Diet and Depression in Community-Dwelling Adults

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MClinEpid

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Statement of Originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository**, subject to the provisions of the Copyright Act 1968.

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Jun Shi Lai Date

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I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Jun Shi Lai Date

List of publications included as part of thesis

In order of appearance

1. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. American Journal of Clinical Nutrition. 2014;99(1):181-97.

2. Lai JS, Attia J, McEvoy M, Hure AJ. Biochemical Validation of the Older Australian's Food Frequency Questionnaire Using Carotenoids and Vitamin E. Nutrients. 2014;6(11):4906-17.

3. Lai JS, Hure AJ, Oldmeadow C, McEvoy M, Byles J, Attia, J. Prospective study on the association between diet quality and depression in mid-aged women over 9 years. European Journal of Nutrition. 2015 Oct 17; doi: 10.1007/s00394-015-1078-8

4. Lai JS, Oldmeadow C, Hure AJ, McEvoy M, Byles J, Attia J. Longitudinal diet quality is not associated with depressive symptoms in a cohort of mid-aged Australian women. British Journal of Nutrition. 2016; 115(5): 842-850

5. Lai JS, Oldmeadow C, Hure AJ, McEvoy M, Hiles S, Boyle M, Attia J. Inflammation mediates the association between fatty acid intake and depression in older men and women. Nutrition Research. 2016; 36(3): 234-245

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Statement of Contribution for Paper 1

We attest that Research Higher Degree candidate, Jun Shi Lai, has substantially contributed to: (1) conceiving the research question and study design; (2) conducting literature search, quality assessment and data extraction; (3) performing of statistical analysis; and (4) preparing the manuscript; for the publication entitled: “A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults”

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Table of Contents

Synopsis

Depression is a highly prevalent mental health disorder that causes severe disability to the individual and results in substantial economic burden. Although depression can be reliably diagnosed and treated, total remission is rarely achieved, and relapses and recurrences are common. Current pharmacological treatments are limited in that they are often associated with severe side effects. Psychological treatments though effective have been shown to be rather costly and require time and commitment. Thus, it is necessary to expand current research to develop universal interventions in relation to mental health promotion, prevention and early intervention in addition to treatment delivery.

An emerging body of evidence has suggested that nutrition plays an important role in mental health. Earlier research on single nutrients or foods and depression has shown that omega-3 fatty acids or fish, folate, vitamin E or zinc may be associated with a reduced risk of depression. Recent epidemiological evidence suggests that consumption of a healthy dietary pattern may be beneficial for preventing depression. This thesis explores the association of overall diet and depression by pooling together current evidence in a meta-analysis and explore primary cohort data to fill some of the gaps in current literature.

Chapter 1 describes the rationale and aims of this research, and provides an overview of the thesis structure linking the published papers to the thesis. The meta-analysis described in Chapter 2 provides a summary of current literature examining the association of overall diet and depression, and synthesised study results using statistical methods. This chapter demonstrated that high intakes of fruits, vegetables, fish and wholegrains are associated with reduced odds of depression (OR = 0.84; 95% CI: 0.76, 0.92; $P<0.001$). However, this finding was largely based on cross-sectional evidence. Thus, the primary research conducted as part of this thesis aims to provide longitudinal evidence supporting the diet-depression relationship.

Chapter 3 presents a brief description of the cohort datasets used for subsequent chapters of this thesis (i.e. Chapters 5-7). Chapter 4 describes the validation study of the food frequency questionnaire used in one of the cohort study (Hunter Community Study) from which the data for Chapter 7 was derived. This chapter confirms that the food frequency questionnaire was able to reasonably rank study participants according to their carotenoids and Vitamin E intakes

(≥68% of individuals were correctly classified within the same or adjacent quartile), thus Chapter 7 can rely on the dietary data as being accurate.

Chapters 5 and 6 examine the temporal association between diet quality and odds of depression: whether higher diet quality is associated with reduced odds of incident depression; and whether changes in diet quality are associated with changes in depressive symptoms. Chapter 5 found that high diet quality was associated with lower odds of incident depression (OR: 0.94, 95% CI: 0.83, 1.00, *P*=0.049). Likewise, women who maintained high diet quality over six years had 14% reduced odds of depression compared to women who consistently had poor diet quality (OR: 0.86; 95% CI: 0.77, 0.96; *P*=0.01). However, Chapter 6 showed no association between diet quality and depressive symptoms. It could be that a dietary effect may not be detectable for sub-clinical depression or depressive symptoms, or comparing between extreme groups of diet quality in Chapter 5 allowed an effect to be detected due to the high between-subject variability in adherence.

Chapter 7 explores whether the inflammatory pathway underlie the association between dietary intakes and depression. Specifically, this chapter examine the association between antioxidants and fatty acids intakes and depression, and determine if inflammatory markers – interleukin-6 and C-reactive protein mediate the associations observed between these nutrients and depression. Results from this chapter support the hypothesis that inflammation is one of the factors driving the diet-depression relationship, but it may only be a small contributor as mediation by inflammatory markers only explained at most 7% of the relationship between dietary factors and depressive symptoms.

This thesis ends with Chapter 8 summarising the main study findings, strengths and limitations of each chapter, and detailing the implications for future research exploring the association between overall diet and depression. In conclusion, this thesis contributes to existing knowledge that a causal relationship between diet and depression is plausible, by summarising current evidence on overall diet and depression, demonstrating through primary research that high diet quality may reduce incident depression, and elucidating the mediation effects of inflammatory markers in the diet-depression relationship. The associations observed between diet and depression from this research is modest in magnitude, which is the case for most studies on

diet and disease. This body of work highlights the need for further research that employs longitudinal analyses and randomised controlled trials to clarify whether diet is truly a causal risk factor for depression. If so, even a modest magnitude of effect would have important implications at the population level.

PART 1: OVERVIEW of TOPIC AREA

CHAPTER 1: Introduction

1.1 Depression

This section presents an overview of the main health outcome of this thesis – depression. The definitions of some commonly used terms in the literature and methods in which depression is identified and diagnosed are described. The epidemiology of depression and the burden of this disorder are also considered. A few proposed mechanisms underlying the pathophysiology of depression and current management strategies are then explored.

1.1.1 Definitions and Diagnosis of Depression

The umbrella term ‘depression’ is commonly used in the literature to indicate either ‘depressed mood’, ‘depressive symptoms’ or depressive disorder, or a combination of these terms. Depressed mood is generally brief and last for a short period of time (1). It is not a condition or disorder that severely impacts on general functioning and wellbeing, but a normal reaction to certain life events where an individual feels sad, pessimistic, hopeless, and has lowered self-esteem. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) identified a list of nine depressive symptoms including feeling depress or irritable most of the day, decreased interest or pleasure in most activities, and significant changes in weight, appetite or sleep (1). The clinical diagnosis of major depression is made based on a collection of these depressive symptoms (five out of the nine symptoms) nearly every day for more than two weeks. Aside from a physician’s diagnosis, several interviews were designed according to diagnostic classification of depression to assess major depression such as the Structure Clinical Interview for DSM-5 (2), and the WHO Composite International Diagnostic Interview for ICD-10 (3). As mentioned, individuals may have a number of these depressive symptoms but not meet the criteria for major depression and are therefore classified as having subthreshold depression. Depressive symptoms can be measured in the community by a number of self-report inventories and checklists, such as the Beck Depression Inventory (4), the Centre for Epidemiologic Studies-Depression Scale (5) and Geriatric Depression Scale(6). These measures are easy to administer to a large number of people at relatively low cost, and can be applied to assess

depressive symptomatology rather than diagnose cases of major depression (7), thereby allowing subthreshold depression to be detected among the general population.

Throughout this thesis, the term ‘depression’ will be used to represent major depression or depressive symptoms. Where the individual is identified to have depression by a medical doctor, terms like ‘clinically-diagnosed’ or ‘physician-diagnosed’ depression will be used. Where an individual is classified as having depression or depressive symptoms based on symptom inventories or checklists, it will be reported as such.

1.1.2 Epidemiology of Depression

Depression is a common mental health disorder estimated to affect 350 million people worldwide (8). In Australia, the 12-months prevalence of depression as of 2011-2012 is approximately 9.7%, and the lifetime prevalence is between 10-20% (9). As a broad disease group, the prevalence of depression seems small in comparison to other non-communicable diseases including cardiovascular disease, diabetes and cancer. However, the burden of this disorder is among the highest, currently ranked as the fourth leading cause of burden of disease and injury in Australia (10).

Depression is a disorder that substantially impacts an individual’s ability to cope with day-to-day activities, and is commonly associated with problems of social interaction and inability to form close relationships (10). The burden of this disease is not just limited to the individual but has a much wider public health impact. It is associated with substantial economic costs to the country mainly because of the individual’s underperformance and absenteeism in workplace and the high health care utilisation (11). It is ranked as one of the most expensive health conditions, costing the government at least 5 billion dollars a year (12). Far beyond this, depression also influences the mortality risk of the individual. Individuals with depression have an increased exposure to health risk factors, poorer physical health and higher rates of suicide (13). Depression has links with health risk states which include tobacco use, illicit drug use, alcohol misuse and dependence, eating disorder and obesity (14). There is evidence suggesting that cardiac mortality risk and even the risk of all-cause mortality is greater in patients with depression (15). In addition, depression is a factor commonly associated with suicide, with a

greater proportion of individuals dying from or being hospitalised for suicide were reported to have depression (14).

