARY PATTERNS AND THEIR INFLAMMATORY POTENTIAL

Relationships between the dietary patterns and *E-DII* were tested using multiple linear regression with the three components as predictors and *E-DII* as the outcome variable. All three dietary patterns were significantly associated with *E-DII*, accounting for 55.3% of the variance in the model (adjusted R^2 = .55, $F_{(3,406}$ = 169.4, p < .001). Higher consumption of *HI-FATS-LO-CARBS* (β = -.15, p < .001), *MEDITERRANEAN* (β = -.12, p < .001) and *HI-FIBRE-LO-SFA* (β = -.72, p < .001) were all associated with significantly lower *E-DII* scores. Thus, all three components were anti-inflammatory dietary patterns, and the *HI-FIBRE-LO-SFA* pattern was particularly strongly anti-inflammatory.

5.4.6.2 DIETARY PATTERNS AND MOOD

To test the possibility that the dietary patterns were directly related to mood, separate multiple linear regressions were conducted, with the three patterns as predictors, and *HADS-A* or *HADS-D* as the outcome variables. *HADS-A* was not significant, but *HI-FIBRE-LO-SFA* was associated with significantly lower *HADS-D* scores (β = -.17, p < .001) and accounted for 2.4% of the variance in the model (adjusted R^2 = .02, $F_{(3,406)}$ = 4.35, p = .01). Given that *HI-FIBRE-LO-SFA* was an anti-inflammatory dietary pattern, and *E-DII* scores and *HADS-D* were positively correlated (see Table 5.2), it was possible that this dietary pattern was indirectly related to *HADS-D* via its anti-inflammatory properties.

To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) model 4, with 5000 bootstrap samples, with *HI-FIBRE-LO-SFA* as the predictor, E-*DII* as mediator, and *HADS-D* as the outcome variable. The direct pathway between *HI-FIBRE-LO-SFA* and *HADS-D* was no longer significant in the mediation model, but the indirect pathway, via *E-DII,* was significant (indirect effect = -0.47, 95% CI [-0.86, -0.08]). Thus, *E-DII* fully mediated the relationship between *HI-FIBRE-LO-SFA* and *HADS-D*.

HI-FATS-LO-CARBS and MEDITERRANEAN were not significantly associated with *HADS-D* in the regression model, but they did relate directly to *E-DII*, and *E-DII* related directly to *HADS-D*. As there were no direct relationships between the two dietary patterns and depression, mediation analysis was conducted to check for indirect effects via *E-DII*. The indirect pathway between *HI-FATS-LO-CARBS* and *HADS-D,* via *E-DII,* was significant (indirect effect = -0.12, 95% CI [-0.27, -0.02]). Similarly, the indirect pathway between *MEDITERRANEAN* and *HADS-D*, via *E-DII*, was significant (indirect effect = -0.09, 95% CI [-0.17, -0.01]). To summarise, *E-DII* fully mediated the relationships between the dietary patterns and depression. Thus, all three patterns were protective of depressive symptoms via their anti-inflammatory properties.

5.4.6.3 DIETARY PATTERNS AND SLEEP

To test for direct associations between dietary patterns and sleep quality, separate multiple linear regressions were conducted with the three components as predictors and the sleep quality variables as outcome variables. In a model approaching significance, higher *Hi-FIBRE-LO-SFA* was associated with significantly lower *Daytime Dysfunction* (β = -.13, *p* = .01) and

accounted for 1.2% of the variance (adjusted R^2 = .012, $F_{(3,406)}$ = 2.63, p = .05). Further, with *ESS* as the outcome variable, higher intakes of *Hi-FIBRE-LO-SFA* were also associated with lower *ESS* scores (β = -.13, p = .01), accounting for 1.3% of the total variance in the model (adjusted R^2 = .01, $F_{(3,406)}$ = 2.80, p = .04). Thus, the *HI-FIBRE-LO-SFA* dietary pattern was protective of sleep, in terms of both *Daytime Dysfunction* (PSQI) and daytime sleepiness (*ESS*).

Given that *HI-FIBRE-LO-SFA* was a significantly anti-inflammatory dietary pattern, and *E-DII* and *Daytime Dysfunction,* and *E-DII* and *ESS,* were positively correlated (see Table 5.2), it was possible that the apparent effect of *HI-FIBRE-LO-SFA* on sleep quality was driven by its anti-inflammatory properties. To test this, mediation analyses were conducted, again using Hayes' PROCESS procedure (v4, http://www.afhayes.com) (model 4, 500 bootstrap samples, as before), with *HI-FIBRE-LO-SFA* as the predictor, *E-DII* as mediator, and either *Daytime Dysfunction* or *ESS* as the outcome variable. Neither the direct nor indirect pathways were significant in either model. Thus, the apparent protective effects of the *HI-FIBRE-LO-SFA* dietary pattern on sleep quality were not driven by its anti-inflammatory properties.

HI-FATS-LO-CARBS and *MEDITERRANEAN* were not significantly associated with *Daytime Dysfunction* or *ESS* in the regression models, but they did both relate directly to *E-DII*, and *E-DII* related directly to the two sleep variables. As there were no direct relationships, mediation analysis was conducted to check for indirect relationships via *E-DII*. The indirect pathway between *HI-FATS-LO-CARBS* and *Daytime Dysfunction,* via *E-DII,* was significant (indirect effect = -0.02, 95% CI [-0.04, -0.002]). Similarly, the indirect pathway between *HI-FATS-LO-CARBS* and *ESS*, via *E-DII*, was significant (indirect effect = -0.09, 95% CI [-0.21, -0.01]). When *MEDITERRANEAN* was tested as the predictor variable, the indirect pathway between

MEDITERRANEAN and *Daytime Dysfunction*, via *E-DII,* was significant (indirect effect = -0.02, 95% CI [-0.06, -0.0003]). Similarly, the indirect pathway between *MEDITERRANEAN* and *ESS*, via *E-DII,* was significant (indirect effect = -0.06, 95% CI [-0.15, -0.004]). Thus, the apparent protective effects of both *HI-FATS-LO-CARBS* and *MEDITERRANEAN* over sleep quality were driven by the anti-inflammatory properties of the two dietary patterns.

5.4.7 RELATIONSHIPS BETWEEN DIET QUALITY, MOOD AND SLEEP QUALITY (DAY SHIFT WORKERS)

As before, non-parametric tests were used to assess bivariate relationships between variables, as illustrated in Table 5.4.

Table 5.4. Spearman's correlations between diet quality, mood and sleep quality in day shift workers (*n* = 295).

Correlations

			ESS	PSQI-global	HADS-A	HADS-D	E-DII
Spearman's rho	ESS	Correlation Coefficient	--				
		Sig. (2-tailed)	.				
		N	295				
	PSQI-global	Correlation Coefficient	.339**	--			
		Sig. (2-tailed)	<.001	.			
		N	295	295			
	HADS-A	Correlation Coefficient	.278**	.471**	--		
		Sig. (2-tailed)	<.001	<.001	.		
		N	295	295	295		
	HADS-D	Correlation Coefficient	.326**	.479**	.615**	--	
		Sig. (2-tailed)	<.001	<.001	<.001	.	
		N	295	295	295	295	
	E-DII	Correlation Coefficient	.095	-.044	.072	.193**	--
		Sig. (2-tailed)	.105	.453	.220	<.001	.
		N	295	295	295	295	295

**. Correlation is significant at the 0.01 level (2-tailed).

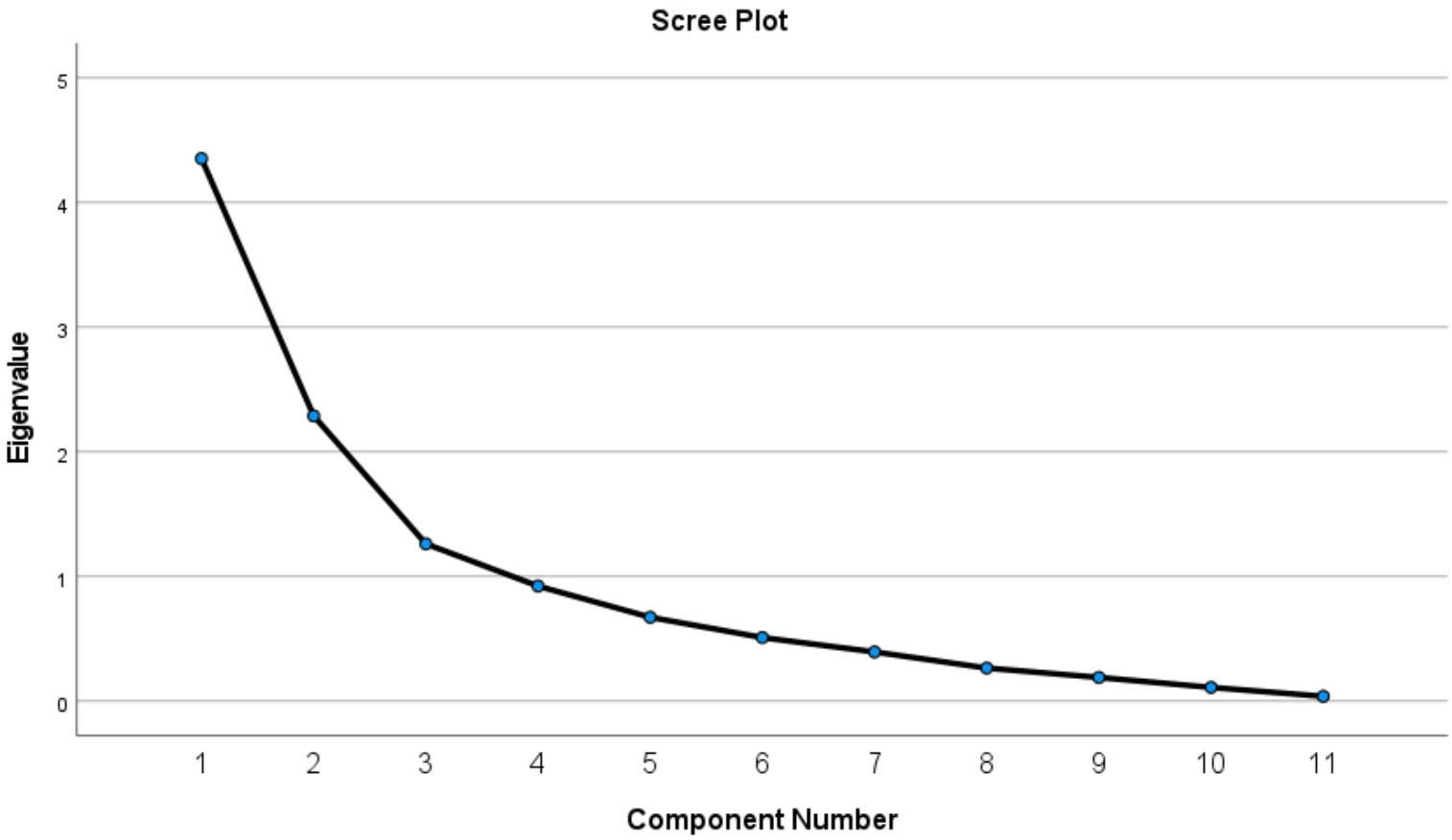
Table 5.4 indicates that nocturnal sleep quality (*PSQI-global*) daytime sleepiness (*ESS*) were moderately correlated. Anxiety (*HADS-A*) and depression (*HADS-D*) were strongly correlated, in line with the combined dataset and published data (e.g., Kessler et al., 1996). Individuals with higher levels of anxiety and depression had significantly poorer sleep quality (i.e., higher *ESS* and *PSQI-global* scores). Again, these results reflect the combined dataset and well-established evidence highlighting the bidirectional relationship between mood and sleep quality. However, unlike in the combined dataset, *ESS* and *PSQI-global* scores did not correlate significantly with *E-DII*, and neither did PSQI subcomponent scores (data not shown). In line with the combined dataset, however, higher *E-DII* scores were associated with

significantly higher *HADS-D* (but not *HADS-A*) scores, indicating that higher levels of diet-derived inflammation were associated with significantly more depressive symptoms. As discussed, this is in accordance with published evidence from recent systematic reviews and meta-analyses (e.g., Chen et al., 2021; Wang et al., 2019). The remainder of this section focusses on exploring the relationship between diet quality, its inflammatory potential, and mood.

5.4.8 EXTRACTION OF DIETARY PATTERNS

As before, to reduce the number of independent variables and identify mutually independent patterns in the dietary data, PCA was conducted on the same set of energy adjusted FFQ variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products* and *Meat and Meat products*). Bartlett's test of sphericity examined the significance of correlations between the dietary variables within the correlation matrix and indicated that the data were suitable for PCA (approx. chi-square$_{(55)}$ = 2325.91, p = .00). The KMO test returned a value of .59, which met the minimum acceptable value for adequate sampling.

Figure 5.2. Scree plot showing eigenvalues of principal components (*n* = 295).



A criterion of eigenvalues > 1 suggested a three-component model, which was also illustrated by the scree plot. The rotated component matrix is shown in Table 5.5.

Table 5.5. Rotated component matrix[a] with dietary loadings (*n* = 295).

	Component		
	1	***2***	***3***
Dietary variables[b]	***HI-FATS-LO-CARBS***	***MEDITERRANEAN***	***HI-MEATS-LO-CARBS***
Carbohydrates (total)	**-.779**	.017	**-.536**
Cholesterol	.353	.084	**.737**
Fibre	-.216	**.854**	-.246
Sugars (total)	**-.694**	.144	**-.474**
MUFA	**.848**	-.235	.070
PUFA	**.778**	.301	.003
SFA	**.553**	**-.609**	-.018
Fish and Fish Products	.164	**.590**	.175
Meat and Meat Products	-.043	-.180	**.892**
Fruit	-.496	**.611**	-.171
Vegetables	.076	**.844**	-.112

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids
a. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations.
b. All EPIC-Norfolk FFQ variables adjusted for total energy intake (residual method).

The three components explained 71.83% of the total variance in the model, and were labelled according to the salient features of their loadings. The loadings were similar, but not identical, to the combined dataset. Here, *MUFA*, *PUFA* and *SFA* loaded positively, and the two carbohydrate variables (total *Carbohydrates* and total *Sugars*) loaded negatively onto Component 1, so this was labelled *HI-FATS-LO-CARBS*. *Fibre, Vegetables, Fruit* and *Fish and Fish Products* loaded positively, and *SFA* loaded negatively onto Component 2, so this component was labelled *MEDITERRANEAN,* again due to its similarity to a Mediterranean-style diet (i.e., high in fruit, vegetables and fish, low in SFA). Component 3 was named *HI-MEATS-LO-CARBS*, along similar lines.

5.4.8.1 DIETARY PATTERNS AND THEIR INFLAMMATORY POTENTIAL

Relationships between the dietary patterns and *E-DII* were tested using multiple linear regression with the three components as predictors and *E-DII* as the outcome variable. Two of the three components were significantly associated with *E-DII,* accounting for 65.1% of the variance in the model (adjusted R^2 = .65, $F_{(3,291)}$ = 183.5, p < .001). Higher consumption of *HI-FATS-LO-CARBS* was associated with significantly higher *E-DII* scores (β = .1, p = .004), whereas

higher consumption of *MEDITERRANEAN* was associated with significantly lower *E-DII* scores (β = -.8, p < .001). Thus, *HI-FATS-LO-CARBS* was a pro-inflammatory dietary pattern and *MEDITERRANEAN* a strongly anti-inflammatory pattern. *HI-MEATS-LO-CARBS* was not significantly related to *E-DII*.

5.4.8.2 DIETARY PATTERNS AND MOOD

To test the possibility that the dietary patterns were associated with mood, separate multiple linear regressions were conducted with the three components as predictors and *HADS-A* or *HADS-D* as the outcome variable. The model with *HADS-A* was not significant, but *MEDITERRANEAN* was associated with significantly lower *HADS-D* scores (β = -.19, p < .001) and accounted for 3% of the variance in the model (adjusted R^2 = .03, $F_{(3,291)}$ = 4.33, p = .01). Thus, the *MEDITERRANEAN* dietary pattern was protective of mood (depressive symptoms). Further, given that *MEDITERRANEAN* is an anti-inflammatory pattern, and *E-DII* scores and

HADS-D were positively correlated (see Table 5.4), it was possible that the apparent effects of *MEDITERRANEAN* on *HADS-D* were mediated by its anti-inflammatory properties.

To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) (model 4, 5000 bootstrap samples), with either *HI-FATS-LO-CARBS* or *MEDITERRANEAN* as the predictor, E-*DII* as mediator, and *HADS-D* as the outcome variable. As indicated in the regression analysis above, there was a direct effect of *MEDITERRANEAN* on *HADS-D*, but the indirect pathway, via *E-DII*, was non-significant. Thus, the apparent protective effect of *MEDITERRANEAN* on mood was not mediated by the anti-inflammatory properties of this dietary pattern.