Although depression is generally regarded as a disorder that can be reliably diagnosed and treated, total remission is rarely achieved, and relapses and recurrences are common (16). Many patients experience fluctuating symptoms over time (17), which can continue to reduce performance and cause considerable distress, and long-term risk of relapse can be as high as 80% (16). Recent studies suggest that major depression is relatively rare while subthreshold depressive symptoms are particularly common (17). This further complicates the ability to accurately diagnose and treat depression among the general population as an individual may have depressive symptoms but did not meet the criteria of having a depressive disorder. These subthreshold symptoms exert similar impacts on life functions and wellbeing as a major depressive disorder but often these individuals were not given similar medical attention (17). Most studies have treated depression as a homogenous entity, dichotomising study subjects into those with depression or without, which may not be an accurate reflection of the disease progression (17).

Who gets depression?

Depression is a disorder that spans a lifetime, with the first onset of depression usually occurring during mid-to-late adolescence or early adulthood, and depressive episodes experienced later in life are often a recurrence (11). The prevalence of depressive disorders decreases with age among those who live in the community but depressive episodes that appear for the first time in later life are more likely to persist if untreated (18). Prognosis of depression also deteriorates with age mainly due to the presence of co-morbidities, and the many cases of depression that goes undiagnosed because of that (18, 19). With a progressively increasing ageing population worldwide, prevention and treatment of depression in later life becomes increasingly important. Therefore, the target population for this PhD is the mature-age and older people (defined as those ≥50 years old). Studying the characteristics of the mature age will provide useful perspectives on the profile of future older people and the trends of health behaviours thus allowing early prevention strategies to be developed.

The high female: male sex ratio in the prevalence of depression is one of the most replicated findings in epidemiology. Approximately twice as many women suffered from depression as men globally (pooled female: male ratios in the range 1.3–2.6) (20). This gender difference in prevalence may be associated with the social-economical-political positions of men and women in terms of opportunities for employment and education, access to birth control, and other indicators of gender role equality (20). Likewise, a higher proportion of females than males in Australia, reported depressive disorder in their lifetime (18% compared to 12%), and having accessed mental health services (41% compared to 28%) (14). In view of this, this thesis has a specific focus on exploring depression in women, and in studies using a combined population of men and women. The analyses will be stratified based on gender to account for the gender differences in depression.

1.1.3 Aetiology of Depression

Depression appears to be affected by a wide variety of factors, from biological to psychosocial factors. Much research has been devoted to understanding the pathophysiology of depression from the biological perspectives in order to develop new strategies for the prevention and treatment of depression. To date, the cause of depression remained unclear, but several biological mechanisms or pathways have been proposed to influence depression risk.

Among the most frequently cited is that depression is caused by decreased monoamine function in the brain (e.g. serotonin and dopamine) – substances known to control alertness and awareness, and regulate the effects of emotional stimuli (21). This theory is mainly supported by the fact that monoamine-based antidepressants are effective at alleviating depressive symptoms, and that depletion of monoamines further impairs the mood of depressed patients or those who are in remission (22).

There is also substantial evidence indicating that depression is caused by a dysfunctional hypothalamic-pituitary adrenal (HPA) axis observed in the majority of depressed patients (23). A dysfunctional HPA axis leads to an increase in glucocorticoid concentrations, which in excess can produce atrophic changes in hippocampal subregions, contributing to hippocampal volume reductions seen in depressed patients (24). The fact that administration of glucocorticoid

antagonists showed therapeutic efficacy (25) further suggest that elevated glucocorticoids level is related to depression.

A significant reduction in hippocampus volume in depressed patients has supported another hypothesis for depression that involves decreased neurotrophic factors, mainly the brain-derived neurotrophic factor (BDNF). Support for this hypothesis comes from literature showing that psychological stress reduces BDNF-mediated signalling in the hippocampus, whereas treatment with antidepressants increases BDNF expression in the hippocampus (26, 27). Further evidence showed that direct infusion of BDNF into the hippocampus produced antidepressant-like effects in rodents (28), and blocking the gene encoding BDNF from forebrain regions resulted in the opposite effect (29).

Other evidence suggests that cytokine-mediated inflammatory processes might play an important role in the neurochemical changes associated with depression. Depressed patients showed high levels of pro-inflammatory cytokines and other proteins involved in the immune response, and in contrast, antidepressant drugs appear to reduce inflammation (30). In addition, depressive mood changes appear to be more common among patients with autoimmune conditions, where there is heightened system-wide inflammation (31).

There has also been recent interest in epigenetic modifications in the pathophysiology of depression. Increased DNA-methylation of the glucocorticoid receptor gene promoter results in a disrupted HPA-axis regulation, and administration of DNA-methylation inhibitors in rodents seem to exhibit antidepressants-like effects (32). Histone-acetylation was also found to play a role in antidepressant action, whereby increased histone acetylation at the BDNF promoter in the hippocampus may be required for the ability of anti-depressive drugs to reverse the effects of social defeat (a depressive-like effect) (33).

1.1.4 Management of Depression

The intervention spectrum for depression can range from development of universal prevention strategies for the general public, early detection and intervention among those at high risk, to treatment and management of those with diagnosis of depression. Research into individualised treatment for depression has a significant history of more than 40 years (34). Population-based epidemiology and prevention research have been slowly gaining attention over the past decade.

Research on antidepressant medication has been well-supported. The use of antidepressants has been the main treatment option for depression in the past 40 years (35). In general, antidepressant medication is efficacious among those with more severe depression, and in those with symptoms that persist over time (35). However, some antidepressants produced severe side effects (e.g. tricyclic antidepressants) which in turn reduce their acceptability (35, 36), while others (e.g. selective serotonin reuptake inhibitors) have large variation in treatment effects (35, 37). This treatment option also has no effect on patients with sub-threshold depressive symptoms or mild depression.

In recent years, psychological treatments have received more attention, and generally have better acceptance from patients (38). Psychological treatments with some efficacy in the treatment of people with depression include: cognitive behavioural therapies, behavioural activation, interpersonal therapy and mindfulness-based cognitive therapy (39). This treatment option has been shown to have better effect over antidepressants, and patients following this treatment are less prone to relapse (40, 41). However, it has been shown to be rather costly in terms of the associated hospital care, community health and social services, and any productivity losses resulting from time off work (42, 43). The amount of time and commitment needed remains a barrier to effective management with this treatment option (44, 45).

In view of the limitations associated with these treatments, the high risk of developing depression over a lifetime, and the burden it has on the individual and society, it is necessary to expand current research to develop strategies in relation to mental health promotion, prevention and early intervention in addition to treatment delivery. On the other hand, new therapeutic options are needed to complement existing treatment to further lower relapse rate, relieve subthreshold depressive symptoms, and enhance the effect of existing treatment. There is some preliminary evidence for other approaches to management of depression such as marital therapy (46), bibliotherapy (47), and physical activity interventions (48), and an emerging area of research suggests that nutrition plays a vital role in depression. The association between dietary factors and depression is the main focus of this thesis.

1.2 The Role of Nutrition in Depression

In recent years, substantive progress has been made in understanding the role of nutrition on depressive symptoms. Several nutrients or foods have been investigated regarding their involvement in the pathophysiology and management of depression. More recently, a shift from examination of individual nutrients or foods towards overall diet on depression risk has been observed. There is evidence to suggest that consumption of some nutrients, foods or certain types of dietary pattern can increase or decrease the risk of depression.

1.2.1 Key Nutrients and Depression

The purpose of this section is to highlight a few epidemiological evidence showing associations between nutrients intake and depression. A number of key nutrients commonly investigated are presented below, but this is not an exhaustive list. Comprehensive reviews have been undertaken by Murakami and Sasaki (49), Sanhueza et al (50) and Manosso et al (51).

Omega-3 Fatty Acids

It is suggested that omega-3 fatty acids exert their effects on depression via a few main mechanisms: (1) altering the regulation of serotonin and dopamine neurotransmission; (2) reducing inflammatory response and oxidative damage; and (3) regulating HPA-axis dysfunction (52). In humans, numerous studies have investigated the anti-depressive action of omega-3 fatty acids, and a number of reviews and meta-analyses have tried to pool the results (52-54). Overall, the reviewed evidence suggests a potential protective role of omega-3 fatty acids for depression but the results remained inconclusive (50-52). A number of cross-sectional studies reported an inverse association between omega-3 fatty acids intake and depressive symptoms (55-57), but other studies showed that this association was strongly attenuated after adjusting for lifestyle confounders (58, 59). Similar discrepancies were also observed in prospective cohort studies (50). The main reason for such variability in findings is a result of significant heterogeneity among studies examined, thus weakening the results of the analyses (52). More homogenous epidemiological and clinical studies are necessary to allow results to be pooled to better clarify the association observed.

Folate

Folate is important for the proper biosynthesis of monoamine neurotransmitters. The active metabolite of folate (5-methyltetrahydrofolate) affects the methylation of homocysteine to S-adenosylmethionine, a substance involved in the biochemical methyl donation reaction forming monoamine neurotransmitters (60). Studies have found low folate intakes to correlate with increased risk of depression as well as more severe depressive symptoms (61, 62). In one study of hospitalised acutely ill older patients, an increased red-cell folate concentration induced by oral nutritional supplementation resulted in a significant improvement of depressive symptoms (63). However, other studies on community-dwelling cohorts did not find a beneficial effect on depression from folic acid supplementation (64, 65). Conversely, it has been demonstrated that having higher folate status or folate supplementation is useful in improving depressive symptoms among patients receiving antidepressant treatment (66, 67).