HI-FATS-LO-CARBS and HI-MEATS-LOW-CARBS were not directly related to *HADS-D* in the regression model, but *HI-FATS-LO-CARBS* was associated with *E-DII*, and *E-DII* was associated with *HADS-D*. As there were no direct relationships between *HI-FATS-LO-CARBS* and *HADS-D,* mediation analysis was conducted to check for indirect effects via *E-DII*. The indirect effect between *HI-FATS-LO-CARBS* and *HADS-D* was non-significant, indicating that there were no indirect pathways linking this dietary pattern to depression.

5.4.8.3 DIETARY PATTERNS AND SLEEP

To test the possibility that the dietary patterns were directly related to sleep, separate multiple linear regressions were conducted with the three components as predictors and the sleep quality variables as outcome variables. None of the models with *PSQI-global* or its

subcomponents were significant. However, with *ESS* as the outcome variable, *MEDITERRANEAN* was negatively related (β = -.11, *p* = .047), and *HI-MEATS-LO-CARBS* was positively associated (β = .16, *p* = .01) with daytime sleepiness, accounting for 3.2% of the variance in the model (adjusted R^2 = .032, $F_{(3,291)}$ = 4.28, *p* = .01). *E-DII* was not directly related to *ESS* (see Table 5.4) (or to *HI-MEATS-LO-CARBS*), so mediation analysis via *E-DII* was not attempted. Thus, higher intakes of *MEDITERRANEAN* appeared to be protective of daytime sleepiness, but this relationship was not driven by the anti-inflammatory properties of this dietary pattern. Conversely, higher intakes of a *HI-MEATS-LO-CARBS* were associated with more daytime sleepiness, but as this dietary pattern was neither significantly pro- nor anti-inflammatory, other factors were responsible for this association.

5.4.9 RELATIONSHIPS BETWEEN DIET QUALITY, MOOD AND SLEEP (NIGHT SHIFT WORKERS)

As before, non-parametric tests were used to assess bivariate relationships between variables, as illustrated in Table 5.6.

Table 5.6. Spearman's correlations between diet quality, mood and sleep quality in night shift workers (*n* = 115).

Correlations

			ESS	PSQI-global	HADS-A	HADS-D	E-DII
Spearman's rho	ESS	Correlation Coefficient	--				
		Sig. (2-tailed)	.				
		N	115				
	PSQI-global	Correlation Coefficient	.254**	--			
		Sig. (2-tailed)	.006	.			
		N	115	115			
	HADS-A	Correlation Coefficient	.203*	.361**	--		
		Sig. (2-tailed)	.029	<.001	.		
		N	115	115	115		
	HADS-D	Correlation Coefficient	.297**	.439**	.489**	--	
		Sig. (2-tailed)	.001	<.001	<.001	.	
		N	115	115	115	115	
	E-DII	Correlation Coefficient	.163	.011	.153	.105	--
		Sig. (2-tailed)	.082	.910	.103	.262	.
		N	115	115	115	115	115

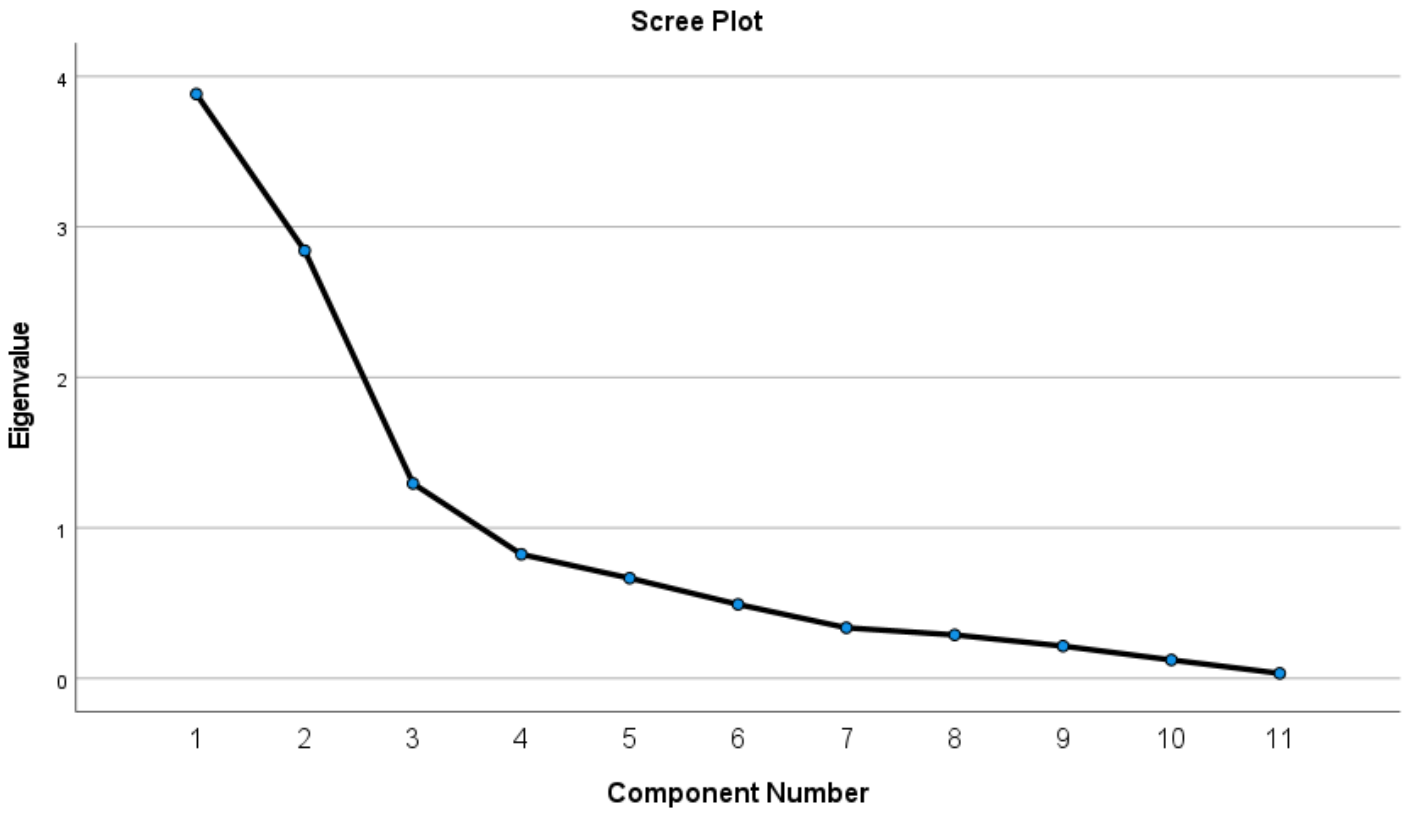
**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

5.4.10 EXTRACTION OF DIETARY PATTERNS

To reduce the number of independent variables and identify mutually independent patterns in the dietary data, PCA with Varimax rotation was conducted on the eleven energy adjusted FFQ variables, as before. Bartlett's test of sphericity indicated that the data were suitable for PCA (approx. chi-square$_{(55)}$ = 876.76, p < .001), and the KMO test of sampling adequacy returned a value of .53, which was close to the minimum acceptable value.

Figure 5.3. Scree plot showing eigenvalues of principal components (*n* = 115).



A criterion of eigenvalues > 1 suggested a three-component model, which was also illustrated graphically. The rotated component matrix is shown in Table 5.7.

Table 5.7. Rotated component matrix[a] with dietary loadings (*n* = 115).

	Component		
	1	2	3
Dietary variables[b]	***HI-FIBRE-LO-SFA***	***HI-FATS-LO-CARBS***	***HI-PROTEIN-LO-CARBS***
Carbohydrates(total)	.133	**-.771**	**-.437**
Cholesterol	-.074	.166	**.784**
Fibre	**.903**	.057	-.257
Sugars (total)	.151	**-.759**	**-.425**
MUFA	-.214	**.868**	-.115
PUFA	.317	**.752**	.296
SFA	**-.706**	.275	-.342
Fruit	**.793**	-.238	-.044
Fish and Fish Products	.396	.363	**.525**
Meat and Meat Products	-.324	.201	**.709**
Vegetables	**.822**	.134	-.232

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids
1. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 6 iterations.
2. All EPIC-Norfolk FFQ variables adjusted for total energy intake (residual method).

The three components explained 72.92% of the total variance and were labelled according to the salient features of their loadings. As before, loadings were similar, but not identical, to the combined dataset. Here, *Fibre*, *Vegetables* and *Fruit* loaded positively, and *SFA* loaded negatively onto Component 1, so in line with the combined dataset, this component was labelled *HI-FIBRE-LO-SFA*. *MUFA* and *PUFA* loaded positively, and two carbohydrates loaded negatively onto Component 2, so again, this was labelled *HI-FATS-LO-CARBS*. Component 3 was named *HI-PROTEIN-LO-CARBS*, along similar lines.

5.4.10.1 DIETARY PATTERNS AND THEIR INFLAMMATORY POTENTIAL

Relationships between the dietary patterns and *E-DII* were tested using multiple linear regression with the three components as predictors and *E-DII* as the predicted/outcome variable. Two of the three patterns were significantly associated with *E-DII* and accounted for 72% of the variance in the model (adjusted R^2 = .72, $F_{(3,111)}$ = 99.02, p < .001). Higher consumption of *HI-FIBRE-LO-SFA* was associated with significantly lower *E-DII* scores (β = -.81, p < .001), as was *HI-FATS-LOW-CARBS* (β = -.14, p = .01), indicating that they were both anti-inflammatory dietary patterns. As was the case in the combined dataset, the *HI-FIBRE-LO-SFA* pattern was a particularly anti-inflammatory dietary pattern.

5.4.10.2 DIETARY PATTERNS AND MOOD

To test the possibility that the dietary patterns were associated with mood, separate multiple linear regressions were conducted, with the components as predictors and *HADS-A* or *HADS-D* as the outcome variable. None of the dietary patterns were significantly associated with mood.

5.4.10.3 DIETARY PATTERNS AND SLEEP QUALITY

To test the possibility that the dietary patterns were associated with sleep, separate multiple linear regressions were conducted with the components as predictors and sleep quality variables as the outcome variable. *PSQI-global* and subcomponent scores were not significant, but with *ESS* as the outcome variable, the dietary pattern *HI-FIBRE-LO-SFA* was

associated with significantly less daytime sleepiness (β = -.19, p = .045) and accounted for 4.6% of the total variance in the model (adjusted R^2 = .046, $F_{(3,111)}$ = 2.84, p = .04). Although *HI-FIBRE-LO-SFA* was an anti-inflammatory dietary pattern, *E-DII* scores were not directly related to *ESS* (see Table 5.6), so mediation analysis via *E-DII* was not attempted.

5.4.11 ADJUSTMENTS FOR POTENTIAL COVARIATES AND CONFOUNDERS

As discussed in Chapter 4, several factors, including age, sex and health status, could be related to the diet, mood and sleep variables and therefore potentially confound the observed relationships. Spearman's correlations in the combined sample revealed that there were no statistically significant relationships between age and the dietary (i.e., E-DII, principal components), mood and sleep quality variables in continuous data.

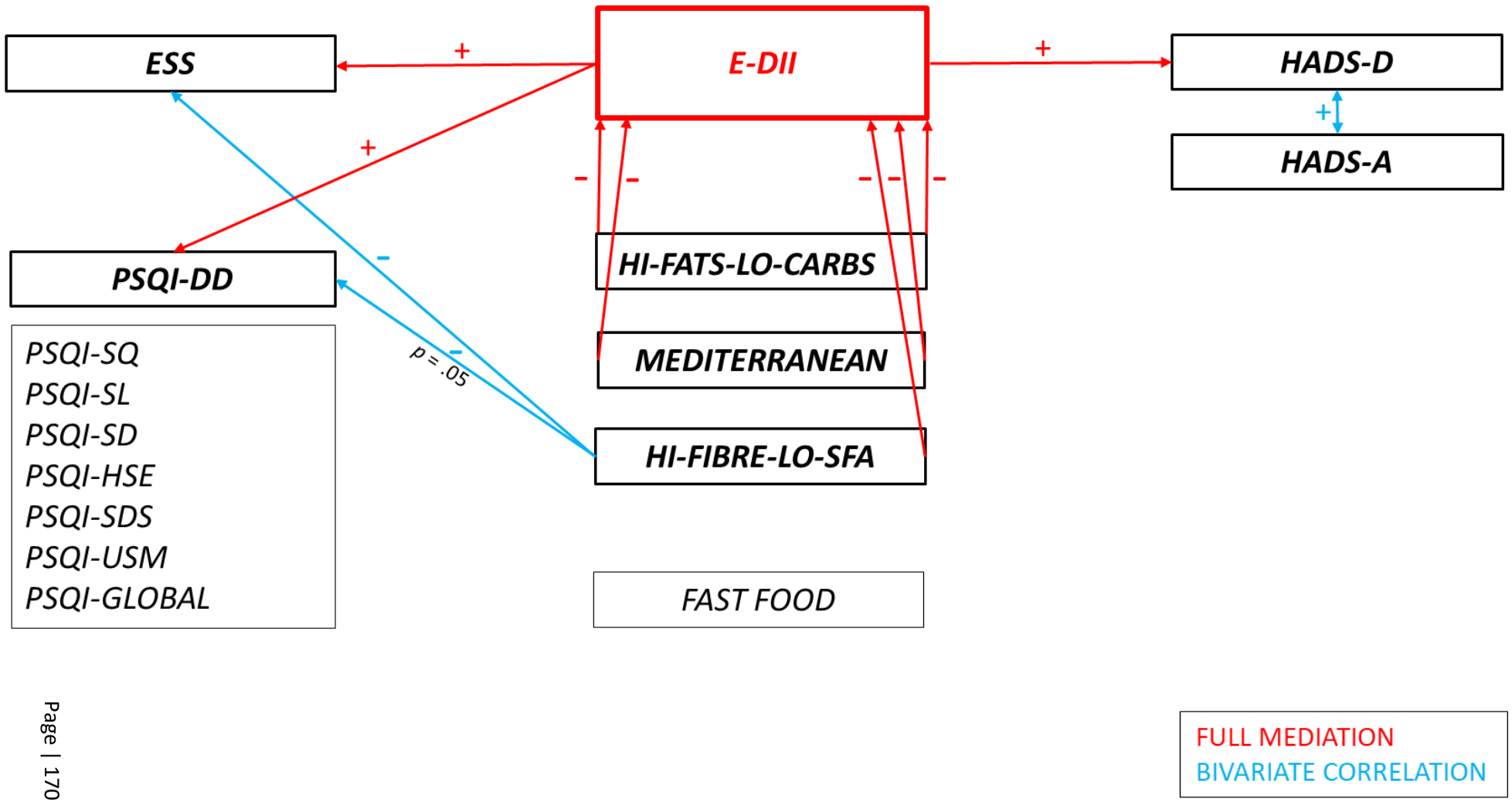
In terms of health status, cardiovascular disease, and chronic diseases associated with pain, such as musculoskeletal conditions (osteoarthritis, chronic "back pain" etc.) could covary with mood and sleep. One participant declared that they were suffering from coronary artery disease, and a total of 39 were taking cardiovascular system drugs (e.g., anti-hypertensives, statins), presumably for primary prevention of cardiovascular disease. Therefore, a categorical variable, *Cardiovascular System Drugs* (yes/no) was created. Eleven participants were suffering from chronic musculoskeletal disorders, so a categorical variable *Chronic Musculoskeletal Disorders* (yes/no) was also created.

Independent samples Mann-Whitney U tests examined relationships between categorical variables (e.g., sex, health status variables) and the continuous diet quality (i.e., E-DII, principal components), mood and sleep quality scores. Sex was not significantly associated with the continuous variables. Both health status variables were associated with increasing age, but they were not related to the mood and diet quality variables. Neither were they associated with ESS or PSQI-global scores, but of the PSQI subcomponents, those declaring chronic musculoskeletal conditions had significantly more sleep disturbance than those without musculoskeletal conditions. However, none of the continuous independent dietary variables (i.e., E-DII scores, principal components) were related to *Sleep Disturbance,* so no statistical adjustments were made for health status.

Although physical activity levels could also be related to diet quality, mood and sleep quality, as discussed, significant problems with the IPAQ data meant that these relationships could not be examined.

The results of Study 2 analyses (combined dataset only) are summarised in Figure 5.4.

Figure 5.4. Schematic showing significant pathways linking diet quality, mood and sleep quality variables in day and night shift workers (for clarity, expected sleep-sleep and sleep-mood relationships not shown).



SQ = Sleep Quality; SL = Sleep Latency; SD = Sleep Duration; HSE = Habitual Sleep Efficiency; SDS = Sleep Disturbances; USM = Use of Sleeping Medication; DD = Daytime Dysfunction.

5.5 DISCUSSION

The current study investigated the interrelations between diet quality, mood and sleep quality in a sample of *N* = 410 shift working police employees. Over one-quarter of the sample (28.05%) worked regular night shifts (most/all of the time or frequently), while almost three-quarters (72%) were regular day shift workers (working nights either occasionally or never). The principal hypothesis was that diet-derived inflammation is one of the mechanisms that connects diet quality to both mood and sleep quality.

PCA and mediation analyses enabled evaluation of the impact of emergent dietary patterns and other dietary behaviours (i.e., regular fast food intake), and their associated inflammatory potential, on the mood and sleep measures. These analyses support the hypothesis insofar as diet-derived inflammation fully mediated the relationships between the dietary patterns and depression in the combined dataset. Thus, all three principal dietary components were protective of depressive symptoms via their anti-inflammatory properties. This finding is supported by Wirth and colleagues, who reported that any form of shift work was associated with a higher risk of mild depression compared to non-shift working day workers, and that the relationship between shift work status and mild depression was partly mediated by DII (Wirth et al, 2017).

In terms of sleep quality, the apparent protective effects of *HI-FATS-LO-CARBS* and *MEDITERRANEAN* over *Daytime Dysfunction* and daytime sleepiness (*ESS*) were fully

mediated by the anti-inflammatory properties of the two dietary patterns in the combined dataset. This therefore supports the hypothesis that the underlying inflammatory properties of the dietary patterns drive their apparent effects on sleep quality. In contrast, although *HI-FIBRE-LO-SFA* was also protective of *Daytime Dysfunction* and daytime sleepiness (*ESS*) in the combined dataset, this relationship was not driven by the anti-inflammatory properties of this dietary pattern. Non-inflammatory mechanisms are not the focus of this thesis, but proposed mechanisms include modulation of the gut microbiome. As discussed in Chapter 4, high fibre diets promote gut microbial eubiosis, and some species synthesise neurotransmitters that are involved in regulating the sleep-wake cycle (e.g., serotonin, dopamine, GABA, acetylcholine, noradrenaline) (Kaur et al., 2019; Kesner & Lovinger, 2021). Certain gut microbial metabolites (e.g., butyrate) also influence serotonin secretion from intestinal cells (Reigstad et al., 2015).

It may seem incongruous that a dietary pattern low in fats (i.e., *HI-FIBRE-**LO-SFA***) was protective of sleep quality yet a pattern high in fats (i.e., ***HI-FATS**-LO-CARBS*) was also protective of the same sleep quality variables. However, this reflects differences in the **types** of fat represented by the two dietary patterns. The former component loaded particularly negatively towards *SFA,* while the latter had the highest *PUFA* loading of all three components. PUFA have a strongly anti-inflammatory effect scores (-0.337), whereas SFA are strongly pro-inflammatory (+0.373), so the relative loadings of these opposing anti-/pro-inflammatory effects contribute towards the overall inflammatory properties of the components as whole dietary patterns. *HI-FIBRE-LO-SFA* was a particularly strongly anti-inflammatory pattern. However, its negative *SFA* loading alone would not necessarily make it so strongly anti-inflammatory overall, but the positive *Fibre* loading in this component is

likely to contribute substantially, as dietary fibre has a strongly anti-inflammatory effect score (-0.663).

Sleep quality in the combined sample was not significantly associated with age. As discussed, self-reported sleep quality typically deteriorates with age (Schwarz et al., 2017), although not in all studies (Schwarz et al., 2017). As was the case in Study 1, the relatively narrow dispersion of the data (*M* = 42.65 years, *SD* = 10.82) may explain why no significant age-related differences in sleep quality were observed in this exclusively working age sample.

When the sample was split according to shift work status, a number of significant differences were observed between day workers and night workers. In terms of self-reported *diagnosed* anxiety and depression, day and night workers did not differ significantly, but in line with the hypothesis, night shift workers had significantly higher *HADS-D* scores than day shift workers. This suggests that mood was indeed worse in night workers, but that some symptoms were subclinical/undiagnosed and *HADS* was sensitive to differences in these symptoms between day and night workers. The current findings are supported by a large volume of published evidence of higher rates of depression in shift workers (e.g., Amlinger-Chatterjee 2016; Angerer et al., 2017; Bara & Arber, 2009; Weston, 2013; Wirth et al., 2017).

As predicted by numerous studies (Brown et al., 2020; Wirth et al., 2014a; Chang & Peng, 2021; Lim et al., 2020) and in line with the current hypothesis, subjective sleep quality/sleep duration in the night shift workers was significantly worse/shorter than the day shift workers.

It was also hypothesised that rates of over-weight and obesity would be significantly higher in the night shift workers than day workers, in line with published evidence (Buchvold et al., 2015; Liu et al., 2018; Proper et al., 2016; Ramin et al., 2015). However, the current data do not support this hypothesis, as BMI was not significantly different between the two groups. However, as hypothesised, diet quality was significantly poorer in the night shift workers, who consumed more *Energy* and less *Fibre*, *Vegetables* and *PUFA* than their day working colleagues. This was expected, because opportunities to eat freshly prepared, nutritious meals while working at night are likely to be limited. Night workers are therefore more likely to rely on convenient but energy-dense ready meals, fast foods and snacks than their day working colleagues. Importantly, and in line with the hypothesis, *DII* scores were 20.39% higher in regular night shift workers than their day working counterparts. Data on DII in shift workers is lacking, but Wirth and colleagues (2017) reported scores around 32% higher among shift workers (day and night) than non-shift working day workers (*N* = 18,875).

Also in line with the hypothesis, rates of chronic inflammatory disease (i.e., diagnosed physical and mental illness combined) were significantly higher in the police night shift workers compared to day workers. This finding is in line with strong published evidence (Barbadoro et al., 2013; Brown et al., 2020; Knutsson, 2003; Lee et al., 2017; Sookoian et al., 2007; Szkiela et al., 2020; Wang et al., 2014; Zhao et al., 2012). Although the aetiology of chronic inflammatory disease in night shift workers is likely to be complex and multi-factorial, given that night workers had significantly higher *E-DII* scores than day workers in the current sample, it is likely that diet-derived inflammation contributes to the increased risk of chronic inflammatory disease in night shift workers.

Study results should be interpreted with limitations in mind. In relation to Study 2 specifically, the observed diet/mood and diet/sleep associations were mediated via *E-DII* only in the combined dataset. This may be due to the smaller numbers of participants in each group when the sample was split according to shift work status. Furthermore, differences in the length of time engaged in shift work was not assessed – only current shift-work status was considered. Individuals may also have recently switched between schedules, from working predominantly nights to predominantly days, or vice versa, and the current study did not differentiate length of time working in the current night/day schedule. It is plausible that individuals with a long history of exposure to night shift work might have poorer diet, mood and sleep than those only recently engaged in it. Alternatively, those who have worked nights for many years may be naturally tolerant to its effects, or may have partially adapted to it over time, thus introducing selection bias into the sample.

In summary, the current study demonstrates that regular night shift work is detrimental to health, in terms of diet quality, mood and sleep quality. Further, diet-derived inflammation may drive the apparent detrimental effects of poor diet on mood and sleep quality. Increased levels of dietary inflammation may contribute not only to poorer mood and sleep in night shift workers, but to the higher rates of chronic inflammatory disease observed in night workers, a statistic that currently remains poorly understood (Szkiela et al., 2020).

6 STUDY 3: DIET, MOOD AND SLEEP IN A GENERAL POPULATION SAMPLE

6.1 INTRODUCTION

Prior to the COVID-19 pandemic, ethical approval had been granted for the third and final study of the PhD. It was to be an interventional study to assess the health effects of mild, chronic sleep restriction on diet and mood in healthy adults. In terms of background, and the rationale behind the study, the literature review illustrated that the vast majority of published sleep restriction studies curtailed sleep severely and acutely, for instance, to four or five hours over just a few nights. However, under normal, day-to-day circumstances, mild sleep deprivation is far more common than severe restriction (Alhola & Polo-Kantola, 2007), and as laboratory studies are necessarily short, it is unclear whether there is a cumulative effect when mild sleep deprivation becomes chronic. Further, as discussed earlier in the thesis, confining participants to the artificial environment of a sleep laboratory limits the ecological validity of these studies. In the study that was planned, participants would remain in their natural environments, continue their daily routines as normal and sleep at home, but they would restrict their sleep to six hours per night for ten nights. Compliance with the sleep-restriction schedule would be monitored by wrist actigraphy. Mood and diet would be assessed subjectively as before, and a blood sample would be taken from each participant at baseline and immediately post-intervention. This would be analysed for biological markers

of inflammation (CRP and pro-inflammatory cytokines). Thus, with objective measures of sleep (actigraphy) and systemic inflammation (inflammatory biomarkers), the final study would build upon the subjective, self-report surveys of studies one and two.

The study was scheduled to take place in April 2020, however, the COVID-19 pandemic forced the UK into lockdown at the end of March, so it could not go ahead. Given that sleep restriction is likely to have a detrimental effect on immune function, it was considered unethical to proceed with any form of sleep restriction schedule while there remained a risk of serious disease from COVID-19 infection. But with only months remaining to finish the PhD, putting the study on hold for an indefinite period was not an option, so the decision was taken to abandon the sleep restriction study and design an alternative, COVID-safe study that could be implemented rapidly.

6.2 AIMS AND OBJECTIVES

COVID-19 put an abrupt end to all face-to-face research at Nottingham Trent University during the 2020 lockdown. This severely limited the type and amount of data that could be collected, so the nature of the final study, and its aims and objectives, had to change drastically. Recruitment into the alternative study would be via email and social media only, there would be no face-to-face contact with participants, and all data would be collected online.

The study was divided into two: parts 3a and 3b. Study 3a consisted of an online survey, similar to studies one and two, but with a few key differences. It would investigate relationships between diet, mood and sleep, as before, but instead of targeting a specific workforce (non-shift working university staff, shift working police staff), Study 3 would be a population-level study, open to anyone over the age of 18. It was hypothesised that this would test the extent to which the findings from the more restricted, university/police samples persist in a wider and more diverse sample, including those working in other fields, students, and others not in work, including retired people. Identification of such patterns would enhance the overall ecological validity of the research. It was also hypothesised that rather than limiting the study to working age individuals, inclusion of a wider age range would allow identification of characteristics of sleep, mood and diet that were not observed in the narrower, working age samples.

Regarding specific unhealthy and healthy dietary behaviours that emerged from the earlier studies, Study 1 indicated that regular consumption of fast food was associated with significantly poorer mood. Thus, it was hypothesised that fast food intake would be related to mood in the current study, a finding that would add weight to the Study 1 finding. In Study 2 (combined dataset), a healthy dietary pattern, namely *MEDITERRANEAN,* was found to be protective of both depressive symptoms and sleep quality. Thus, a validated questionnaire specifically assessing adherence to a Mediterranean-style diet was added to Study 3a (further details to follow in Materials and Methods). *MEDITERRANEAN* was a dietary pattern identified by principal components analysis in Study 2, so it was hypothesised that the addition of a validated Mediterranean diet adherence screener to Study 3 would add weight to the PCA findings.

Having completed Study 3a, a subset of participants would be invited to participate in Study 3b. Studies 1 and 2 indicated that higher *PUFA* intake was associated with better mood and sleep quality, but it was not possible to ascertain whether the apparent association was related to omega-3 or omega-6 PUFA intake, or a combination of both, because the EPIC-Norfolk FFQ does not provide separate data on each type of PUFA. Technological advances since the start of the PhD meant that a new, online 24-hour dietary recall system was now available. "Intake24" provides automatic coding to nutrients, and separate outputs for omega-3 and omega-6 PUFA. Thus, the objective of Study 3b was to investigate whether omega-3 and omega-6 PUFAs are differentially related to the outcomes observed in studies one and two. Intake24 also provides data on *trans* fat intake, which is not available from the FFQ. As explained in Chapter 1, *trans* fatty acids (TFA) are artificial fats manufactured by the food industry to stabilise and prolong the shelf life of processed products. They have been

shown to increase dietary inflammatory burden(Baer et al., 2004; Mozaffarian, 2006), and in terms of DII, have a pro-inflammatory effect score (+0.23/gram) (Shivappa et al., 2014a). TFA have been linked to cardiovascular disease (Mozaffarian et al., 2009) and depression (Sánchez-Villegas et al., 2011; Akbaraly et al., 2013), and it was hypothesised that *trans* fat intake would be associated with higher DII scores and poorer mood and sleep quality in the current sample.

One of the limitations of the earlier studies was that the EPIC-Norfolk FFQ appeared to underestimate daily energy intake, suggesting that portions sizes are also underestimated. The semi-quantitative questionnaire includes standard portion sizes, such as "one slice" of bread, "one bowl" of soup, but these are open to interpretation, and misreporting of energy intake is widely recognised in nutritional epidemiology (Carlsen et al., 2010; Mahabir et al., 2006). Intake24 presents images of different sized portions for the participant to select, which may provide a more precise, visual depiction of portion size (further details to follow in Materials and Methods).

Given that Study 3 was conducted during the first wave of COVID-19, the psychological effects of an unfolding pandemic and national lockdown, as well as the effects of COVID infection (physical and psychological) in those who caught the virus early on, would need to be considered. Post-COVID syndrome, or "long-COVID", was also emerging. This is a post-viral syndrome in which symptoms persist for 12 weeks or more after the initial infection (O'Dowd, 2021). These include persistent respiratory symptoms, fatigue, "brain fog", muscle/joint aches, sleeping difficulties and depression (O'Hare, 2021). Thus, a further hypothesis was that long COVID sufferers would have significantly poorer mood and sleep quality scores than

patients who made a full recovery. As it is currently poorly understood, an exploratory analysis would investigate whether individuals suffering from long-COVID were significantly different from those who made a full recovery, in terms of diet quality, mood and sleep quality.

6.3 MATERIALS AND METHODS

6.3.1 STUDY SAMPLE

Participants were over the age of 18; no other eligibility criteria were applied, including employment status.

6.3.2 STUDY DESIGN AND DATA COLLECTION

The overall design of Study 3a remained the same, i.e., a cross-sectional, retrospective analysis of diet, mood and sleep. It was approved by Nottingham Trent University Research Ethics Committee and all participants provided written, informed consent. Participation was voluntary and anonymous, and individuals were invited to take part via social media and email. As before, the study consisted of a self-report survey, hosted via the online survey platform Qualtrics (Provo, Utah, USA), and included a battery of validated instruments assessing diet quality, mood and sleep quality, plus an additional questionnaire of 35 items about demographics, lifestyle and health (including COVID status).

6.3.2.1 DIET AND DIET QUALITY

Dietary data were collected using the semi-quantitative EPIC-Norfolk food frequency questionnaire (Version 6: CAMB/PQ/6/1205; EPIC-Norfolk: DOI 10.22025/2019.10.105.00004), as before. Detailed information about the questionnaire and how the output is processed can be found in Chapter 4. Again, the study focussed on the following macronutrient variables (grams per day): *Cholesterol*, *Carbohydrates*, *Sugars*, *Fibre*, *MUFA*, *PUFA* and *SFA*, and the following food groups: *Fish and Fish Products*, *Fruit*, *Vegetables*, *Meat and Meat Products*. Total calorie intake was included for energy adjustment, and the same dichotomous variable, *Fast Food* (once a week or more: yes/no) was created from the free-text section of the FFQ.

6.3.2.1.1 DIETARY INFLAMMATORY INDEX

E-DII scores were calculated as a measure of the inflammatory potential of participants' diets (Shivappa et al., 2014a). Further information, including a list of the 25 Epic-Norfolk FFQ variables used to calculate the scores, is provided in the Materials and Methods section of Chapter 4.

6.3.2.1.2 MEDITERRANEAN DIET ADHERENCE SCREENER

An additional questionnaire measured adherence to a Mediterranean-style dietary pattern. The Mediterranean Diet Adherence Screener (MEDAS) (Schröder et al., 2011) is a short (14-

item) screening questionnaire, originally developed for use in a Spanish population. It was chosen for the current study because it has also been validated in the UK, and has acceptable concurrent validity and test-retest reliability when compared to food records (Papadaki et al., 2018).