Vitamin E

Few animal studies have investigated the mechanism of action of Vitamin E on depression, but several epidemiological studies have demonstrated an association between Vitamin E and depression. Depressed patients appears to have lower serum levels of vitamin E (68, 69), and one study found that an increase of 1mg of vitamin E intake decreased the odds for depression by 27% (70). The actual mechanisms of action is unclear due to the limited preclinical studies, but it is suggested that the possible beneficial effect of this vitamin on depression is through its anti-inflammatory properties (71).

Zinc

Several studies have demonstrated that (1) low serum zinc levels are found in patients with depression (72); (2) high dietary zinc intake is associated with reduced risk of depression (73-75) (3) zinc supplementation as an adjunct to antidepressants treatment may be effective in reducing depressive symptoms (76). As reviewed by Swardfager et al, the underlying mechanisms linking zinc and depression include modulating inflammation, neuroendocrine interactions and neurogenesis (72). These mechanisms have been demonstrated in a number of studies. Maes et al showed that low zinc status is associated with increased pro-inflammatory cytokines in depressed patients (77). One preclinical study suggest that reduced levels of zinc

contributes to a dysfunctional HPA-axis (78). Zinc was also shown to increase brain-derived neurotrophic factor (BDNF) gene expression in the hippocampus or cortex (79, 80).

1.2.2 The Whole Diet Approach and Depression

Earlier research on the relationship between nutrition and depression has focused on single nutrients such as omega-3 fatty acids, folate, vitamin E or zinc or foods containing high amounts of these nutrients. However, several reviews found no strong or compelling consistency in the findings to allow a firm conclusion to be drawn regarding specific nutrients or foods and depression risk (49-51).

The limited success in finding an association between individual nutrients and depression suggest that it may be desirable to use the “top down” approach, starting with the larger units – dietary patterns, and working down to individual food components or nutrients that provide protection from disease (80). This approach may lead to the discovery of new nutrients or food constituents that are important for depression prevention but were not previously explored. For example, dietary fibre (81), vitamin E, folate, iron, zinc and magnesium intake did not explain the association of wholegrains and total mortality (82, 83), suggesting that something else, or a range of factors in wholegrains is beneficial for health, such as the high phytochemical content and the low glycaemic index (84). Therefore, the use of this “top down” approach in examining overall diet and depression may prompt further investigation to identify and characterise individual food constituents relevant to depression that have not been studied.

In addition, there are important limitations to studying individual nutrients or foods on health given the complex combinations of foods and interactions between nutrients in an individual’s diet. It is therefore difficult to attribute the difference in disease prevalence or symptomatology to a single nutrient or food. The study of single nutrients or foods is also likely to be confounded by overall dietary pattern. Furthermore, the whole diet approach may be more practical, and more closely reflect the eating behaviour of the general population. Individuals typically consume a variety of foods rather than a single nutrient or dietary component. As such, examining the overall diet is becoming a popular approach in nutritional epidemiology.

A number of methods are used to measure overall dietary intakes including the 24-hour recall, food record, food frequency questionnaire (FFQ) and diet history (85). The 24-hour recall and

food record methods are based on actual dietary intakes on one or more specific days (85). These short term methods allow greater specificity for describing food intakes. The FFQ or diet history, on the other hand, is based on individual's estimation of usual intake over a longer period of time and may be less precise (85). For most nutritional epidemiologic investigations, the measurement of primary interest is usual or "habitual" intake rather than intake on a single day or several days. Thus, the FFQ remains the most popular measure used in research studies, as it is representative of usual intake. Conceptually, the ability of the FFQ to measure average long-term dietary intake is more important than intake on a few specific days because dietary factors will need to reach a substantial concentration to have an effect on disease outcome, which can only be accumulated through long-term consumption (85). Therefore, it may be more relevant to obtain crude dietary information for an extended period of time, rather than precise data over a short-time. Moreover, for large, population-based studies, this method is significantly less expensive than food records and dietary recalls, and easier to be completed by study subjects (85).

Salient characteristics of the overall diet may be derived using statistical modelling or captured using diet quality scores or indices (86). While both methods reflect the overall dietary intake, the difference lies in the way the results are to be interpreted. Dietary patterns derived via statistical method can help determine the types of diet evident within the population, and which of these dietary patterns are associated with depression (86). The use of diet quality scores or indices provides useful insights into how well the population adheres to current dietary guidelines (86), and from there the effects of these discrepancies in adherence on depression risk can be examined.

Principal component analysis and factor analysis are among the most frequently used statistical methods to derive dietary patterns (87). These methods identify foods that are commonly consumed together to form specific dietary patterns. These methods have been validated and results were reproducible over time and across different dietary assessment methods (88) but they are not without limitations. These methods include subjective criteria in consolidating food items into food groups, determining the number of factors to be extracted, and in deciding on when components or factors are relevant and when factor loadings are important to maintain foods in the pattern (87). Due to the highly correlated nature of dietary variables, it is likely that

the measurement error in assessing each food item is correlated. For example, if consumption of one vegetable is over-reported, consumption of other vegetables will also be over-reported. This error correlation may distort the definition of the derived dietary pattern (87). Furthermore, a major concern for using these methods is comparability across studies (86). Given the subjectivity in the analytical approaches, even if foods commonly consumed within similar dietary pattern is matched closely, the actual food items may not be the same across studies.

The majority of dietary indices are based on national dietary guidelines and recommendations specific to the country where the tool was developed (89). Some indices also included an assessment of dietary variety or diversity as it has been proposed that a more varied diet is associated with better health outcome (90, 91). Compared to using the statistical method, the use of dietary indices may be more objective, as they used existing dietary recommendations as guiding principles which are based on existing knowledge of optimal dietary intakes associated with decrease risk of chronic diseases (87). The use of the same index can strengthen comparison across studies among the same study population. In practical terms, dietary indices facilitate self-evaluation among the general public and summary measures of overall dietary quality are easy to understand and interpret (87). However, dietary guidelines are generally not disease specific; hence adherence to them may reduce the risk of some diseases but not others. Unless the dietary index is built on prior knowledge of dietary predictors of that disease, studies may experience difficulty in finding an association between dietary quality and the outcome of interest (87). Furthermore, the major problem facing the use of diet quality is the lack of variation in population dietary intakes or when individuals consumed a far from optimal diet (86), which could potentially contribute to a null association with health outcomes.

1.2.3 Epidemiological Evidence for the Association between Diet and Depression

A systematic review and meta-analysis has been carried out as part of this thesis that included studies published up to August 2013 (Chapter 2). To provide a more updated perspective on the current evidence, an electronic literature search was conducted on Medline using the same keywords and index terms in the meta-analysis to identify articles published from September 2013 to July 2015. Eligible studies were identified and quality assessed via the same methods

as in the meta-analysis. A brief description of studies from the recent literature search included here can be found in **Table 1.1** and **Table 1.2**. The following sections will include a summary of findings from the meta-analysis, further supported with findings from recently published studies.

Healthy Diet or High Diet Quality and Depression

Much of the evidence for the diet-depression relationship has been cross-sectional. Results from the meta-analysis demonstrated that consumption of a Healthy diet (characterised by high intakes of fruits, vegetables, fish and whole grains; or defined as achieving high scores in diet quality) is associated with reduced odds of depression (OR 0.84; 95% CI 0.76, 0.93) (92). Studies that could not be pooled in the meta-analysis showed similar findings, generally supporting high intakes of fruits and/or vegetables with lower likelihood of developing depression (93-96). An Australian study found that moderate intake of meat and poultry, and low-fat dairy products is an important contributor to the beneficial effect observed between healthy eating habits and depression risk (97). Three additional cross-sectional studies were identified in the recent literature search. All three produced results consistent with the meta-analysis (98-100). One study showed that high intakes of vegetables, fruit, cooked whole grains and whole grain bread reduced the likelihood of developing depression (98). Likewise, the other two studies found significant associations between high diet quality scores and lower odds of depression (99, 100).

Overall, findings from cross-sectional studies provide a compelling argument for the beneficial effect of healthy eating habits and depression risk, but they pose limitations in determining causality. As the exposure and outcome are measured at the same time in cross-sectional studies, it is not known whether the identified dietary patterns precede the development of depression or if having depression prompts such eating behaviour. Prospective cohort studies are designed to address this limitation. Current evidence on the association between diet and depression reported in prospective studies is mixed. Our meta-analysis demonstrated that the association between the Healthy diet and lower odds of depression is not statistically significant (OR 0.83; 95% CI 0.66, 1.05); this could be due to the large Nurses' Health Study showing no association between the Healthy (or Prudent) diet and depression (101) and the Whitehall II study that found a significant association between diet quality and depression in women but not in men. It is also possible that the non-significant association is the result of a lack of cohort

studies, as the cohort studies have a remarkably similar OR to cross-sectional studies and overlapping 95% CIs. Two recent studies examining the association between the Healthy (or Prudent) diet and depression risk supported an inverse association (102, 103), but one of the studies found the association to be apparent among the older aged cohort only (102).

One issue remains, that is adequate control of confounding which can only be addressed by carrying out randomised controlled trial (RCT). This is important especially when the adoption of a particular dietary pattern can be a marker of other lifestyle and sociodemographic factors closely related to depression. Our meta-analysis found large discrepancies among studies in the adjustment for potential confounders, and the rationale behind the choice of confounders is usually unclear. Several subgroups and tests of associations using different combination of confounders are often carried out, which may result in finding associations that are statistically significant instead of a true association. Furthermore, residual confounding is likely to exist with observational studies. Note, however, that RCT presents its own set of limitations in nutrition epidemiology, namely high cost, low compliance, relatively short intervention period, and usually targets specific groups of individual (discussed further in Section 8.2) (104). One RCT with rigorous methodology was published since our meta-analysis. The PREDIMED Study randomised community-dwelling men and women aged 60-80 years to two Mediterranean diets and a low-fat diet (control group), and showed no significant difference in depression risk among participants assigned to either Mediterranean diets compared to the control group (105). However, depression was not the primary outcome of this study. The main outcome was cardiovascular events, thus participants with high risk of cardiovascular disease were included for the study, which again may confound the diet-depression relationship. The focus on specific group of individuals also limits the generalisability of study findings to a wider population.