6.3.2.1.3 INTAKE24 (Study 3b participants only)

Following completion of Study 3a, a subset of participants was invited to participate in Study 3b, which consisted of an additional dietary assessment. Intake24 (intake24.co.uk) is an open-source, online 24-hour dietary recall platform developed by Newcastle and Cambridge Universities. It provides a more detailed assessment of fat intake than the FFQ because it splits PUFA into its constituent types (omega-3 and omega-6) and also provides data on *trans* fatty acid (TFA) intake. Based on a database of over 2800 foods and more than 2500 images, participants are required to enter everything they consumed from midnight to midnight the previous day, with image-guided estimation of portion size. Response data are automatically coded into 62 food parameters, including energy, alcohol, macronutrients and micronutrients. Validated against trained-interviewer-led multiple pass 24-hour recalls, mean intakes were within 4% of the interviewer-led assessments, and energy intake was underestimated by an average of just 1% compared to the interviewer-based recalls (Bradley et al., 2016). Each recall takes less than 20 minutes to complete, on average. Participants completed the online recalls on their home computers or mobile devices on three non-consecutive days, including two weekdays and one weekend day.

6.3.2.2 MOOD

Mood was assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), as before. This is a well validated measure of psychological distress experienced over the previous week (see Chapter 4, Materials and Methods, for further details).

6.3.2.3 SLEEP QUALITY

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and Epworth Sleepiness Scale (ESS; Johns, 1991). Both are validated instruments used in studies 1 and 2, and as before, detailed information can be found in Chapter 4.

6.3.2.4 PHYSICAL ACTIVITY

Physical activity was assessed using the short-form International Physical Activity Questionnaire (IPAQ; Booth, 2000; Craig et al., 2003). This is a validated scale that assesses physical activity and sedentary behaviour over the previous seven days. It consists of eight items to assess moderate and vigorous activity and sedentary behaviour (i.e., time spent sitting).

6.3.3 DATA MANAGEMENT/STATISTICAL ANALYSES

The IBM SPSS Data Analysis version 28 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. An alpha level of .05 was set as the significance criterion for all statistical tests and reported *p* values are all 2-tailed.

The EPIC-Norfolk FFQ and Intake24 data were energy adjusted via the residual method (Willett & Stampfer, 1986). DII scores were calculated from FFQ data and adjusted via the energy-density method, as before, to yield E-DII scores.

Preliminary analyses consisted of an examination of the distributions. If non-normal distributions were observed, non-parametric tests were used to assess bivariate relationships. Data were also checked for missing values and outliers. As before, if fewer than 10% of values were missing from individual scales, these items were replaced by the mean score for that variable, or in the case of *Sleep Duration*, the mode was used. FFQ and Intake24 data were excluded if participants reported extreme energy intakes (< 500 or > 4000 calories/day), in line with widely used criteria (e.g., Katagiri et al., 2014). Descriptive statistics enabled the demographic, lifestyle and health characteristics of participants to be described. Pearson's chi-square tests of independence and Fisher's exact tests were used to examine the relationship between dichotomous categorical variables, such as sex and smoking status. Independent samples *t*-tests or Mann-Whitney U tests (where a non-parametric approach was indicated) tested for sex differences in continuous variables such as age, mood, sleep quality and diet quality, including E-DII scores.

To reduce the number of independent variables and identify mutually independent patterns in the dietary data, a principal components analysis was carried out on the energy-adjusted EPIC-Norfolk FFQ variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products*, and *Meat and Meat Products*). The relationship between the dietary patterns that emerged as principal components, and *E-DII*, mood and sleep variables, was then examined with multiple linear regression, with the dietary patterns as predictors. Where these tests of direct effects indicated the possibility of an indirect pathway between a dietary pattern and a mood or sleep variable via *E-DII*, Hayes' PROCESS procedure (v4, http://www.afhayes.com) was used to test whether the indirect effect was significant. Together, these analyses enabled evaluation of the potential impact of emergent dietary patterns and two other dietary behaviours (regular fast food intake and adherence to a Mediterranean-style dietary pattern), and their inflammatory potential, on the mood and sleep measures.

6.4 RESULTS

6.4.1 PARTICIPANT CHARACTERISTICS

6.4.1.1 DEMOGRAPHICS

A total of *N* = 466 complete survey responses were received from Study 3a. Demographic, lifestyle and health characteristics of the participants are summarised in Table 6.1.

Table 6.1. Demographic, lifestyle and health characteristics of a population-based sample [*N* = 466 unless otherwise stated].

Sex (%)	
Male *n*	108 (23.2)
Female *n*	358 (76.8)
Age (y)	
Range	18 - 85
Median	33
Educational attainment (%)	
Degree level or above	185 (39.7)
A/AS level	128 (27.47)
BTEC/GNVQ or equivalent	74 (15.88)
Other qualification(s)	27 (5.8)
Working status [*n* = 457] (%)	
Full time	261 (56.01)
Part time	87 (18.67)
Student	82 (17.6)
House duties	16 (3.43)
Retired	11 (2.36)
Smoking status (%)	
Current smokers	87 (18.67)
Non-smokers	373 (80.04)
Withheld	6 (1.29)
Median cigarettes/day	10

Range	1 – 44
Alcohol consumption at least weekly (%)	
Yes	247 (53)
No	219 (47)
Median units/week	11
Range	1 – 40
BMI [*n* = 453]	
Under weight	9 (1.99)
Normal	209 (46.14)
Over-weight	123 (27.15)
Obese	87 (19.21)
Morbidly obese	25 (5.52)
Physical activity [*n* = 439]	
Low	50 (11.39)
Moderate	206 (46.92)
High	183 (41.69)
General health (%)	
Chronic illness (total)	92 (19.74)
Physical illness	54 (11.59)
Anxiety and/or depression	44 (9.44)
Withheld	4 (0.86)
Regular prescription medication	191 (40.99)
Withheld	3 (0.64)

Preliminary analyses included Shaprio-Wilk and Kolmogorov-Smirnov tests of normality in conjunction with inspection of Q-Q plots. Only *E-DII* and *MEDAS* scores had approximately normal distributions. Based on this, median rather than mean descriptive statistics are reported, and non-parametric tests (Spearman's rho) were used to examine bivariate relationships between variables.

Participants ranged from 18 to 85 years of age and over three-quarters (76.80%) were female. An independent samples Mann-Whitney U test indicated that males and females did not differ significantly in age. In total, 83.69% described themselves as White, with low numbers across a range of other ethnic groups, so no further analysis of ethnicity was undertaken. Over half worked full time (56.01%), 18.67% worked part time and 17.60% were students.

Thus, almost 93% of the sample were engaged in some form of work or study and almost three-quarters were employed (74.68%). Almost 5% reported working regular night shifts (4.29%).

6.4.1.2 LIFESTYLE

Over 18% of the sample were current tobacco smokers (18.67%). This is above the national average of 13.9% according to the latest (2020) national figure for England (ons.gov.uk, 2021). A Pearson's chi-square test of independence revealed that the relationship between sex and smoking status was not significant, so males were no more likely to smoke than females. Over half (53%) reported drinking alcohol at least once a week and 17% of drinkers admitted consuming more than the recommended limit of 14 units per week. This is lower than the latest national figure of 24% (UK government National Statistics, 2020).

Thirteen participants had missing data which meant that BMI could not be calculated. Of the remaining 453, less than half (46.14%) had a normal BMI (18.50 – 24.99). Over a quarter (27.15%) were over-weight (BMI 25.00 – 29.99), almost 20% were obese (19.21%) (BMI 30.00 – 39.99) and 5.52% were morbidly obese (BMI $\geq$ 40.00).

n = 27 participants had missing data which meant that physical activity levels could not be calculated. Of the remaining 439, 41.69% declared high weekly physical activity levels, 46.92% had moderate levels and 11.39% reported low levels of physical activity.

6.4.1.3 GENERAL HEALTH

Almost 20% of the sample (19.74%) were suffering from at least one diagnosed chronic illness (physical and/or mental). The commonest conditions were anxiety and/or depression, of which almost 10% of the total sample declared (9.44%). 1.72% were suffering from sleep disorders, namely, insomnia (*n* = 3), obstructive sleep apnoea (*n* = 1), narcolepsy (*n* = 2) and sleep paralysis (*n* = 1).

Almost 40% of the sample were taking regular prescribed medications (39.91%). The commonest drugs were hormonal contraceptives (*n* = 56) followed by antidepressants (*n* = 50), of which 10.73% of respondents were taking.

Almost 10% of participants (46/466 = 9.87%) reported that they had received a confirmed positive COVID-19 test result since the start of the pandemic, and 15 of those (32.61%) believed they were currently suffering from long-COVID. This is in line with current estimates that one third of patients have persistent symptoms at twelve weeks (O'Dowd, 2021). Independent samples Mann-Whitney U tests indicated that mood and sleep quality in long-COVID patients did not differ significantly from COVID patients who had made a full recovery. However, in terms of the EPIC-Norfolk FFQ variables, independent samples Mann-Whitney U tests indicated that long-COVID sufferers had significantly lower intakes of PUFA than patients who made a full recovery $U(N_{\text{long-COVID}} = 15, N_{\text{recovered}} = 46) = 101$, $z = -2.49$, $p = .01$. They also had significantly higher BMIs than COVID patients who had made a full recovery $U(N_{\text{long-COVID}} = 15, N_{\text{recovered}} = 46) = 315$, $z = 2.17$, $p = .03$.

6.4.2 DIET AND DIET QUALITY

Preliminary analysis of the EPIC-Norfolk FFQ data indicated that *n* = 16 participants reported either extremely high or low energy intakes (< 500 or > 4000 kcal per day). These individuals' responses were excluded from the dietary analyses. Independent samples Mann-Whitney U tests revealed that males consumed significantly more *Energy* (*Mdn* = 1530.92 kcal/day) than females (*Mdn* = 1419.34 kcal/day), $U(N_{male}= 102, N_{female} = 348) = 14876.00$, $z = -2.59$, $p = .01$. Following energy adjustment, males consumed significantly more *Meat and Meat Products*, (*Mdn* = 124.25 grams/day) than females (*Mdn* = 89.04 grams/day), $U(N_{male}= 102, N_{female} = 348) = 13721.00$, $z = -3.49$, $p < .001$. Males also consumed significantly more *Carbohydrates* (*Mdn* = 179.40 grams/day) than females (*Mdn* = 163.08 grams/day), $U(N_{male}= 102, N_{female} = 348) = 20506.00$, $z = 2.39$, $p = .02$, and significantly more *Sugars* (*Mdn* = 80.30 grams/day) than females (*Mdn* = 77.90 grams/day), $U(N_{male}= 102, N_{female} = 348) = 20634.00$, $z = 2.50$, $p = .01$. Females consumed significantly more *Fruit* (*Mdn* = 134.00 grams/day) than males (*Mdn* = 108.60 grams/day) $U(N_{male}= 102, N_{female} = 348) = 20710.00$, $z = 2.56$, $p = .01$), more *Fibre* (*Mdn* = 12.36 grams/day) than males (*Mdn* = 11.90 grams/day) $U(N_{male}= 102, N_{female} = 348) = 20962.00$, $z = 2.78$, $p = .01$, and more *Vegetables* (*Mdn* = 215.46) than males (*Mdn* = 191.61) $U(N_{male}= 102, N_{female} = 348) = 20723.00$, $z = 2.58$, $p = .01$.

As stated above, *E-DII* scores (derived from the FFQ data) were normally distributed and ranged from -3.98 (most anti-inflammatory) to +3.31 (most pro-inflammatory). Scores calculated from 25 to 30 food parameters can range from -5.5 to +5.5 (Hébert et al., 2019). The mean score was -0.3 (*SD* = 1.6), which is within the neutral range of inflammatory diet

(Wirth et al., 2021). Scores did not differ significantly between males and females, so subsequent analyses were not stratified by sex.

MEDAS data were also normally distributed, ranging from 0 to 10 (possible range 0 - 14) with a mean score of 5.16 (*SD* = 1.96). This compares with a mean of 5.5 (*SD* = 2.1) in a UK validation study of *n* = 99 adults recruited from General Practices in Bristol (Papadaki et al., 2018). Mean *MEDAS* scores did not differ significantly between males and females.

6.4.3 MOOD

Circa one third (33.91%) of the sample scored on or above the clinical threshold for depressive symptoms (*HADS-D* $\geq$ 8). Half of all participants (50%) were suffering from clinical levels of anxiety (*HADS-A* $\geq$ 8). Females had higher *HADS-D* scores (*Mdn* = 6) than males (*M*dn = 4), and an independent samples Mann-Whitney U test revealed that this difference was significant $U(N_{male} = 108, N_{female} = 358) = 24124$, $z = 3.92$, $p < .001$. Females also had significantly higher *HADS-A* scores (*Mdn* = 8.5) than males (*Mdn* = 5), and an independent samples Mann-Whitney U test revealed that this difference was significant $U(N_{male} = 108, N_{female} = 358) = 25333.5$, $z = 4.90$, $p < .001$. Again, this is in line with the published literature, in which females typically have higher rates (Breeman et al., 2015). Older adults tend to report poorer mood than younger individuals (Thielke et al., 2010), but in the current sample, neither *HADS-A* nor *HADS-D* scores were significantly associated with age.

6.4.4 SLEEP QUALITY

ESS scores ranged from 0 to 22 (possible range 0 – 24) with a median score of 6. Almost 23% of participants (22.96%) reported excessive daytime sleepiness according to the clinical threshold (ESS > 10). A Spearman's correlation revealed that scores were related to age (r_s = .10, p = .04, N = 466); sleep quality in terms of daytime sleepiness deteriorated with age, in line with normative data (e.g., Schwarz et al., 2017). An independent samples Mann-Whitney U test revealed that *ESS* scores did not differ significantly between males and females.

Nocturnal sleep quality scores (*PSQI-global*) ranged from 0 to 18 (possible range 0 - 21) with a median score of 7. Circa 65% (65.02%) had unsatisfactory sleep quality according to the clinical cut-off (*PSQI-global* scores > 5). Spearman's correlations revealed that *PSQI-global* scores were not significantly related to age, but the subcomponent scores *Sleep Quality* (r_s = .1, p = .03, N = 466), *Sleep Duration* (r_s = .24, p < .001, N = 466), *Sleep Disturbance* (r_s = .16, p < .001, N = 466) and *Use of Sleeping Medications* (r_s = .12, p = .008, N = 466) all increased with age. This indicates that older individuals reported some aspects of poorer sleep quality than younger individuals, in line with normative data (e.g., Schwarz et al., 2017). Females reported significantly worse sleep quality (*Mdn* = 8) than males (*Mdn* = 7), and an independent samples Mann-Whitney U test revealed that this difference was significant $U(N_{male} = 108, N_{female} = 358) = 23587.50$, z = 3.48, p < .001. Again, this is in line with published literature, in which females typically report more problematic sleep than males (Sander et al., 2016; Mong and Cusmano, 2016).

6.4.5 RELATIONSHIPS BETWEEN DIET QUALITY, MOOD AND SLEEP QUALITY

Non-parametric tests (Spearman's rho) were used to examine bivariate relationships between variables, as illustrated in Table 6.2.

Table 6.2. Spearman's correlations between diet quality, mood and sleep quality in a general population sample (*N* = 466).

Correlations

			ESS	PSQI-global	HADS-A	HADS-D	MEDAS	FAST FOOD	E-DII
Spearman's rho	ESS	Correlation Coefficient	--						
		Sig. (2-tailed)	.						
		N	466						
	PSQI-global	Correlation Coefficient	.096*	--					
		Sig. (2-tailed)	.039	.					
		N	466	466					
	HADS-A	Correlation Coefficient	.181**	.463**	--				
		Sig. (2-tailed)	<.001	<.001	.				
		N	466	466	466				
	HADS-D	Correlation Coefficient	.196**	.530**	.590**	--			
		Sig. (2-tailed)	<.001	<.001	<.001	.			
		N	466	466	466	466			
	MEDAS	Correlation Coefficient	-.021	-.077	-.088	-.107*	--		
		Sig. (2-tailed)	.648	.096	.057	.022	.		
		N	465	465	465	465	465		
	FAST FOOD	Correlation Coefficient	.020	.117*	.038	.099*	-.179**	--	
		Sig. (2-tailed)	.672	.012	.411	.032	<.001	.	
		N	466	466	466	466	465	466	
	E-DII	Correlation Coefficient	.024	.078	.081	.167**	-.505**	.171**	--
		Sig. (2-tailed)	.608	.097	.085	<.001	<.001	<.001	.
		N	450	450	450	450	449	450	450

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 6.2 indicates that anxiety (*HADS-A*) and depression (*HADS-D*) were strongly correlated. As discussed in Chapter 1, anxiety and depression are frequently comorbid (Kessler et al.,

1996). Daytime sleepiness (*ESS*) and nocturnal sleep quality (*PSQI-global*) were also correlated.

As expected, the two sleep quality measures were significantly related to mood. Individuals with higher levels of anxiety and depression had significantly poorer sleep quality (higher *ESS* and *PSQI-global* scores). These results are in line with well-established published research highlighting the bidirectional relationship between sleep and mood, as previously discussed.

In terms of healthy and unhealthy dietary behaviours, *E-DII* scores correlated negatively with *MEDAS* and positively with *Fast Food*, indicating that higher adherence to a Mediterranean-style diet was a significantly anti-inflammatory dietary habit, while regular intake of fast food was a significantly pro-inflammatory dietary behaviour. *MEDAS* scores correlated negatively with *Fast Food*, indicating that individuals with higher adherence to a Mediterranean-style diet were less likely to be regular consumers of fast food.

E-DII scores correlated positively with *HADS-D* scores, indicating that diets more pro-inflammatory in nature were associated with significantly poorer mood. *MEDAS* and *Fast Food* were also both associated with mood. Higher adherence to a Mediterranean-style dietary pattern was associated with significantly lower levels of depression. Conversely, regular intake of fast food was associated with significantly higher rates of depression. Given that both *MEDAS* and *Fast Food* were associated with *E-DII* scores, and *E-DII* was directly related to *HADS-D*, it was possible that the relationships between diet and mood were driven by the inflammatory properties of the two dietary patterns. To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com), model 4,

with 5000 bootstrap samples, with *MEDAS* or *Fast Food* as the predictor, *E-DII* as mediator, and *HADS-D* as the outcome variable. With *MEDAS* as predictor, the direct pathway between *MEDAS* and *HADS-D* became non-significant, and the indirect pathway, via *E-DII*, was significant (indirect effect = -0.14, 95% CI [-0.24, -0.04]). Thus, the observed inverse association between adherence to a Mediterranean-style diet and depressive symptoms was fully mediated by the anti-inflammatory properties of this dietary behaviour. With *Fast Food* as predictor, both the direct (direct effect = 0.98, 95% CI [0.3, 1.92]) and indirect effect (indirect effect = 0.26, 95% CI [.07, .51]) were significant. Thus, the association between regular fast food intake and poorer mood was partially mediated by the pro-inflammatory properties of this dietary behaviour.

E-DII scores did not correlate significantly with *ESS* or *PSQI-global* scores. Of the PSQI subcomponents, higher *E-DII* scores were associated with significantly longer *Sleep Latency* (r_s = .09, p = .046, n = 450) and more *Daytime Dysfunction* (r_s = .12, p = .01, n = 450) (PSQI subcomponent data not tabulated for clarity).

Fast Food correlated positively with *PSQI-global* scores. Of the PSQI subcomponents (not tabulated for clarity), *Fast Food* was also associated with significantly longer *Sleep Latency* (r_s = .14, p = .004, N = 466) and more *Sleep Disturbance* (r_s = .1, p = .04, N = 466). Given that *Fast Food* was a pro-inflammatory dietary behaviour, and *E-DII* was also directly related to *Sleep Latency* (but not *Sleep Disturbance or PSQI-global*), it was possible that the relationship between regular fast food intake and *Sleep Latency* was driven by the pro-inflammatory properties of *Fast Food*. To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) as before, with *Fast Food* as the predictor,

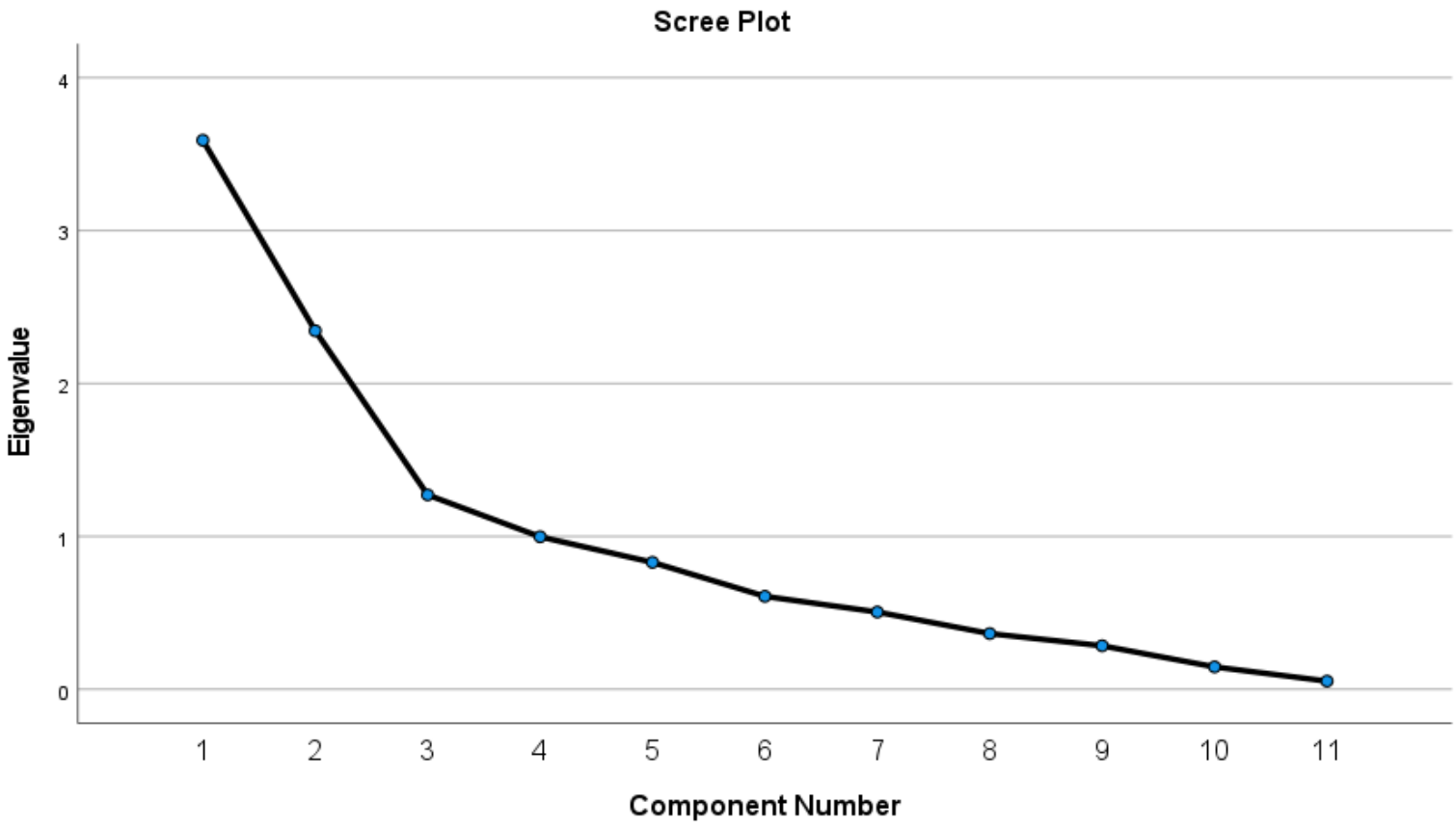
E-DII as mediator, and *Sleep Latency* as the outcome variable. Both the direct (direct effect = 0.27, 95% CI [0.05, 0.49]) and indirect effect (indirect effect = 0.03, 95% CI [0.0002, 0.07]) were significant in the mediation model, indicating that the association between fast food intake and *Sleep Latency* was driven in part by the pro-inflammatory nature of this dietary behaviour.

MEDAS was not significantly related to *ESS* or *PSQI-global* scores, but of the PSQI subcomponents, *MEDAS* correlated negatively with *Habitual Sleep Efficiency* (r_s = -.1, p = .04, N = 465) and *Daytime Dysfunction* (r_s = -.09, p = .046, N = 465), indicating that higher adherence to a Mediterranean-style dietary pattern was associated with better sleep efficiency and less daytime dysfunction (subcomponent data not tabulated). Given that *MEDAS* was an anti-inflammatory dietary behaviour, and *E-DII* was also directly related to *Daytime Dysfunction*, it was possible that the relationship between *MEDAS* and *Daytime Dysfunction* was driven by the anti-inflammatory properties of this dietary pattern. To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com), as before, but with *MEDAS* as the predictor, *E-DII* as mediator, and *Daytime Dysfunction* as the outcome variable. Neither the direct nor indirect pathway was significant in the mediation model, indicating that the apparent protective effect of the Mediterranean-style diet over sleep quality was not driven by the anti-inflammatory properties of this dietary behaviour.

6.4.6 EXTRACTION OF DIETARY PATTERNS

PCA with Varimax rotation was conducted on the eleven energy-adjusted EPIC-Norfolk FFQ variables (*Carbohydrates, Sugars, Fibre, MUFA, PUFA, SFA, Cholesterol, Fruit, Vegetables, Fish and Fish Products* and *Meat and Meat products*). Bartlett's test of sphericity examined the significance of all the correlations within the correlation matrix and indicated that the data were suitable for PCA (approx. chi-square$_{(55)}$ = 2714.04, p = .00). The KMO test returned a value of 0.56, which approached the minimum acceptable value for adequate sampling. A KMO test on the Intake24 data (n = 24) returned a value of .39, indicating that these data were not suitable for PCA.

Figure 6.1. Scree plot showing the eigenvalues of components (n = 450).



A criterion of eigenvalues > 1 suggested a three-component model, which was also clearly indicated by the scree plot. The rotated component matrix is shown in Table 6.3.

Table 6.3. Rotated component matrix[a] with dietary loadings (*n* = 450).

	Component		
	1	**2**	**3**
Dietary variables[b]	***HI-FIBRE-LO-SFA***	***HI-FATS-LO-CARBS***	***HI-CARBS-LO-MEATS***
Carbohydrates (total)	.294	**-.662**	**.538**
Cholesterol	-.168	.081	**-.740**
Fibre	**.890**	.148	.257
Sugars (total)	.108	**-.610**	**.523**
MUFA	-.250	**.789**	.022
PUFA	.212	**.732**	.192
SFA	**-.799**	.221	.007
Fish and Fish Products	.211	.366	-.131
Fruit	**.689**	-.162	.269
Meat and Meat Products	-.135	-.083	**-.875**
Vegetables	**.754**	.366	.145

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids
a. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations.
b. All EPIC-Norfolk FFQ dietary variables adjusted for energy intake (residual method).

The three components explained 65.53% of the total variance in the model and were labelled according to the salient features of their loadings. *Fibre*, *Vegetables* and *Fruit* loaded positively, and *SFA* loaded negatively onto Component 1, so this component was labelled *HI-FIBRE-LO-SFA*. As *MUFA* and *PUFA* loaded positively, and the carbohydrate variables (total *Carbohydrates* and total *Sugars*) loaded negatively onto Component 2, it was named *HI-FATS-LO-CARBS*. Component 3 was labelled *HI-CARBS-LO-MEATS*, along similar lines.

6.4.6.1 DIETARY PATTERNS AND THEIR INFLAMMATORY POTENTIAL

The relationships between the dietary patterns and *E-DII* were analysed using multiple linear regression, with the three components as predictors and *E-DII* as the outcome variable. *HI-FIBRE-LO-SFA* was associated with significantly lower *E-DII* scores (β = -.83, $p < .001$), accounting for 69% of the variance in the model (adjusted $R^2 = .69$, $F_{(3,446)} = 331.13$, $p < .001$), indicating that this was a strongly anti-inflammatory dietary pattern. The remaining two dietary components were not significantly associated with *E-DII.*

6.4.6.2 DIETARY PATTERNS AND MOOD

To test the possibility that the dietary patterns were directly related to mood, separate multiple linear regression analyses were conducted, with the three dietary components as predictors and *HADS-A* or *HADS-D* as the outcome variable. *HADS-A* was not significant, but with *HADS-D* as the dependent variable*, HI-FIBRE-LO-SFA* was associated with significantly lower *HADS-D* scores (β = -.15, $p < .001$) accounting for 3% of the variance in the model (adjusted $R^2 = .03$, $F_{(3,446)} = 5.57$, $p < .001$). Given that *HI-FIBRE-LO-SFA* was an anti-inflammatory dietary pattern and *E-DII* scores and *HADS-D* were positively correlated (see Table 6.2), it was possible that *HI-FIBRE-LO-SFA* was indirectly related to *HADS-D*, via *E-DII*.

To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) as before, with *HI-FIBRE-LO-SFA* as the predictor, *E-DII* as mediator, and *HADS-D* as the outcome variable. The direct pathway between *HI-FIBRE-LO-SFA* and

HADS-D became non-significant in the mediation model, and indirect pathway was significant (indirect effect = -0.68, 95% CI [-1.24, -0.10]). Thus, the apparent protective effect of *HI-FIBRE-LO-SFA* over depressive symptoms was fully mediated by the anti-inflammatory properties of this dietary pattern.

6.4.6.3 DIETARY PATTERNS AND SLEEP QUALITY

To test the possibility that the dietary patterns were directly related to sleep, separate multiple linear regressions were conducted with the three dietary components as predictors and the sleep quality variables as outcome variables. The dietary patterns were not significantly associated with ESS, global PSQI or PSQI subcomponent scores. However, given that *HI-FIBRE-LO-SFA* was an anti-inflammatory pattern, and *E-DII* scores were positively correlated with the PSQI subcomponents *Sleep Latency* and *Daytime Dysfunction*, it was possible that *HI-FIBRE-LO-SFA* was indirectly related to the two sleep quality variables via *E-DII*.

To test this, mediation analyses were conducted using Hayes' PROCESS procedure (v4, http://www.afhayes.com) as before, with *HI-FIBRE-LO-SFA* as the predictor, *E-DII* as mediator, and each of the two PSQI variables as the outcome variable. The indirect pathways were non-significant in the mediation models, demonstrating that there were no indirect relationships between *HI-FIBRE-LO-SFA* and sleep quality mediated via E-DII.

6.4.7 ADJUSTMENTS FOR POTENTIAL COVARIATES AND CONFOUNDERS

As discussed in chapters four and five, several factors, including age, sex and health status, could be related to the diet, mood and sleep variables and therefore potentially confound the observed relationships.

Spearman's correlations revealed a number of significant relationships between age and continuous diet, mood and sleep quality variables. To test whether the bivariate relationships observed between continuous diet variables (i.e., *E-DII*, *MEDAS* and *HI-FIBRE-LO-SFA*) and mood, and diet and sleep quality variables were independent of age, the non-normally distributed variables were log-transformed, and then partial Pearson's correlations, controlling for *log10_age,* were undertaken on the significant pairs of variables. The only bivariate relationships to lose their significance when controlling for the effects of age, were between *MEDAS* and *Daytime Dysfunction* (p = .05), and *MEDAS* and *Habitual Sleep Efficiency* (p = .76). The same results were obtained when these relationships were tested using linear regression, with age entered into the model as the confounding independent variable, alongside MEDAS. MEDAS itself correlated positively with age (r_s = .14, p = .004, N = 465), indicating that older individuals were more likely to be higher adherers to a Mediterranean-style diet than younger individuals. However, the other bivariate relationships between continuous variables all remained significant in partial correlations, indicating that these relationships were independent of the effects of age.

In terms of health status, cardiovascular disease, and chronic diseases associated with pain, such as musculoskeletal conditions, could covary with mood and sleep, so as before, two

categorical variables, *Cardiovascular System Drugs* (yes/no) and *Chronic Musculoskeletal Disorders* (yes/no) were created. 32 individuals declared taking cardiovascular system drugs, and 15 were suffering from chronic musculoskeletal disorders. Independent samples Mann-Whitney U tests revealed that both health status variables were associated with increasing age, but they were not related to the continuous mood and diet quality variables. Neither were they associated with ESS or PSQI-global scores, but of the PSQI subcomponents, those declaring chronic musculoskeletal conditions had significantly poorer *Sleep Quality* (PSQI subcomponent) than those without musculoskeletal conditions. However, none of the dietary variables were related to *Sleep Quality,* so no statistical adjustments were made for health status.

Independent samples Mann-Whitney U tests also examined relationships between the categorical variable *Sex* and the continuous diet quality (i.e., *E-DII, HI-FIBRE-LO-SFA*, *MEDAS*), mood and sleep quality variables. *Sex* was not significantly related to *E-DII*, *HI-FIBRE-LO-SFA* or *MEDAS*, but females had significantly higher *HADS-D* scores and higher *Sleep Disturbance*, *Habitual Sleep Efficiency*, *Daytime Dysfunction* and *PSQI-global* scores. These five variables were therefore log-transformed, but partial correlations revealed that all relationships remained significant after controlling for the effects of sex. The same results were obtained when these relationships were tested using linear regression, with sex entered into the model as the confounding independent variable, alongside HADS-D.