Western/Unhealthy Diet and Depression

There were only four studies that could be pooled in our meta-analysis, mainly due to the inconsistencies in the definition of a Western or Unhealthy Diet. Results from our meta-analysis suggest a trend toward a positive association between Western Diet and depression but this was not significant (OR 1.17; 95% CI 0.97, 1.41). Four other studies that could not be pooled showed conflicting results. One study found a lower depression score among women consuming ‘charcuterie and starchy foods’ (β: -0.15; 95% CI: 0.32, 0.02; P=0.06) (94), but the

other three studies found no association between depression and intake of processed meats, sweet biscuits, cakes, meat pies or confectioneries (96, 106, 107). The updated literature search found three prospective studies and one cross-sectional study. One of the prospective studies found a strong positive association between an inflammatory dietary pattern (similar in components to a Western Diet) and depression risk (108), but this association was not observed in the other two studies (102, 103). The cross-sectional study also showed no association between an unhealthy dietary pattern and depression, but found a positive association between frequent consumption of sweet foods (e.g. cookies/cake, chocolate/candy, ice cream, pastries) and odds of depression (98).

Gaps in literature

Multiple exposure assessments throughout the follow-up using reliable and valid measures are essential. This can help determine whether dietary intake changes over time, and the impact of these changes in relation to depression. If diet is indeed associated with depression, it would be expected that a change in diet would result in a change in depression risk. Furthermore, repeated assessments of dietary intake provide a stronger test of cumulative exposure on depression. Only two studies from our meta-analysis and one other study in the recent search have done so. This is particularly important for studies with long follow-up period (e.g. >10years), as there is a possibility of significant alterations with dietary intake at the population level influenced by a change in food supply and dietary recommendations.

As described in **Section 1.2.1 Key Nutrients and Depression**, nutrients exert their effects on depression by modulating the substances involved in the biological pathways proposed to cause depression. Studies examining the underlying mechanisms linking diet and depression are limited. The common approach to nutritional epidemiological research is the reductionist strategy, in which individual nutrients and the associated pathophysiologic pathways are investigated, then put together to form a more complex picture of overall diet and health (82). However, the approach of starting with overall diet then isolating into individual nutrients and biological activity is equally useful as such approach may point out a new way to group foods which are more relevant to the outcome of interest (82). Lucas et al are among the first to examine whether the association between dietary pattern and depression is mediated in part by inflammation (108). The inflammatory dietary pattern identified using reduced rank regression

statistical method may be a better predictor of depression as it incorporates existing knowledge on the biochemical factors involved in the pathophysiology of depression. This study suggests that inflammation may underlie the relationship between dietary intake and depression, although further studies are needed to confirm this. As there are many factors in relation to pathogenesis of depression, other pathways than inflammation may also be relevant in the evaluation of diet-depression relationship. Such studies are needed to explain the fundamental processes on how dietary factors influence depression, and provide a stronger support for causal biological relationships.

While most research on this topic have focused on examining diet as a modifiable risk factor in the prevention of depression, it is also important to determine whether dietary interventions have the potential to act as a treatment for depressive symptoms. Studies conducted among depressed patients aiming to explore whether a healthy diet reduces depressive symptoms are cross-sectional in nature (109, 110). Although they found that high diet quality or 'plant foods and fish' dietary pattern was associated with lower depressive symptom score, there is a possibility that having depression (or the co-occurrence of related medical conditions) affected the adherence to a particular dietary pattern. Therefore, it is unclear whether dietary intakes can be effective in relieving depressive symptoms in individuals diagnosed with depression. Further strong methodological prospective studies or RCTs are necessary to elucidate the direction of this relationship.

1.2.4 Concluding Statement

Depression causes substantial morbidity, disability, and mortality, and brings burden to health resources and society (34). Effective universal preventive strategies are needed to bring about a reduction in depression prevalence at a population level. Preventative efforts can focus on modifiable lifestyle factors such as diet, physical activity and smoking that potentially have greater plasticity and reach (111). There is now increasing evidence that habitual dietary intake influences the risk of developing depression; although the majority of studies are cross-sectional, which limits the ability to determine causality. The lack of RCTs also means that the associations between diet and depression are affected by residual confounding. Prospective cohort studies in addition to RCTs of rigorous methodology are needed considering the

limitations of RCTs in examining research questions of this nature. Therefore, this thesis is comprised of three primary research studies examining associations between diet and depression using data from two large Australian prospective cohorts.

The two main approaches used to define overall diet – statistical derivation of dietary patterns (included in Chapter 2) or diet quality indices, have their own strengths and limitations. Two of the primary research studies within this thesis (Chapters 5 and 6) will use diet quality score to assess overall diet as the score was developed based on current evidence of what constitutes a healthy diet (86). Findings on diet quality can provide useful information on how well the study population comply with dietary guidelines, and how their diet quality tracks over time. The use of this approach also facilitates comparison across studies (86). Furthermore, if an association is found between diet quality and depression, the findings can be easily translated to specific diet and nutrition messages for the general public (87).

Of equal importance is the need for research into new therapeutic strategies to reduce depressive symptoms among those with depressive disorder or subthreshold depression. This is because depressive symptoms have been shown to result in more medical service utilisation, suicide attempts, and disability (e.g. high levels of household strain, social irritability, limitations in physical or job functioning, and poor health status) due to their high prevalence among the community (34). As such, this thesis will include a component to examine the role of diet quality on depressive symptoms rather than depression cases.

Finally, the development of interventions for depression needs to be closely link to evidence not just from epidemiology but should also include knowledge on biological sciences. Therefore, this thesis will seek to uncover the biological pathways underpinning the association between dietary intakes and depression.

Table 1.1: Study characteristic of one RCT examining the association of dietary patterns and depression included in the updated literature review

Author, Year, Country, Duration	Subjects	Study groups (*n*)	Intervention: dietary components:	Dietary assessment	Depression assessment	Adjustment for confounders	Main findings
Sanchez-Villegas, 2013, Spain, 3y (94)	The PREDIMED trial, men aged between 55 and 80 years, women aged between 60 and 80 years with no previously documented CVD. Inclusion criteria: - Have diabetes mellitus type 2 - At least three of the following: current smoker, hypertension, LDL cholesterol >4.11mmol/L, HDL cholesterol <1.03 mmol/L, overweight/obese, family history of premature CHD.	C (n=1184): low-fat diet according to American Heart Association guidelines I_1 (n=1446): intensive education to follow the Mediterranean diet supplemented with extra virgin olive oil (1L/week) I_2 (n=1293): intensive education to follow the Mediterranean diet supplemented with mixed nuts (15g walnuts, 7.5g hazelnuts, 7.5g almonds per day).	Mediterranean Diet: - Abundant use of olive oil - Increase consumption of fruit, vegetables legumes and fish - Reduced total meat consumption, more white meat instead of red or processed meat - Prepare homemade sauce with tomato, garlic, onion, spices, with olive oil - Avoid butter, cream, fast food, sweets, pastries, sugar-sweetened drinks, - moderate consumption of wine (for alcohol drinkers)	FFQ, 137-item, validated against dietary records, measured at baseline and follow-up 97% retention rate	Self-reported physician diagnosis and/or habitual use of antidepressant drugs.	Age, sex, recruiting centre, BMI, smoking, physical activity, education, marital status, alcohol and total energy intake, presence of disease(s) at baseline (cancer, diabetes, hypertension, hypercholesterolemia, fractures, Parkinson disease, chronic bronchitis	Each intervention group to control: I_1: HR 0.91; 95% CI 0.67, 1.24 I_2: HR 0.78; 95% CI 0.55, 1.10 All intervention participants to control: HR 0.85; 95% CI 0.64, 1.13

Table 1.2: Characteristics of observational studies examining the association of dietary patterns and depression included in the updated literature review

Cohort studies

Author, Year, Country, Duration	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Jacka, 2014, Australia, 12y (92)	The Personality and Total Health (PATH) Through Life Study n = 3663 Three age cohorts: 20-24, 40-44, 60-64 Gender: 1612 male, 2035 female	FFQ, 74 items, validated against daily diet records; measured at baseline	Principal component analysis: tertile of factor scores	Prudent Diet – fresh vegetables, salad, fruit, grilled fish Western Diet – roast meat, sausages, hamburgers, steak, chips, crips, soft drinks	Goldberg Depression Scale; measured at baseline and every 4 years; depression ≥6	Gender, education, income, labour-force status, hardship, childhood poverty, occupational skill level, income support dependent, area disadvantage, physical activity, smoking, CVD risk factors	Results presented for oldest cohort (≥60) only (P<0.05) Lowest vs Highest Tertile: Prudent Diet: OR 1.18; 95% CI 1.01, 1.39 Western Diet: OR 1.14; 95% CI 0.98, 1.34
Lucas, 2014, USA, 12y (97)	The Nurses' Health Study (NHS) n = 6446 Age: ≈62	FFQ, 131 item, validated against diet records; measured at baseline and every 4 years	Reduced rank regression – quintiles of inflammatory dietary pattern score	Inflammatory dietary pattern – high in sugar-sweetened soft drinks, refined grains, red meat, soft drinks, margarine, vegetables (corn, celery, mushrooms, green pepper, eggplant, summer squash, mixed vegetables); low in fish, low in wine, coffee, olive oil, green leafy and yellow vegetables	Strict definition: self-reported both a clinical diagnosis of depression and use of antidepressants Broad definition: self-reported use of antidepressants or clinical diagnosis of depression	Age, BMI, smoking, menopausal status, use of postmenopausal hormone therapy, marital status, retirement, education, ethnicity, physical activity, SF-36 (MHI-5 score), cancer, high blood pressure, hypercholesterolemia, heart disease, diabetes	Highest vs Lowest Quintile: Strict definition: RR 1.37; 95% CI 1.20, 1.57; P-trend across quintiles <0.001 Broad definition: RR 1.31; 95% CI 1.20, 1.43; P-trend across quintiles <0.001

Table 1.2 *(continued)*

Author, Year, Country, Duration	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Ruusunen, 2014, Finland, 16.5y (93)	The Kuopio Ischemic Heart Disease Risk Factor (KIHD) study, middle-aged or older mean from Eastern Finland n = 1003 Age: 46-65	FFQ, 142 items, validated against food records, measured at baseline	Factor analysis: continuous factor scores	Prudent Diet – fresh vegetables, cooked vegetables, fruits, whole-grain bread, poultry, berries, low-fat cheese and fish. Western Diet – sausages, meats, sweet snacks, soft drinks and sweetened juices, baked potatoes and French fries, French rolls, processed foods, high fat cheese and eggs.	Hospital discharge diagnosis of depression	Age, examination year, history of mental illnesses, education, 4-year depression score (assessed with Human Population Laboratory depression scale)	Prudent Diet: HR 0.66; 95% CI 0.47, 0.93, *P*=0.018 Western Diet: HR 0.91; 05% CI 0.63, 1.32, P=0.615
Cross-sectional Studies							
Dipnall, 2015, USA (88)	The National Health and Nutrition Examination Surveys (NHANES) 2009-2010 n = 4656 Age: 20-75 Gender: 50.4% male, 49.6% female	24-h dietary recall	Principal component analysis: continuous factor scores	Healthy Diet – vegetables, leafy/lettuce salad, fruit, cooked whole grains, whole grain bread Sweets Diet – cookies/cake, chocolate/candy, ice cream, pastries foods Unhealthy Diet – fried potatoes, cheese, red or processed meat, pizza, non-fried potatoes, regular soft drinks	Patient Health Questionnaire (PHQ)-9 depression ≥10	Gender, age group, marital status, education, race/ethnicity, smoking status, adult food insecurity, BMI, ratio of family income to poverty, C-reactive protein, diabetes	Healthy Diet: OR 0.68; 95% CI 0.59, 0.80; *P*<0.001 Sweets Diet: OR 1.15; 95% CI 1.00, 1.33; *P*=0.045 Unhealthy Diet: OR 1.10; 95% CI 0.96, 1.27; *P*=0.161
Loprinzi, 2014, USA (89)	NHANES 2005-2006 n = 2574 Age: 46.3 Gender: 51.3% female	24-h dietary recall	Healthy Eating Index (HEI) 2005 (0-100): healthy diet ≥60th percentile population average	High intake of fruit, vegetables, legumes, whole grains, low-fat milk; moderate intake of lean meat/poultry; low intake of saturated fat, sodium, alcohol, added sugars	PHQ-9; depression ≥10	Age, gender, race/ethnicity, BMI, poverty-to-income ratio, comorbidity index (arthritis, coronary heart disease, stroke, cancer, diabetes, kidney disease, hypertension)	Healthy Diet vs Unhealthy Diet: OR 0.51; 95% CI 0.27-0.93; *P*=0.03

Table 1.2 *(continued)*

Author, Year, Country	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Yu, 2014, Canada (90)	The Atlantic Partnership for Tomorrow's Health study cohort, resident of Atlantic Canada provinces, aged 35-69 years. n = 4511 Gender: 1382 male, 3129 female	FFQ, validated against dietary recalls	HEI 2005 (0-100): higher scores indicate greater adherence to dietary guidelines; top quintile of HEI score indicate high quality diet	High intake of fruit, vegetables, legumes, whole grains, low-fat milk; moderate intake of lean meat/poultry; low intake of saturated fat, sodium, alcohol, added sugars	PHQ-9; mild depression (5-9), major depression (≥10)	Age, sex, investigation site, year and season of interview, ethnicity, education, marital status, chronic disease	Major vs No depression: All: OR 0.76; 95% CI 0.61, 0.93 Men: OR 0.78; 95% CI 0.43, 1.41 Women: OR 0.75; 95% CI 0.60, 0.94

1.3 Aims and Structure of Thesis

The overall aim of this PhD is to fill some of the gaps in the literature raised previously by examining the longitudinal relationship between the overall diet and the likelihood of developing depression, among various cohorts of middle aged and older Australians. Multiple assessments of dietary intakes were used where possible. Depression was explored from both preventative and treatment perspectives and treated as both dichotomous and continuous outcome. In addition, the underlying biological pathway linking diet and depression, namely the inflammation hypothesis, was explored. This PhD comprises of five papers outlined below, which has been incorporated into separate parts of the thesis:

- Paper 1: A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults.
- Paper 2: Biochemical validation of the Older Australians' food frequency questionnaire using carotenoids and vitamin E
- Paper 3: Prospective study on the association between diet quality and depression in mid-aged women over 9 years
- Paper 4: Longitudinal diet quality is not associated with depressive symptoms in a cohort of mid-aged Australian women
- Paper 5: The association between diet and depression may be mediated by inflammation.

1.3.1 Part 1: Overview of Topic Area (Chapters 1 and 2)

Chapter 1 provides the background and rationale to the conduct of this thesis, highlighting the impact of the disease, and presents a case for encouraging dietary interventions as a strategy to target depression. The overall aim and structure of this thesis is described, and how each study contributes to this thesis is also explained.

Chapter 2 (Paper 1) is a systematic review and meta-analysis of the current evidence on the association of dietary patterns and depression. This review included a critical appraisal of current literature and a synthesis of study findings using statistical methods. Previous reviews on overall diet and depression did not conduct a quantitative synthesis of study findings. With the conflicting study findings, a meta-analysis with best evidence synthesis is a valuable contribution to this topic area, as it provides a more reliable estimate of the overall effect due to

increased statistical power and at the same time allowing the inconsistencies between studies to be formally assessed and more accurately quantified. This review also identified the gaps in literature which provided the rationale for the study design of Chapters 5 and 6 (Papers 3 and 4).

1.3.2 Part 2: Methods (Chapters 3 and 4)

This PhD involves a series of secondary data analyses using two existing datasets: the Australian Longitudinal Study on Women's Health (ALWSH) and the Hunter Community Study (HCS). Chapter 3 presents a brief description of the datasets used and the appropriateness of using them to form the main study population of this thesis.

Chapter 4 (Paper 2) is the validation study of the FFQ used in the HCS. While the FFQ presents data that is more reflective of usual intakes, it has a number of limitations that reduces the accuracy of the dietary data collected. For example, it is highly reliant on respondent's memory, it is restricted to a fixed list of foods, and the arbitrary portion size for each food items is highly influenced by the respondent's perception (85). As Chapter 7 (Paper 5) used the dietary data collected with the HCS FFQ to investigate whether the association of dietary intake and depression is mediated by inflammation, it is important to quantify the validity of the FFQ in measuring the exposure to allow a better interpretation of study findings. If results indicate that the FFQ is valid, then Chapter 7 can rely on the dietary data as being accurate, and results arising from this investigation are less likely to be biased by measurement errors of the exposure. If the results of this study indicate poor validity, this limitation will be addressed in the discussion section of Chapter 7 regarding how this can bias the study findings. Chapter 4 compared dietary intakes measured by the HCS FFQ to plasma carotenoids and vitamin E as their circulating levels are more responsive to intake and less influenced by homeostatic regulation (85). Furthermore, dietary antioxidants (i.e. carotenoids and vitamin E) are the main exposure variables in Chapter 7, thus this validation study can provide an insight into how well these variables were measured.

1.3.3 Part 3: Results (Chapters 5-7)

The main aim of this thesis was investigated in three separate chapters – Chapters 5-7. This PhD takes the "research from the top-down" approach (82), starting off with the investigation of

overall diet and depression, and then ending it with a study on individual foods and nutrients and potential biological activity.

Chapter 5 (Paper 3) explores the association between overall diet and incident depression, whereby overall diet is defined using a diet quality score and depression is treated as a dichotomous outcome. This study seeks to support the case for the inclusion of dietary intervention as an effective preventive strategy to new onset of depression. The use of a prospective design in this study allows the temporal relationship between diet quality and incident depression to be established. Furthermore, assessment of dietary intakes was conducted at multiple time-points, providing a stronger test of cumulative dietary exposures on depression. From this, study subjects with consistently high diet quality were compared to subjects with consistently poor diet quality over time. In addition, study subjects who improved or worsened their diet quality were identified and the association with incident depression was examined. This will provide further support for encouraging long term adherence to a high quality diet as preventative towards depression, and potentially show that improving the quality of diet could be more advantageous than maintaining a poor diet quality.