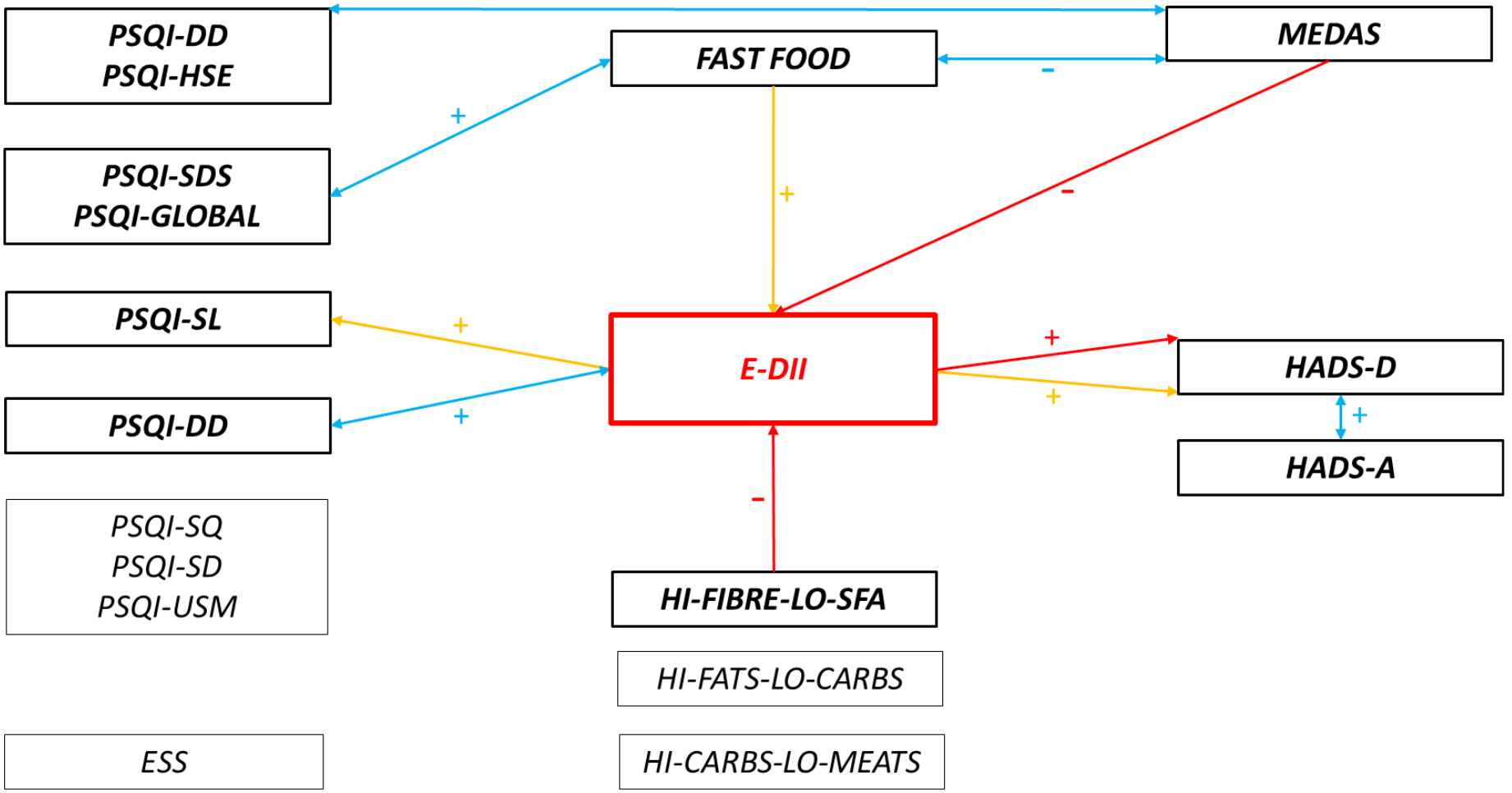
Pearson's chi-square tests of independence revelated that there were no significant differences between the categorical diet quality variable *Fast Food* and the two health status

variables, or *Sex*, and an independent samples Mann-Whitney U test indicated that there was not a significant association between *Fast Food* and *Age*.

Although physical activity levels could also be related to diet quality, mood and sleep quality, as discussed previously, significant problems with the IPAQ data meant that these relationships could not be examined.

Results of Study 3 analyses are summarised in Figure 6.2.

Figure 6.2. Schematic showing significant pathways linking diet, mood and sleep quality variables in a general population sample (for clarity, expected sleep-sleep and sleep-mood relationships not shown).



SQ = Sleep Quality; SL = Sleep Latency; SD = Sleep Duration; HSE = Habitual Sleep Efficiency; SDS = Sleep Disturbances; USM = Use of Sleeping Medication; DD = Daytime Dysfunction.

6.4.8 RELATIONSHIPS BETWEEN INTAKE24 FATS, MOOD AND SLEEP QUALITY (Study 3b participants only)

Of the participants who competed Study 3b, the Intake24 dietary recall (*n* = 24), no cases were excluded for reporting extreme energy intakes. Table 6.4 summarises bivariate correlations between Intake24 fat variables (*omega-3 PUFA, omega-6 PUFA, MUFA, SFA, TFA*), their inflammatory potential, and the mood and sleep variables.

Table 6.4. Spearman's correlations between Intake24 fats, their inflammatory potential, mood and sleep quality in a general population sample (*n* = 24).

Correlations

			ESS	PSQI_global	HADS_A	HADS_D	Intake24_SFA	INTAKE24_MUFA	Intake24_omega-3_PUFA	Intake24_omega-6_PUFA	Intake24_TFA	E-DII
Spearman's rho	ESS	Correlation Coefficient	--									
		Sig. (2-tailed)	.									
		N	466									
	PSQI_global	Correlation Coefficient	.096*	--								
		Sig. (2-tailed)	.039	.								
		N	466	466								
	HADS_A	Correlation Coefficient	.181**	.463**	--							
		Sig. (2-tailed)	<.001	<.001	.							
		N	466	466	466							
	HADS_D	Correlation Coefficient	.196**	.530**	.590**	--						
		Sig. (2-tailed)	<.001	<.001	<.001	.						
		N	466	466	466	466						
	Intake24_SFA	Correlation Coefficient	.369	.412*	.031	-.043	--					
		Sig. (2-tailed)	.076	.046	.885	.843	.					
		N	24	24	24	24	24					
	INTAKE24_MUFA	Correlation Coefficient	.007	-.035	.134	-.125	.269	--				
		Sig. (2-tailed)	.973	.871	.534	.562	.204	.				
		N	24	24	24	24	24	24				
	Intake24_omega-3_PUFA	Correlation Coefficient	-.055	-.515**	-.201	-.071	-.263	.317	--			
		Sig. (2-tailed)	.800	.010	.346	.742	.214	.131	.			
		N	24	24	24	24	24	24	24			
	Intake24_omega-6_PUFA	Correlation Coefficient	.056	-.219	-.063	-.076	-.047	.775**	.537**	--		
		Sig. (2-tailed)	.794	.305	.771	.724	.828	<.001	.007	.		
		N	24	24	24	24	24	24	24	24		
	Intake24_TFA	Correlation Coefficient	.543**	-.125	-.192	.030	.331	.010	.027	.037	--	
		Sig. (2-tailed)	.006	.559	.368	.890	.114	.961	.902	.864	.	
		N	24	24	24	24	24	24	24	24	24	
	E-DII	Correlation Coefficient	.024	.078	.081	.167**	.492*	-.134	-.483*	-.343	.049	--
		Sig. (2-tailed)	.608	.097	.085	<.001	.023	.563	.027	.128	.832	.
		N	450	450	450	450	21	21	21	21	21	450

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 6.4 shows a significant negative correlation between *omega-3 PUFA* and *E-DII* scores, indicating that this type of PUFA had anti-inflammatory properties, whereas *omega-6 PUFA* was not significantly associated with *E-DII* scores. Conversely, there was a significant positive correlation between *SFA* and *E-DII* scores, confirming that saturated fats were pro-inflammatory; *MUFA* and *TFA* were not significantly related to *E-DII* scores in the current (small) sample.

Intake24 fats were not significantly associated with mood, but they were associated with sleep quality. *Omega-3* (but not *omega-6*) *PUFA* correlated negatively, and *SFA* positively, with *PSQI-global* scores, and *TFA* correlated positively (and strongly) with *ESS* scores. Of the PSQI subcomponents (not tabulated for clarity), higher *TFA* intakes were strongly associated with poorer *Habitual Sleep Efficiency* (r_s = .57, p < .001, n = 24). Higher *SFA* intakes were also strongly associated with poorer *Habitual Sleep Efficiency* ($r_{s\ (24)}$ = .65, p < .001), and shorter *Sleep Duration* (r_s = .60, p = .002, n = 24). In contrast, higher intakes of *omega-3* (but not *omega-6*) *PUFA* were strongly associated with **better** *Habitual Sleep Efficiency* (r_s = -.42, p = .04, n = 24) and **longer** *Sleep Duration* (r_s = -.57, p = .004, n = 24); they were also strongly associated with better *Sleep Quality* (r_s = -.63, p = .001, n = 24).

In terms of potential confounders, females had significantly worse *Habitual Sleep Efficiency* than males, so partial correlations, controlling for the effect of *Sex* on the relationships between *TFA* and log-transformed *Habitual Sleep Efficiency* and *SFA* and log-transformed *Habitual Sleep Efficiency* were performed. Both bivariate correlations remained significant, indicating that these relationships were independent of sex.

In summary, higher intakes of pro-inflammatory *trans* fats were strongly associated with daytime sleepiness and poorer habitual sleep efficiency. Further, higher intakes of pro-inflammatory saturated fats were strongly associated with poorer nocturnal sleep quality, while higher intakes of anti-inflammatory omega-3 (but not omega-6) PUFA were strongly associated with better nocturnal sleep quality. Mediation analysis (via *E-DII*) was not attempted due to the small size of the dataset (also, *TFA* was not significantly associated with *E-DII*).

6.5 DISCUSSION

The current study investigated interrelations between diet quality, mood and sleep quality in a general population sample of *N* = 466 adults. PCA and mediation analyses enabled evaluation of the impact of emergent dietary patterns and other dietary behaviours (i.e., regular fast food intake, adherence to a Mediterranean-style diet), and their associated inflammatory potential, on the mood and sleep quality measures. PCA identified one, strongly anti-inflammatory dietary pattern, which was high in fibre and low in saturated fat. This dietary pattern was associated with significantly fewer depressive symptoms, and in support of the hypothesis, the apparent protective effect was fully mediated by the strong anti-inflammatory properties of this dietary pattern. Similarly, higher adherence to a Mediterranean-style diet (higher *MEDAS* scores) was associated with significantly fewer depressive symptoms, also fully mediated by the anti-inflammatory properties of this dietary behaviour. Thus, the addition of a validated Mediterranean diet scale to Study 3 reinforces the Mediterranean-style diet/mood and diet/sleep relationships that emerged from principal components analysis in studies 1 and 2.

Higher adherence to a Mediterranean-style diet (higher *MEDAS* scores) was also associated with better sleep quality, in terms of less daytime dysfunction and better habitual sleep efficiency, but these relationships were not mediated by the anti-inflammatory properties of higher *MEDAS* scores. Mediterranean-style diets are high in fruit, vegetables and wholegrains, which are high in dietary fibre. Thus, other, non-inflammatory mechanisms could include high fibre levels favouring gut microbial eubiosis, culminating in increased

serotonin and melatonin production, both of which are involved in regulating the sleep/wake cycle.

Diets featuring a regular intake of fast food were associated with significantly more depressive symptoms, and longer sleep onset latency, and both these relationships were partially mediated by the pro-inflammatory properties of fast food. Non-inflammatory, psychological mechanisms could also be mediating these relationships. In terms of mood, it is widely known that diets high in fast food are "unhealthy", so individuals who reported consuming it regularly might have experienced feelings of guilt for doing so. This negative emotion could have had a detrimental effect on mood, culminating in the observed higher *HADS-D* scores. In terms of both mood and sleep, another non-inflammatory mechanism could be related to the lack of dietary fibre in fast food, and its knock-on effects on the intestinal microbiota. As discussed in previous chapters, microbes in a eubiotic gut microbiome synthesise an array of neurotransmitters and hormones, including dopamine and serotonin (Cryan & Dinan, 2012), and act as sources of these neurotransmitters in the central nervous system (Kaur et al., 2019). A low fibre diet, leading to a dysbiotic microbiome deficient in these commensal/beneficial species, may reduce brain dopamine and serotonin levels, leading to poor mood. These neurochemicals are also involved in regulation of the sleep/wake cycle, and serotonin is the precursor of the sleep-regulatory hormone melatonin, so this could also account for the observed increase in sleep latency. The exact mechanisms underlying the crosstalk between gut microbiota and the brain are currently the subject of intense research.

Studies 1 and 2 indicated that polyunsaturated fats may be protective of mood and sleep quality, but it is unclear whether this is related to omega-3 or omega-6 PUFA intake (or both) because the EPIC-Norfolk FFQ does not distinguish between the two types of dietary PUFA. Omega-3 fatty acids have a strongly anti-inflammatory effect score (-0.436) whereas omega-6 are only slightly anti-inflammatory (-0.159). Inclusion of Intake24 in Study 3b revealed that the association between higher PUFA intake and better sleep quality was observed *only* with the (strongly anti-inflammatory) omega-3, not the omega-6 PUFA. This is important additional information that the FFQ could not provide, and may be a novel finding.

Intake24 also provides data on *trans* fat intake, which has a strongly positive inflammatory effect score (+0.229), so it was hypothesised that *trans* fat intake would be detrimental to sleep quality via its pro-inflammatory properties. Higher *trans* fat intakes were strongly associated with daytime sleepiness (*ESS* scores) and poorer nocturnal sleep efficiency, so the findings support this hypothesis, although given the small sample size, it was not possible to test whether this relationship was mediated via DII. As far as I am aware, the association between *trans* fat intake and sleep quality is a novel finding, and given the small sample size (n = 24), the strength of the correlations is notable. However, these findings need to be replicated in larger samples. It was also hypothesised that higher *trans* fat intake would be associated with poorer mood. This was not supported by the current data, but again, the hypothesis needs to be tested in larger samples.

Another advantage of Intake24 is its image-guided estimation of portion sizes. Sixteen responses had to be excluded from the EPIC-Norfolk FFQ dataset due to extremely high or low energy intakes (< 500 or > 4000 calories per day), but no responses were excluded from

Intake24 on the basis of extreme energy intakes. This suggests, as hypothesised, that Intake24 provides a more accurate estimation of daily food and total calorie intake than the semi-quantitative FFQ.

No selection criteria were applied in the current study, and it was hypothesised that this population-level sample would display characteristics not observed in the narrower, exclusively working age samples. In terms of sleep quality, the current data support this hypothesis. Sleep quality is known to deteriorate with age (Schwarz et al., 2017), and this was observed in the current sample, but not in studies one and two.

Almost 10% of participants reported COVID-19 infections, and 32.61% of those believed they were suffering from long-COVID. This is in line with current estimates that one-third of patients have persistent symptoms at twelve weeks (O'Dowd, 2021). It was hypothesised that long-COVID sufferers would have significantly poorer mood and sleep quality than COVID patients who had made a full recovery. This was not the case, but when long-COVID patients were compared to the whole sample (i.e., patients who had made a full recovery *and* those who had not contracted COVID), long-COVID patients had significantly higher *HADS-D* scores than the rest of the sample, and significantly worse sleep quality in terms of *Sleep Disturbance* (data not shown).