Chapter 6 (Paper 4) is an expansion of Chapter 5 in the investigation of the diet-depression relationship but from the treatment perspective. Unlike Chapter 5 which focused on new cases and excluded study subjects with a history of depression, this study included all subjects regardless of their depression status, and examined the influence of diet quality on depressive symptoms. Findings from this study will further support the role of diet in effectively relieving depressive symptoms in individuals with depressive disorder and individuals with subthreshold depression. Depression is treated as a continuous outcome variable in this study as this condition is better conceptualised along a spectrum with constant changes in severity of symptoms, and may vary from non-specific depressive symptoms (that do not amount to a disorder diagnosis) to major depression. This study also aims to describe the trends in diet quality and how this affects changes in depressive symptoms, which is important for studies with long follow-up period (as explained earlier).

Chapter 7 (Paper 5) aimed to provide an added understanding as to how a healthy or a high quality diet works in preventing incident depression or relieving depressive symptoms by

investigating the biological pathways that underlie the association between dietary intakes and depression. This chapter also aimed to uncover characteristics (i.e. nutrients, food constituents or food groups) of a healthy diet that contributed to the beneficial effect observed on depression. A healthy or a high quality diet is characterised by high intakes of fruits, vegetables, fish and whole grains, which has been shown to reduce the odds of depression (described further in Chapter 2). Foods within this dietary pattern has high contents of antioxidants, phytochemicals and essential fatty acids that are believed to be anti-inflammatory (112), and it is proposed that the anti-inflammatory properties of these foods contribute to reducing depression risk (113). Therefore, this last study aimed to (1) determine if the beneficial effect of fruit and vegetables on depression is attributable to their antioxidant content (i.e. carotenoids and Vitamin E), and which fatty acids are associated with depressive symptoms; and (2) examine whether these associations were mediated by inflammation. Findings from this study could potentially identify characteristics of foods that are essential in the construct of dietary patterns relevant to depression. While there are a number of pathways proposed to be responsible for the diet-depression relationship, it is beyond the scope of this PhD to explore all of them.

1.3.4 Part 4: Discussion and Concluding Remarks (Chapter 8)

The final part of this thesis provides a summary of findings including the strengths and limitations of each study. This chapter also includes a discussion on the implications for future research and practice.

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CHAPTER 2: A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults

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2.1 Abstract

Background

Studies of single nutrients on depression have produced inconsistent results and they fail to consider the complex interactions between nutrients. An increasing number of studies are investigating the association of overall dietary patterns and depression in recent years.

Objective

This study aims to systematically review current literature, and conduct meta-analyses of studies addressing the association between dietary patterns and depression.

Methods

Six electronic databases were searched for articles published up to August 2013, examining the association of total diet and depression among adults. Only studies considered methodologically rigorous were included. Two independent reviewers completed study selection, quality rating and data extraction. Effect sizes of eligible studies were pooled using random effects models. A summary of findings was presented for studies that could not be meta-analysed.

Results

A total of 21 studies were identified. Results from 13 observational studies were pooled. Two dietary patterns were identified. The 'Healthy' diet was significantly associated with a reduced odds of depression (OR = 0.84; 95% CI: 0.76, 0.92; $P<0.001$). No statistical significant association were observed between the 'Western' diet and depression (OR = 1.17; 95% CI: 0.97, 1.68; $P=0.094$), however the studies were too few for a precise estimate of this effect.

Conclusion

Results suggest that high intakes of fruit, vegetables, fish and whole grains may be associated with reduced depression risk. However, there is a need for more high quality randomised controlled trials and cohort studies to confirm this finding, specifically the temporal sequence of this association.

2.2 Introduction

Depression is a common mental health disorder estimated to affect 350 million people worldwide (1). It is expected to be the world's second leading cause of disease burden by the year 2020. Depression is associated with decreased productivity, poor psychosocial outcomes, and decreased quality of life and wellbeing (2). In addition, health care services to manage this condition cost governments billions of dollars each year (1). In view of its public health impacts, there is a need for new approaches to prevent depression or to delay its progression.

There has been much debate recently regarding the development of universal interventions to prevent those at high risk of developing depression, and those with current depressive symptoms, from developing major depressive disorder (3, 4). However, the majority of research for depression has been devoted to tertiary treatment, including individualised pharmacologic and psychological treatments (5). There is a need for more research focused on the prevention of depression, among community-dwelling individuals.

An emerging body of evidence has suggested that nutrition plays an important role in mental health (6, 7). In the past, the majority of studies focused on the association of depression with specific nutrients or foods (6). However, the effect of nutrition on health is complex, and often involves interactions between different nutrients and a variety of food components, in addition to health behaviours. In view of this, there has been a shift in focus from the study of single nutrients towards total diet and dietary patterns in recent years (8). Two main approaches have been used to identify patterns of dietary intake. The *a priori* approach uses diet quality scores or indices, based on dietary guidelines, to assess an individual's adherence to a predefined dietary pattern (8). The *a posteriori* approach makes use of statistical exploratory methods to identify major dietary patterns based on dietary intake reported by a population (8).

As new studies investigating the association of dietary patterns with depression emerge, a systematic collection and evaluation of these findings will provide a better understanding of the role of total diet on the risk of depression. This systematic review aims to critically appraise current literature and conduct meta-analyses to synthesise the results of studies on dietary patterns and depression among the general population.

2.3 Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used for writing up this systematic review (9).

2.3.1 Search strategy

An electronic literature search was conducted of six databases for articles published up to August, 2013: Medline, Embase, PsycInfo, CINAHL, Scopus, and Proquest using the following keywords and index terms: ('nutrition' or 'diet*' or 'dietary pattern' or 'diet quality' or 'food habits' or 'nutrition surveys' or 'diet surveys' or 'food frequency questionnaire' or 'diet records') AND ('depression' or 'depressive disorder' or 'affect*' or 'psychological stress' or 'depressive symptoms'). All searches were limited to human studies published in the English-language.

2.3.2 Study selection

Titles and abstracts of all articles retrieved in the initial search were evaluated independently by two reviewers (JSL and SH). Articles not meeting the eligibility criteria were excluded using a hierarchical approach based on study design, population or exposure, and outcome. The reference lists of relevant review papers identified during this process were also examined to include additional studies. Full-text articles were retrieved if the citation was considered eligible, and subjected to a second evaluation for relevance by the same reviewers. Any disagreements were discussed and resolved by consensus, or by a third independent reviewer (AJH) if necessary.

2.3.3 Eligibility criteria

Relevant articles were obtained and included in this review if they: (i) examined whole diet (regardless of methods used to define dietary patterns) and included measurements of all dietary components using 24-hour recall, food record, food frequency questionnaire (FFQ), or similar instruments; (ii) included depressive symptoms, depressive disorder or dysthymia as an outcome measure; (iii) enrolled community-dwelling adults. Articles were excluded if they: (i) only examined individual nutrients or did not examine all dietary components; (ii) did not report depression data in a format that could be extracted; (iii) comprised study samples that were not population-based, or only focused on a subgroup of individuals with nutritional needs that are

different from the general population, or individuals with health conditions that may confound the diet-depression relationship. **Table 2.1** outlines a detailed inclusion and exclusion criteria for the selection of studies based on three main items: population, exposure and outcome.

Table 2.1: Inclusion and exclusion criteria for selecting studies

	Population	Exposure	Outcome
INCLUDE	Community-dwelling adults, ≥18 years old Study sample must be selected from free-living settings instead of institutional care When health status was not specified, the sample was assumed to be broadly representative of the general population	Dietary pattern defined using diet quality scores or indices, or using statistical exploratory method (e.g. pattern analysis) Assessment of whole diet (i.e. using FFQ, 24-hour recall, food record, diet history, or similar) or whole diet intervention Analysis of association must include all dietary components	Depressive disorder or depressive symptoms as primary or secondary outcome Depression data must be in a format that can be extracted
EXCLUDE	Adults with nutritional needs different from the general population (e.g. pregnant and lactating women, athletes) Only included subgroup of the general population with health condition that may confound the diet-depression relationship (e.g. obese, hypertensive, hypercholesterolemia)	No measure of whole diet or only measured specific dietary components (e.g. dietary screeners) or individual nutrients Dieting or disordered eating behaviours (e.g. binge eating or other eating disorders) Eating patterns or dietary habits (e.g. regular meals, meals with diverse foods, snacking habits)	Depressed mood Postnatal or postpartum depression Bipolar disorders, overall mood states, or psychological stress where depression data could not be isolated and extracted

2.3.4 Quality assessment

Articles considered for inclusion after the second evaluation were assessed for methodological quality independently by two reviewers (JSL, and SH or AJH). The quality of all articles was assessed using the American Dietetic Association Quality Criteria Checklist for primary research (10). The articles were rated based on four questions addressing relevance to practice and ten validity questions addressing scientific soundness. The articles were subjected to validity assessment only if the answers to all relevance questions were 'Yes'. For each validity question, the reviewers assigned 'Yes' if the criterion was met, 'No' if the criterion was not met, 'Unclear' if the criterion was not clearly described, or 'N/A' if the criterion did not apply to the

study. The answers for each article were tabulated, and a rating of positive, negative or neutral was assigned. Any disagreements that arose between the reviewers were resolved through discussion. Positive articles with six or more of the answers to the validity questions being 'Yes', including all four priority questions, were considered methodologically rigorous and were included. Negative articles with six or more of the answers to the validity questions being 'No' or 'Unclear', did not meet the criteria of a strong quality study and were therefore excluded. If at least one of the answers to the priority validity questions was 'No' or 'Unclear', the articles were rated 'Neutral', and these were subjected to a second quality assessment. This second stage assessed the quality of the dietary assessment tool used in each 'Neutral' article. All 'Neutral' articles utilised a food frequency questionnaire (FFQ) to assess dietary intake. If the FFQ was validated, the full text of the validation study was retrieved and assessed using the European micronutrient Recommendations Aligned Network of Excellence (EURRECA) scoring system (11). Dietary assessment tools scoring greater than 5 were rated 'excellent', scoring 3.5 to 5 were rated 'good', scoring 2.5 to 3.5 were rated 'acceptable', and scoring less than 2.5 were rated 'poor'. If the FFQ was not validated, it was rated 'poor'. Neutral articles that used 'poor' dietary assessment tool were excluded.