The findings of this study should be interpreted with some limitations in mind. No selection criteria were applied to employment status, and 5.75% of participants reported working night shifts frequently or most/all of the time. Diet, mood and sleep may all be impacted by night shift work, as illustrated by Study 2. However, due to the small numbers reporting regular

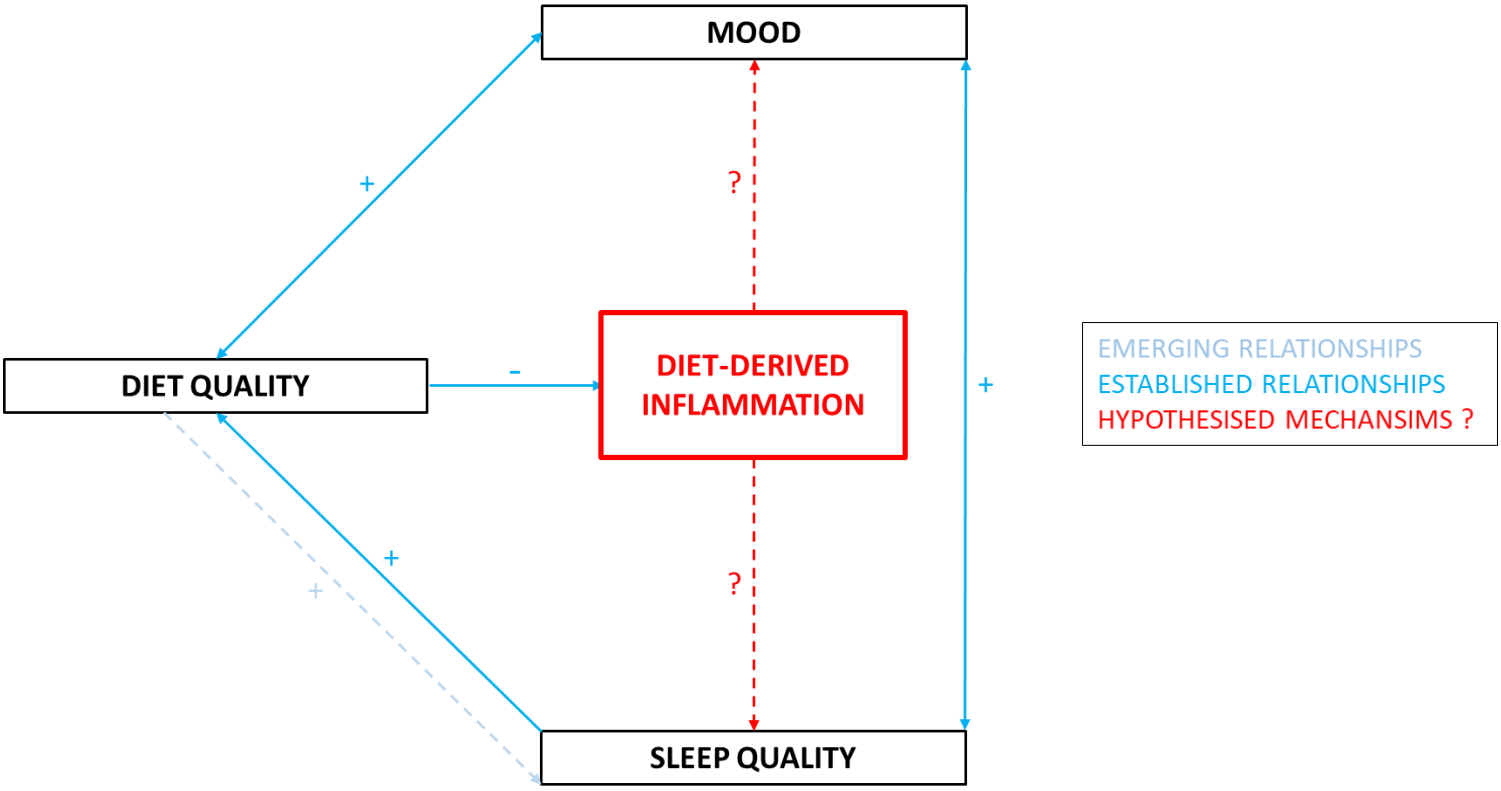
night work (*n* = 20), no attempt was made to stratify the sample according to day/night shift work status.

7 SYNTHESIS, IMPLICATIONS, LIMITATIONS AND FUTURE DIRECTIONS

7.1 SYNTHESIS

The final chapter of this thesis begins with a summary of the key findings across the three studies, bringing these individual strands together into a final synthesis. The main objective was to investigate potential mechanisms connecting diet to mood and sleep. Close relations exist between the three, but studies investigating the triad are scarce, so mechanisms driving the interrelations are poorly understood. The primary hypothesis was that subclinical, diet-derived inflammation drives the relationship that connects diet quality to mood and sleep quality. A reminder of the emerging and established pathways, and hypothesised mechanisms is presented below.

Figure 7.1. Schematic showing emerging and established pathways, and hypothesised mechanisms connecting diet quality to mood and sleep quality.



First, there was a consistent relationship between mood and sleep quality (*ESS* and *PSQI-global*) across all three studies. Further, all seven PSQI subcomponents were associated with mood across the three studies except for one subcomponent in Study 1 and one in Study 2. Thus, as hypothesised, poorer sleep quality was associated with significantly poorer mood in terms of both anxiety and depression. This finding is supported by a large evidence base of published literature, and indicates that the three samples under study were typical, in terms of mood/sleep relationships at least. The findings herein are therefore likely to be generalisable to the wider population.

As hypothesised, there was a consistent relationship between diet quality and mood, a pattern that was observed across all three studies. In general terms, diets high in fruit, vegetables, fibre, fish and polyunsaturated fats, and low in saturated fats were protective against depressive symptoms, and the relationships were ofttimes mediated, either partially, or fully, by the anti-inflammatory properties of these dietary patterns. The foods/macronutrients that loaded positively onto these dietary components are also reminiscent of a Mediterranean-style diet, and this was corroborated in Study 3, with the inclusion of the Mediterranean Diet Adherence Screener. Higher MEDAS scores were associated with significantly better mood, in terms of both anxiety and depressive symptoms, and the relationship was fully mediated by the anti-inflammatory properties of this dietary pattern. Full mediation indicates that the association between MEDAS and depression was better explained by the mediator. In other words, the influence was entirely through the robust anti-inflammatory properties of MEDAS. In contrast, regular (at least weekly) intake of takeaways was a significantly pro-inflammatory dietary behaviour across all three studies, and associated with significantly higher levels of depression in studies one and three. In both studies, the apparent detrimental effect of takeaway intake on mood was partially mediated by the pro-inflammatory properties of this dietary behaviour. Together, the consistency across three diverse samples is testament to the robustness of these diet quality/mood associations.

There was also a consistent, albeit limited relationship between diet quality and sleep quality across the studies. In general terms, as hypothesised, healthy dietary patterns, high in fruit, vegetables, fibre, unsaturated fats, and low in saturated fats, and diets resembling a Mediterranean pattern (i.e., high fruit, vegetables, fish, PUFA and low in meat products), were

associated with better sleep quality. In Study 1, dietary patterns high in fruits and low in fats were protective of daytime sleepiness (ESS). In Study 2, diets low in sugars and high in unsaturated fats (MUFA and particularly PUFA), and diets resembling a Mediterranean pattern (i.e., high in vegetables, fruit, fish and low in meat products) were also protective of daytime sleepiness (ESS), and both relationships were fully mediated by the anti-inflammatory properties of these two dietary patterns. Similarly, the diet resembling a Mediterranean pattern was also protective of *Daytime Dysfunction* (PSQI). Again, the relationship was fully mediated by the anti-inflammatory properties of this dietary pattern, and this finding was further supported by an inverse bivariate correlation between *MEDAS* scores and *Daytime Dysfunction* in Study 3 . In bivariate correlations between ESS and PSQI subcomponents, *Daytime Dysfunction* was the subcomponent with the strongest (positive) correlation with *ESS* across all three studies (Spearman's rho approximately .5). This suggests that although ESS and PSQI are two different instruments, the daytime impairment they identify is similar, and the fact that diet quality, in terms of its (anti-)inflammatory potential was associated with these measures of daytime impairment, demonstrates the consistency in these mediated relationships.

There were no significant direct associations between sleep quality measures and the three main dietary patterns (PCA) in Study 3, and in the first two studies, the observed relations were limited to ESS and just one of the seven PSQI subcomponents. Why were the sleep/diet associations so limited overall? One possible explanation is that none of the cohorts were clinical samples (i.e., patients with diagnosed sleep disorders), so associations between sleep difficulties and diet quality may not have been strong enough to reach significance in other PSQI sub-components and global sleep quality.

It is also important to note that ESS is only a measure of daytime sleepiness, not nocturnal sleep quality. Thus, although sleepiness during the day may well coincide with sleeping difficulties at night (and PSQI scores), the two scales are independent measures. For instance, individuals who regularly consume a large meal with alcohol at lunch time may score highly on daytime sleepiness, but their ESS score *per se* is not a measure of their nocturnal sleep quality.

Results across the three studies indicate that dietary fats were a key player in the current research, and that the different types of fat shared very different relationships with the mood and sleep variables. Dietary components with negative loadings towards saturated fats were associated with better mood and sleep quality across the first two studies, and in Study 3, higher SFA consumption (Intake24) was associated with poorer sleep quality (*PSQI-global*). Conversely, dietary components loading positively towards polyunsaturated fats were associated with significantly better mood (*HADS-D*) and sleep quality in studies one and two, but it is unclear whether this relationship was with omega-3 or omega-6 PUFAs (or a combination of both) because the EPIC FFQ does not provide information on the individual PUFAs. The inclusion of Intake24 in Study 3 helped clarify this by providing data on both omega-3 and omega-6 PUFA intakes. Results corroborate the first two studies, showing that PUFA was protective of sleep quality, but importantly, they revealed that the association was attributable *only* to omega-3 PUFA intake, not omega-6 PUFA. Higher omega-3 *PUFA* (a significantly anti-inflammatory nutrient in terms of DII scores) was moderately-to-strongly associated with **longer** *Sleep Duration*, **better** *Habitual Sleep Efficiency* and better *Sleep Quality,* and strongly associated with better overall sleep quality (*PSQI-global* scores), while higher *SFA* (a significantly pro-inflammatory nutrient in terms of DII scores) was associated

with significantly **shorter** *Sleep Duration* and **poorer** *Habitual Sleep Efficiency.* These inverse relationships with the two PSQI subcomponents illustrate how the two fats (omega-3 *PUFA* and *SFA*), with their opposing inflammatory properties, had opposing associations with sleep. Furthermore, even though omega-3 and omega-6 are both polyunsaturated fats, the former, anti-inflammatory fat, was moderately-to-strongly associated with improved sleep quality, whereas the latter shared no relationship with sleep quality at all, and was also not significantly pro- or anti-inflammatory in terms of *E-DII* scores. By providing separate outputs for omega-3 and omega-6 PUFA, Intake24 added important new information that the FFQ could not provide.

Intake24 also provides data on *trans* fat intake which were not available in the first two studies. Higher *TFA* intake was strongly associated with more daytime sleepiness (*ESS* scores), and strongly associated with poorer *Habitual Sleep Efficiency* (PSQI). The strength of the Intake24 fats associations with sleep is particularly noteworthy given the small size of the Intake24 dataset (*n* = 24).

This synthesis of key findings indicates that emergent dietary patterns were similar across the three studies, and that the relationship between the patterns and mood/sleep variables persisted across different working and non-working groups. As well as the consistencies across studies, there are also some differences to note.

7.1.1 LIFESTYLE ACROSS THE STUDIES

The police shift workers (Study 2) had the lowest rates of alcohol consumption (15.49%) above recommended limits (> 14 units/week) while the non-shift working university staff (Study 1) had the highest (20.31%). This is perhaps surprising, given the differences in education between the two samples: the university staff had well over double the rates of education to degree level (87.22%) than the police shift workers (31.22%). However, it may simply be that any form of regular shift work leaves fewer hours in the day to "relax with a drink after work", and some studies support this, reporting lower rates of drinking in shift workers (Dorrian & Skinner, 2012). Smoking rates were highest in the general population sample (18.67%) and lowest in university staff (8.33%). Smoking rates in the general population sample were also higher than the current national average (13.8%) (ons.gov.uk, 2021), although the reason for this is unclear. It is unlikely to be related to education, because rates of education to degree level were higher in the general population sample (39.70%) than the police workers (31.22%), yet the percentage of smokers (18.67%) was double that of the police sample (9.02%).

7.1.2 DIET QUALITY ACROSS THE STUDIES

The university staff had the most anti-inflammatory diets, and the police night workers diets were the most pro-inflammatory, although mean *E-DII* scores across the three samples were all within the neutral range (-1 to +0.99). A more interesting finding is that within Study 2, night workers' scores were on average over 20% higher than their day working colleagues, indicating that regular night shift work is associated with significantly more diet-derived inflammation than regular day shift work. This is perhaps understandable, given that

opportunities to eat wholesome food may well be limited at night, leading to an increased reliance on fast food, ready meals and snacks. The night shift workers were the only group with a positive mean *E-DII* score: their day shift working colleagues, the university workers and the general population sample all had negative mean *E-DII* scores. Pro-inflammatory diets of night workers may contribute towards the higher rates of chronic inflammatory disease consistently observed in the night shift workforce a whole (Brown et al., 2020; Lee et al., 2017; Liu et al., 2018; Szkiela et al., 2020).

7.1.3 MOOD ACROSS THE STUDIES

Of the three samples, the university employees had the best mood (HADS-D), while the police shift workers (combined sample) had the worst mood in terms of percentage of individuals scoring on or above the clinical cut-off score for depression. The general population sample was the least anxious (HADS-A) in terms of clinical cut-off scores, while the police shift workers were the most anxious. It stands to reason that the police workers had the worst mood, given that a sizeable proportion worked at night, which is known to be psychosocially challenging (Angerer et al., 2017); at least for those in front-line roles, police work is also likely to be psychologically demanding. It is perhaps more surprising that the university staff had the lowest rates of depressive symptoms, given some of the data presented in Chapter 1, including the report suggesting that they have more mental health problems than those working in the police force or medical profession (Kinman, 2018). This appears not to be the case in the current data.

7.1.4 SLEEP QUALITY ACROSS THE STUDIES

In terms of the clinical cut-off scores for both sleep quality measures, the university staff reported the best sleep quality, and the police shift workers had the worst. Given the challenges of trying to sleep during the day in those engaged in regular night work, it stands to reason that as a combined group, the Study 2's shift workers reported the worst sleep quality across the three studies. Self-report sleep quality typically deteriorates with age (Schwarz et al., 2017), but this was only observed in Study 3, it was not significantly associated with age in either the university staff or the shift workers. This may be related to the age demographic of the samples: participants in studies one and two were all working age (18 – 65; 18 – 66), whereas the general population sample included retired people, so the age range was wider (18 – 85), and it is likely that the older individuals contributed to the age-related decline in sleep quality observed in Study 3.

7.2 IMPLICATIONS

Diet, mood and sleep share complex, multi-dimensional relationships that are not fully understood (Bremner et al., 2020; Campanini et al., 2017; Du et al., 2021; Mamalaki et al., 2018; Molendijk et al., 2018). However, a major implication of this work is that reducing the silent inflammatory burden in individuals who habitually consume a poor-quality diet, may improve mood and sleep, and help to reduce the risk of mental illness and problematic sleep before clinical symptoms manifest. Prevention is better than cure, not least because antidepressants and sleeping medications have side effects, and some hypnotic drugs are addictive. Further, dietary interventions may improve risk profiles in specific groups, such as night shift workers, who are at particularly high risk of chronic inflammatory disease. Diet is an unavoidable daily health exposure, but it is also a modifiable behaviour, so interventions to reduce its inflammatory potential may provide safe and effective alternatives to pharmacological treatments for inflammatory diseases. Even in terms of primary prevention, drugs to reduce the incidence of cardiovascular events, such as statins, anti-hypertensives and anti-platelet agents (e.g., aspirin), carry risks of serious side effects. In contrast, anti-inflammatory diets have no side effects, and we all have to eat, so the opportunity already exists.

Perhaps the most important implication of this work comes from the findings relating to specific dietary fats. In terms of polyunsaturates, the ratio of omega-3 to omega-6 fats may be more important than the absolute levels (Simopoulos, 2011) and the benefits observed in

Study 3 were attributable to omega-3 only, not omega-6 PUFA. Although Western diets generally contain an abundance of omega-6 fatty acids, they may be relatively deficient in omega-3 (Lachance et al., 2016), so the current findings add weight to dietary advice to increase omega-3 intakes.

The current work also demonstrated an association between *trans* fats and sleep quality, with higher intakes strongly associated with more daytime sleepiness and poorer nocturnal sleep efficiency. These findings support other evidence that *trans* fats are detrimental to health (e.g., Islam et al., 2019), and also suggests that avoiding regular intake of fast foods, which can contain high levels (Pipoyan et al., 2021), may protect against daytime sleepiness and poor nocturnal sleep efficiency.

The Dietary Inflammatory Index was designed specifically to assess the inflammatory potential of the diet, using 45 food parameters which were each assigned an inflammatory effect score. However, it should also be noted that inflammation is not the only mechanism associated with high quality diets. For instance, oily fish is rich in both omega-3 PUFA and vitamin D (Hansen et al., 2014). Vitamin D has a negative inflammatory effect score (-0.446), but it is also thought to be involved in serotonin and melatonin regulation (Huiberts & Smolders, 2021), both of which are key regulators of mood and the sleep-wake cycle. Similarly, although omega-3 PUFA has a strongly anti-inflammatory effect score (-0.436), EPA and DHA are also involved in serotonin secretion (Del Brutto et al., 2016). Thus, although these mechanisms are not the focus of the thesis, these other, non-inflammatory pathways that impact mood and sleep, may have contributed to the observed diet/mood and diet/sleep relationships.