2.3.5 Data extraction

Data extractions were performed by two independent reviewers (JSL, SH or EG) and entered into a predefined data extraction form. Discrepancies in data extraction were discussed and resolved by consensus. If there were multiple publications originating from the same study cohort, the article reporting the largest sample for the diet and depression measures was chosen.

The following information was extracted: first author, publication year and country; study design; study duration (for cohort studies), sampling frame, sample size, and number of cases and controls (if available); dietary assessment tool and validation method (if applicable); method of identifying dietary patterns; dietary patterns identified; depression assessment tool; confounders adjusted for in analysis; main findings including the estimates of association. When a study provided several estimates with adjustment for different confounders, results were reported for the one adjusting for the largest number of factors.

2.3.6 Data synthesis

Only the most common patterns of dietary intake or dietary interventions were considered for meta-analysis. As the labelling of dietary patterns varied across studies, as long as the selected patterns were similar with regards to the most frequently consumed foods, these studies were grouped and analysed together regardless of their original label. For example, most studies examined dietary patterns with high intakes of fruits and vegetables, fish and whole grains, and these studies were pooled and analysed together, and the corresponding dietary pattern was labelled 'Healthy'. Studies not eligible for inclusion in the meta-analysis were summarised in a narrative review.

2.3.7 Statistical analysis

The original studies reported the results of dietary pattern either as categories of dietary factor scores, as continuous diet quality scores or standardised dietary factor scores. To combine the results, a meta-analysis was conducted in which we evaluated depression outcomes for higher versus lower intakes of dietary patterns: highest versus lowest categories of dietary pattern or standardised dietary factor scores. For observational studies with depression as a binary outcome, odds ratios (OR) and 95% confidence intervals (CI) from individual studies were combined. If studies reported relative risk (RR) instead of OR, it was treated the same as OR if the reported incident depression was ≤20%. If studies treated depression as a continuous variable by way of regression coefficients or as mean difference in depression score between categories of dietary pattern, standardised coefficients or standardised mean difference (SMD) and their corresponding standard errors (SE) were multiplied by 1.81 to convert them to log odds ratio (lnOR) and the corresponding SE_{lnOR} according to the Hasselblad and Hedges method (12, 13).

Random-effects models were used for the analysis. Heterogeneity was assessed using the I^2 statistic (14). If results showed significant heterogeneity, potential sources of heterogeneity were explored using meta-regression and subgroup analysis, with the following covariates: age (as continuous variable, and age groups: <65 or 65+ years), gender, country (USA or European countries), study design, methods used to identify dietary patterns (*a posteriori* or *a priori*), dietary intake assessment (FFQ or dietary recalls), depression measure (symptom inventories

or diagnostic), percentage of depression cases at baseline (as continuous variable, and <20% or ≥20%), and methodological quality ('Positive' or 'Neutral'). Publication bias was examined through a contour-enhanced funnel plot to look for asymmetry (15). All statistical analyses were conducted using Stata version 11 (16).

2.4 Results

2.4.1 Search results

Figure 2.1 shows the flow chart detailing the process of study selection. The search yielded 3477 citations (excluding duplicates, *n*=1025). Initial screening of title and abstract excluded 3290 citations. Hand-searching of reference list of review articles further identified 11 references. Full-texts for eligible citations were obtained for further evaluation. Assessment of methodological quality was performed on 45 full-text articles. The final number of articles eligible for inclusion in this review was 25. However, data from only 21 of the articles was included, to avoid duplicating the results of any individual participant (i.e. there were four articles which duplicated data from three cohorts). In total, there were 20 observational studies (17-36) and one RCT (37). Due to a lack of RCTs, subsequent results focus on the observational studies.

2.4.2 Quality

All 45 full-text articles scored 'Yes' to all the relevance questions and were subjected to validity assessment. Out of a maximum of 10 'Yes' answers for validity questions, the highest score was nine and the lowest score was two (**Table 2.2**). Ten studies were rated 'negative', scoring less than five 'Yes', and were excluded. Thirteen studies were rated 'neutral'. These 'neutral' studies were subjected to the EURRECA scoring system (results not shown). Nine of the 'neutral' studies used a non-validated FFQ to assess dietary intake and were therefore eliminated from this review. These nine eliminated studies either used self-constructed FFQ with no mention of whether they were validated, or used modified versions of validated FFQs that were not re-validated. The FFQs in the remaining four studies were rated 'good', scoring between 3.5 and 5.

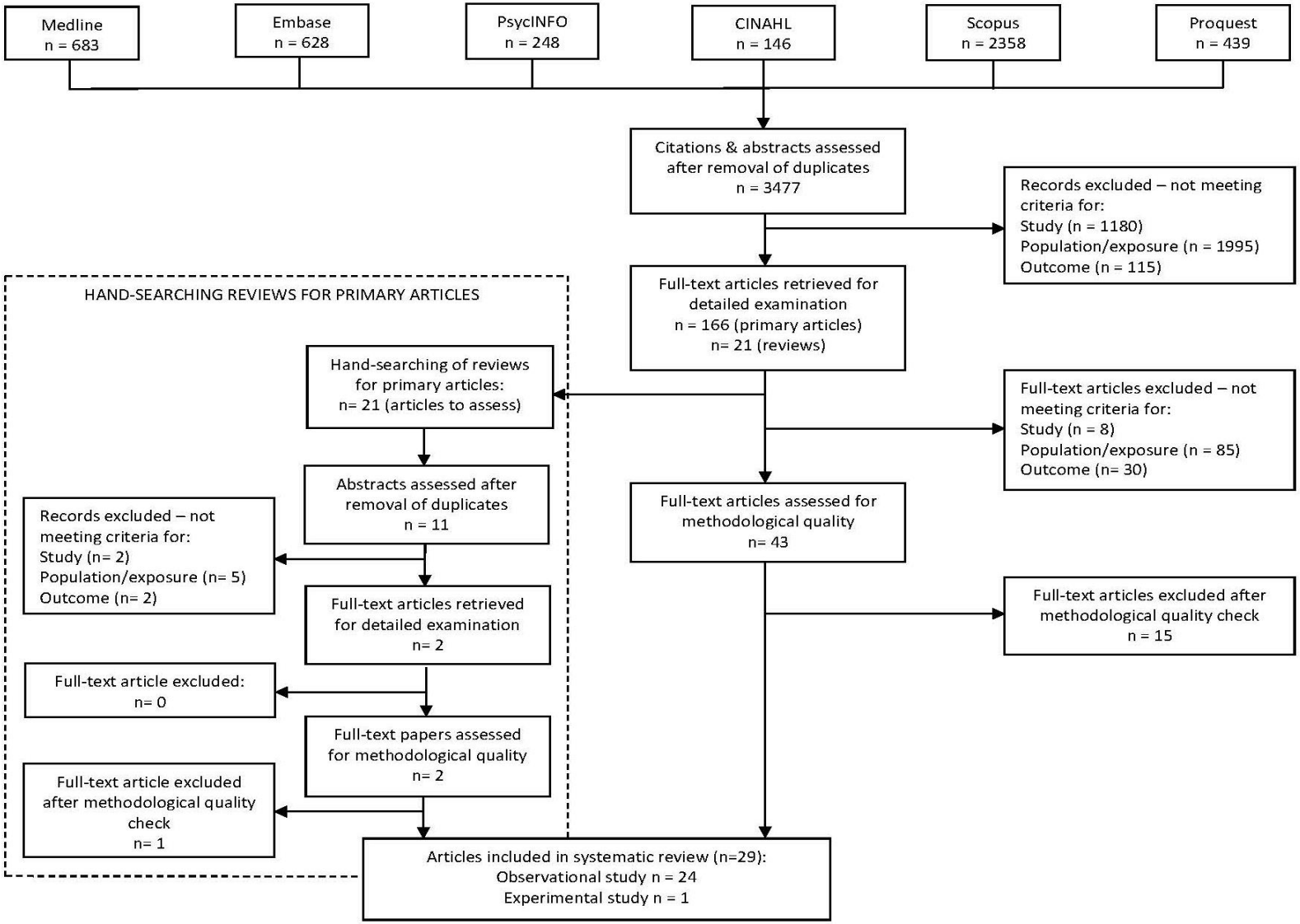

Figure 2.1: Flowchart of the study selection process for meta-analysis of dietary patterns and depression

Table 2.2: Quality assessment of studies examining the association of dietary patterns and depression (ADA Quality Criteria Checklist: Primary Research)