The Mediterranean-style diet has long been associated with reduced risk of a wide range of chronic, inflammatory diseases. The current research indicates that adherence to a Mediterranean-style diet is protective of both mood and sleep quality. However, despite its benefits being promoted around the world (Martinez-Lacoba et al., 2018), studies suggest that even in Southern Italy, where the Mediterranean diet originated, traditional dietary practices are giving way to Western-style diets, particularly in younger adults (Caparello et al., 2020; Veronese et al., 2020). Ferranti and colleagues (2016) found that only 6% of Sicilian children and adolescents reported high Mediterranean diet adherence, and in Study 3 of the current work, older individuals were significantly more likely to adhere to a Mediterranean-style diet than younger individuals The implications of the current findings may therefore be particularly relevant from a public health perspective, given that the health benefits of adhering to a Mediterranean-style diet appear not to be getting across, even in Mediterranean countries.

In the UK, despite evidence that interventions to improve diet quality are effective adjuvant treatments for depression (Firth et al., 2019; Kris-Etherton et al., 2021), current (March 2022) National Institute for Health and Care Excellence (NICE) guidelines for treating depression in adults do not include diet (https://www.nice.org.uk/guidance/cg90/chapter/Key-priorities-for-implementation). Further, the National Health Service (NHS) website currently lists physical exercise as a treatment for mild depression, but again, diet is not mentioned (https://www.nhs.uk/mental-health/conditions/clinical-depression/treatment/).

Public health advice on diet-related disease risk has traditionally been contradictory and confusing, particularly regarding fat intake. Forty years ago, advice aimed at reducing the risk

of cardiovascular disease focussed on reducing saturated fat intake, such as butter, and replacing it with lower fat alternatives, including vegetable-based spreads. However, these contained high levels of *trans* fats, which are now known to pose more cardiovascular disease risk than saturated fats (Islam et al., 2019). More recently, we were advised to replace saturated fats with polyunsaturates. However, vegetable-based polyunsaturated oils high in omega-6 fatty acids were then criticised for being primarily pro-inflammatory, and therefore likely to increase cardiovascular disease risk (Hamazaki & Okuyama, 2003; Mariamenatu & Abdu, 2021; Simopoulos, 2008). The latest advice based on other epidemiological evidence, is that omega-6 polyunsaturated fats are protective against cardiovascular disease (Harris et al., 2009), and should not be avoided (AHA, 2019).

Dietary public health advice remains confusing, so an alternative, clearer approach might be to focus on the inflammatory potential of the diet. The COVID pandemic has put the human immune system and inflammation in the spotlight, so now might be a good time to focus public attention on the inflammatory burden of the Western-style diet, and how to reduce it. DII is a relatively quick, easy and cost-effective tool to implement, which could lend itself to primary prevention strategies, such as health education programmes in schools. If this approach was adopted in primary prevention, silent dietary inflammation could be prevented from taking hold at an early age, years before it manifests in clinical inflammatory disease.

7.3 LIMITATIONS

Limitations specific to each study were discussed at the end of each empirical chapter, but some apply across the three. Firstly, recruitment into all three studies was subject to selection bias. People with an interest in nutrition and diet-related disease risk might have been particularly motivated to participate, and some of these may have better than average-quality diets. Similarly, as no selection criteria were applied in terms of health status, individuals with mood or sleep disorders may be particularly inclined to participate in research into mood and sleep. Almost 2% of the general population sample were suffering from diagnosed sleep disorders, including two cases of narcolepsy. This sleep disorder has a prevalence of approximately 1 in 2500 in the UK (www.narcolepsy.org.uk), so the relatively high rate observed in the sample (2 in 466) suggests that the study was subject to selection bias. However, given that the samples came from three diverse groups, it is likely that the ecological validity of this research as a whole is high.

Also in terms of ecological validity, principal components analysis was used to identify patterns of dietary behaviour emerging from each dataset. However, these are specific to the dietary data within each sample, and therefore do not necessarily generalise to the wider population. That said, the dietary patterns that did emerge were very similar across the three studies, suggesting that they are likely to be representative of the wider population.

All the assessments used in the current work were subjective, self-report measures, all of which involve a degree of measurement error. In many cases this is recall bias associated with relying on memories of things that happened in the past. In terms of sleep quality, PSQI may not be a good measure of some of its subcomponents, such as sleep latency, unless the individual has a particularly long, or short, habitual sleep onset latency.

With regard to subjective dietary assessments, social desirability bias may occur, in which subjects respond in ways that conform to societal norms (Hebert et al., 1997). For example, over-weight/obese individuals may under-report consumption of high calorie foods, leading to underestimation of total energy intakes. Underestimation of self-reported calorie intake is well recognised in nutritional epidemiology. Reports vary in magnitude, for example, Carlsen and colleagues (2010) reported 11% underestimation, compared to 42% by Mahabir et al. (2006). The latter study compared FFQ data to double labelled water, an objective biomarker of calorie intake (Mahabir et al., 2006). In the three studies reported here, median daily calorie intakes were 1569.19, 1553.08 and 1442.29 (males and females combined). These are likely to be underestimates, given that the recommended daily intakes are 2500 for males and 2000 for females (www.nhs.uk, 2021).

Problems were encountered with the physical activity questionnaire, which did not come to light until data were analysed after completion of Study 3. Firstly, IPAQ may have overestimated activity levels across all three studies, and this has been reported in a number of published studies (Sebastião et al., 2012; Biernat & Piątkowska, 2016), including two that compared it with accelerometery, both of which reported overestimations of physical activity and underestimation of time spent sitting (Grimm et al., 2012; Wanner et al., 2016). A

systematic review also reported overestimation of activity levels by an average of 84% (range 36% - 173%) (Lee et al., 2011). Further, several participants had missing data for physical activity across all three studies. This may be due to the format that was chosen for the questionnaire, which consisted of slide bars. These proved problematical because some participants initially reported physical activity, but then failed to move the slide bar to indicate how much activity they engaged in. Thus, total physical activity levels could not be calculated in many cases, including almost one third of participants in Study 1. IPAQ did provide a ranking of individuals' activity levels within each study, but given the extent of missing data, and that absolute levels may have been overestimated, a decision was made not to include the IPAQ data in the analysis. The effects of physical activity on mood and sleep are well known, so an assessment of its effects on the outcome variables was not considered essential. However, it may have been a confounding factor in the relationships under study, in which case, statistical adjustment would have been advantageous.

Study 1 did not include a measure of BMI, so comparisons across the three samples could not be made. However, no hypotheses were made about differences in BMI between the university, police and general population samples. The objective was to test the hypothesis that regular night shift workers have higher average BMIs than their day working colleagues, although this was not supported by the Study 2 data.

For reasons beyond my control, only 24 participants completed the Intake24 dietary recalls, so they can only be used as pilot data, and findings should be considered preliminary. The small sample size also limited the scope of the analysis; for example, the KMO value indicated that the data were not suitable for PCA. Furthermore, the correlation between *trans* fats and

DII was non-significant, despite their strongly pro-inflammatory DII effect score (+0.229), although it was in the expected direction (i.e., positive). Failure to reach significance may be due to the small sample size (*n* = 21), but unfortunately it meant that it was not possible to test the hypothesis that DII mediates the strong relationship that was observed between *trans* fat intake and sleep quality. Takeaway food can contain high levels of *trans* fats, but again, due to the small sample size, it was not possible to ascertain whether higher *trans* fat intakes were associated with higher takeaway consumption in the Intake24 data.

Finally, it should be noted that the cross-sectional design of these studies means that the direction of the observed relationships cannot be determined. However, the mediation analysis does shed some light on the directionality of the associations, based on a priori knowledge of the likely direction and underlying biological pathways. For instance, given that oily fish contains high levels of omega-3 fatty acids, which have known anti-inflammatory actions, it is plausible that consuming oily fish leads to lower systemic inflammation which in turn leads to better sleep quality. In terms of the reverse relationship, given that experimental sleep restriction increases circulating pro-inflammatory cytokines (Vgontzas et al., 2004; Haack et al., 2007; Pejovic et al., 2013), improvements in sleep quality may lead to lower levels of pro-inflammatory cytokines, but it is unlikely that having lower levels of silent/asymptomatic inflammation leads people to consume more oily fish.

Directionality may be less easy to tease apart in diet/mood relationships. This is because there is a robust reciprocal relationship between the two (e.g., poor diet is associated with poor mood and vice versa). E-DII partially mediated the relationship between takeaway intake and depression in Study 1, indicating that regular takeaway intake was a pro-

inflammatory dietary behaviour leading to increased inflammation, which in turn impacted mood. Other partial mediation in this relationship could be behavioural, running in the opposite direction. Thus, depression may lead to emotional eating of takeaways, as a means of counteracting negative emotions and reducing psychological distress (Freeman & Rapaport, 2011). In this pathway, the reward-sensitive brain areas (Stice et al., 2013) and dopamine release (Ferreira et al., 2012) would be the mediators, rather than DII. However, the emotional eating behaviour would then lead to higher diet-derived inflammation which would then impact mood, creating a self-perpetuating cycle that reinforces itself.

In summary, it should be noted that there are other, equally as important, non-inflammatory mechanisms driving the relationship between diet, mood and sleep. These include the reward circuitry of the brain, increased tryptophan availability from diets high in carbohydrate (Doherty et al., 2019), and high fibre diets favouring gut microbial eubiosis, with both pathways culminating in increased serotonin and melatonin production.

7.4 FUTURE DIRECTIONS

To my knowledge, the current studies are the first to investigate dietary inflammatory index in university staff, and the first to do the same in UK police workers. A substantial evidence base links DII to mental health outcomes, and an increasing number in relation to sleep, in non-UK samples across the world. In contrast, DII research in UK samples is scarce: there is one validation study in an elderly Scottish sample, and two studies using the Whitehall II dataset, but to my knowledge, these are the only primary investigations, so future work should focus specifically on UK samples. These studies would be longitudinal rather than cross-sectional in design, and large enough to allow adjustment for potential covariates and confounding factors, including physical activity levels.

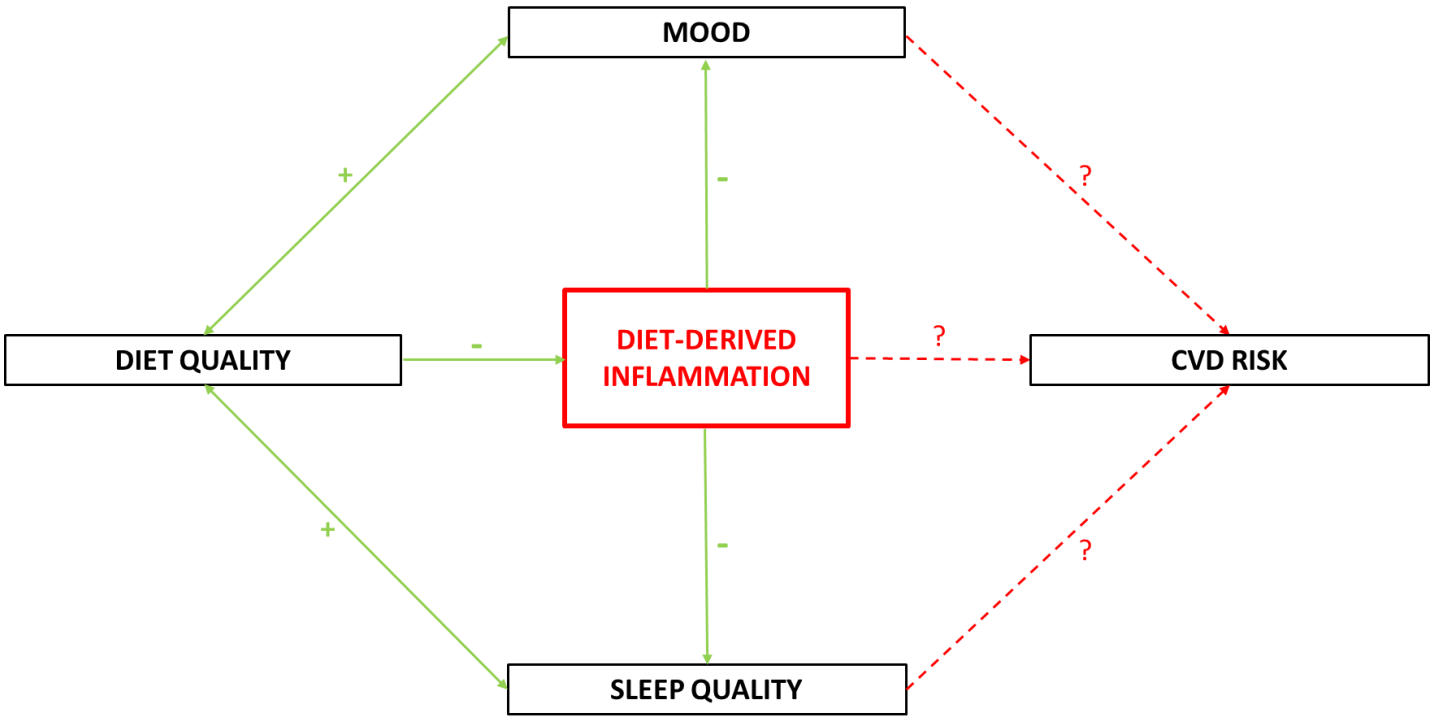
The current work demonstrated that higher intakes of polyunsaturated fats were associated with significantly better mood and sleep quality. Moreover, in Study 3, the associations were found only with omega-3, not omega-6 PUFA. This may be a novel finding, and given that Western-style diets are rich in omega-6 fatty acids and relatively deficient in omega-3, this contributes important information to the field of nutritional research. Future studies need to confirm these findings in larger samples, and investigate potential differential effects of omega-3 and omega 6 fatty acids in more detail. This could include measurement of erythrocyte membrane omega-3:omega-6 fatty acid ratios together with biomarkers of systemic inflammation (plasma cytokine and CRP levels). Further, the strong correlation that was observed between *trans* fat intake and sleep efficiency/daytime sleepiness may also be

a novel finding, which warrants further investigation in larger samples. This could include objective measures of sleep quality, such as actigraphy, as well as subjective, self-report questionnaires. In summary, future directions for this work will include further investigation of the relationships between dietary fats (namely, omega-3, omega-6 and *trans* fatty acids), mood and sleep, but in a larger sample with a longitudinal design. This study will be better placed to assess directionality and the inflammatory mechanisms mediating the observed relationships.

Another, novel direction would be an investigation into risk factors associated with the development of long-COVID. In Study 3, long-COVID sufferers had significantly lower PUFA intakes and higher BMIs than COVID patients who had made a full recovery. Although there were no significant differences in E-DII scores between the two groups in this small COVID sample (n = 45), in a larger sample, low PUFA diets may well be pro-inflammatory. Further, obesity is also a pro-inflammatory condition (Setayesh et al., 2021), so individuals with high BMIs, and those with low PUFA intakes may have higher levels of systemic inflammation, and this may present a common risk factor for long-COVID. In their recent review, Hathaway and colleagues (2020) discuss the "anti-inflammatory, immunomodulating, and possible antiviral effects" of omega-3 fatty acids in COVID-19. However, interventional studies of omega-3 PUFA supplementation in long-COVID patients are non-existent (Storz, 2021), and although the current results did not differentiate omega-3 from omega-6 PUFA, this finding warrants further investigation. Furthermore, as well as having lower PUFA intakes, long-COVID patients in the current sample had significantly more sleep disturbance and higher HADS-D scores than the rest of the sample, and it is postulated that omega-3 fatty acids may mitigate against the psychological as well as physical effects of the pandemic (Chang et al., 2020).

Finally, a novel thesis is that healthy dietary patterns may reduce cardiovascular disease risk, directly, and also indirectly via improvements in both mood and sleep quality. Likewise, if poor diet, poor mood and poor sleep are all risk factors for cardiovascular disease and diet-derived inflammation is the mechanism driving these associations, this represents a significant improvement in our understanding of their shared contribution to cardiovascular disease. With cardiovascular disease and depression set to top the global burden of disease by the end of this decade (WHO, 2011), determining these pathological mechanisms is an essential future direction for this work. The hypothesis is summarised in Figure 7.2.

Figure 7.2. Schematic showing relationships observed between diet quality, mood and sleep quality, and the hypothesised direct and indirect relationships connecting diet quality to cardiovascular disease (CVD) risk via diet-derived inflammation.



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