Citation	Clear Research Question?	**Free of Selection Bias?**	**Study Groups Comparable?**	Method of handling withdrawals described?	Blinding?	**Intervention described?**	**Clear outcomes, valid & reliable measurements**	Appropriate statistical analysis	Conclusions supported by results?	Bias due to funding/ sponsorship unlikely?	**(-) or (Φ) or (+)**
Akbaraly, 2009 (38)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Akbaraly, 2013 (36)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Appleton, 2007(39)	Yes	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Yes	Φ
Baines, 2007 (40)	Yes	Yes	No	No	Unclear	No	No	Yes	Yes	Yes	-
Beezhold, 2010 (41)	Yes	No	No	Yes	Unclear	No	No	Yes	Yes	Yes	-
Beezhold, 2012 (37)	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Φ
Beydoun, 2009 (42)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Beydoun, 2010 (17)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Beydoun & Wang, 2010 (18)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Bountziouka, 2009 (43)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Chocano-Bedoya, 2013 (19)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Crichton, 2013 (20)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Feart, 2009 (21)	Yes	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Yes	Φ
Hintikka, 2005 (44)	Yes	Yes	Yes	No	Unclear	No	Yes	No	Yes	Unclear	Φ
Hyland & Sodergren,1998 (45)	Yes	No	Unclear	No	No	No	No	Unclear	Yes	Unclear	-
Iwasa, 2009 (46)	Yes	Yes	No	Yes	Unclear	No	Yes	No	Yes	Yes	Φ
Jacka, 2010 (23)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Jacka, 2011 (22)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Jackson, 2006 (47)	Yes	No	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	No	-
Jeffrey, 2009 (48)	Yes	Unclear	No	No	Unclear	No	Yes	Unclear	Yes	Yes	-
Kimura, 2009 (49)	Yes	Unclear	Unclear	No	Unclear	No	Yes	Unclear	No	Yes	-
Klassen, 2009 (24)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	+
Konttinen, 2010 (50)	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	Φ
Krauchi, 1988 (25)	Yes	No	Yes	N/A	Yes	Yes	Yes	No	No	Yes	Φ
Kronish, 2012 (26)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Kuczmarski, 2010 (51)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Le Port, 2012 (52)	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Φ

Table 2.2 *(Continued)*

Citation	Clear Research Question?	**Free of Selection Bias?**	**Study Groups Comparable?**	Method of handling withdrawals described?	Blinding?	**Intervention described?**	**Clear outcomes, valid & reliable measurements**	Appropriate statistical analysis	Conclusions supported by results?	Bias due to funding/ sponsorship unlikely?	**(-) or (Φ) or (+)**
Link, 2008 (53)	Yes	No	Unclear	No	Unclear	No	Yes	No	Yes	Yes	-
Mamplekou, 2010 (27)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
McMillan, 2011 (54)	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	No	-
Meyer, 2013 (28)	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	+
Michalak, 2012 (55)	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Φ
Mikolajczyk, 2009 (56)	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	Φ
Nanri, 2010 (29)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Panagiotakos, 2008 (57)	Yes	Yes	No	No	Unclear	No	Yes	Yes	Yes	Yes	Φ
Park, 2010 (58)	Yes	Unclear	No	Yes	Unclear	No	Yes	No	No	Yes	-
Rienks, 2013 (30)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Samieri, 2008 (31)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Sanchez-Villages, 2009 (32)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Sarri, 2008 (59)	Yes	Unclear	No	No	Unclear	Yes	Yes	No	No	Unclear	-
Skarupski, 2012 (33)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	+
Sorensen, 2010 (60)	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Yes	No	No	Φ
Sugawara, 2012 (34)	Yes	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Φ
Tsai, 2012 (35)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	+
Weidner , 1992 (61)	Yes	Yes	No	Unclear	No	Yes	No	No	No	Yes	-

2.4.3 Description of studies

The characteristics of the studies included in this review are presented in **Table 2.3**. Six studies were conducted in European countries (21, 22, 25, 27, 31, 32), six in the United States of America (17-19, 24, 26, 33), four in Australia (20, 23, 28, 30), two from Japan (29, 34), one from Taiwan (35), and one from the United Kingdom (36). The total number of participants ranged from 52 to 50,605. Participants' ages ranged from 20 to 94 years at the time of study. Five studies were restricted to female subjects (19, 23-25, 30). The remaining 15 examined both sexes with five examining men and women separately (17, 18, 22, 31, 36) and 10 in combination (20, 21, 26-29, 32-35). The majority of observational studies were cross-sectional (*n*=13) and measured dietary intake and depression concurrently (17, 18, 20-24, 26-29, 31, 34). Four were prospective cohorts which measured dietary intake at baseline and used repeated measures of depression outcomes at baseline and at each follow-up (30, 32, 33, 35). Another two prospective cohort studies used repeated measure of dietary intake and depression outcomes at baseline and at every follow-up (19, 36). There was one case-control study of dietary patterns in people with and without seasonal affective disorder (25). Dietary variables were measured using a variety of instruments. Most studies used validated FFQs (*n*=16) (19-23, 25-27, 29-36), while the remaining studies used 24-hour dietary recalls (*n*=4) (17, 18, 24, 28). Depression was assessed using depressive symptom inventories (*n*=15) (17, 20-22, 24-27, 29-31, 33-36), diagnostic interview schedules (*n*=2) (18, 23) or self-reported clinical diagnosis (*n*=3) (19, 28, 32). The Centre for Epidemiologic Depression Scale was the most commonly (*n*=12) used symptom inventories to assess depressive symptoms (17, 20, 21, 24, 26, 29-31, 33-36). Other symptom inventories include: Hospital Anxiety and Depression Scale (22), Geriatric Depression Scale (27), and a self-developed seasonal affective disorder questionnaire (25). Diagnostic interview schedules include: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (23), and World Health Organization Composite International Diagnostic Interview (18).

The *a priori* approach (diet quality scores or indices) was the most common method used to define dietary patterns (*n*=13) (17, 18, 20-27, 32, 33, 36). Diet quality scores or indices included the Mediterranean diet score (20, 21, 27, 32, 33), the US Department of Agriculture Healthy Eating Index (17, 18), the Alternative Healthy Eating Index (36), and the Australian

Recommended Food Score (23), and various other self-developed diet quality rating tool (22, 24-26). Included in this were three studies that used both the *a priori* and *a posteriori* method of defining dietary patterns (22, 23, 36), but only results for the *a priori* method were pooled for meta-analysis of the Healthy diet as it was the most commonly used method in other studies. Five studies used the *a posteriori* approach which included factor analysis (*n*=5) (19, 29, 30, 34) and cluster analysis (*n*=1) (31). Although dietary patterns observed across studies varied according to country and methods used for defining dietary patterns, it was possible to identify two dietary patterns with similar characteristics that were common to the majority of the studies. The Healthy dietary pattern was characterised by high intakes of fruits, vegetables, fish and whole grains. A second dietary pattern, the Western diet, was identified in studies using the *a posteriori* method. The Western diet generally consisted of refined grains, processed meat foods or snacks, and high sugar and high fat products. The remaining two studies performed separate analyses for each food group and depression (28, 35).

Table 2.3: Characteristics of observational studies examining the effects of dietary interventions and depression

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Akbaraly, 2009 (38), UK, Cohort (5 years)	The Whitehall II Study cohort, civil servants working in London offices (n = 3486, age: 35-55 years, gender = 73.8% men, cases = 416)	FFQ, 127 items, validated against 7-day diet diary and biomarkers; measured at baseline	Factor analysis: tertiles of factor scores	'Processed food' – high intakes of sweetened desserts, chocolates, fried food, processed meat, pies, refined grains, high-fat dairy, condiments	CES-D, 20 items, measured at baseline and 5 years follow-up; depression >15	Age, gender, energy intake, employment grade, educational level, marital status, smoking, physical activity, hypertension, diabetes, CVD, stroke, antidepressants use, cognitive functioning	Highest tertile of 'processed food' pattern: OR 1.58, 95% CI 1.11-2.23.
Akbaraly 2013 (36), UK, Cohort (15 years)	(n=4215, cases=260)	(as above); measured at baseline and 10 years later	Alternative Healthy Eating Index, AHEI (0-10) – higher scores indicate greater adherence	High intake of fruit and vegetables (except potatoes), nuts & soy, cereal fiber; higher fish/poultry: red/processed meat ratio, PUFA:MUFA ratio; low intake of trans fat; moderate alcohol intake; long term multivitamin use	(as above); measured at baseline, 10 years, and 15 years follow-up; depression >15 at both follow-ups	Age, ethnicity, energy intake, SES, retirement, marital status, smoking, physical activity, hypertension, coronary artery disease, HDL cholesterol, central obesity	Women who maintained a high AHEI score to women who maintained a low score over 10 years: OR 0.35, 95% CI 0.19-0.64 Men who maintained a high AHEI score to men who maintained a low score over 10 years: OR 1.38, 95% CI 0.91-2.11

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Chocano-Bedoya, 2013 (19), USA, Cohort (12 years)	The Nurses' Health Study cohort, female US registered nurses (n=50,605, age ~62 years, cases: 6-15%)	FFQ, 131 items, validated against four 1-wk diet records; measured at baseline and every 4 years	Factor analysis: quintiles of factor scores	Prudent – higher loadings from fruit, vegetables, fish, whole-grain products, low-fat dairy Western – higher loadings of red & processed meats, French fries, desserts, high-fat dairy, refined grains	Strict definition: self-reported both a clinical diagnosis of depression and use of anti-depressants after baseline Broad definition: self-reported use of anti-depressants or clinical diagnosis of depression after baseline	Age, total caloric intake, BMI, smoking status, physical activity, menopause status, use of hormonal replacement therapy, marital status, multivitamin use, retired, participation in community groups, caffeine intake, diagnosis of cancer, diabetes, hypertension, hypercholesterolemia, heart disease, psychological stress or wellbeing at baseline	Strict definition incident depression: Prudent: RR 1.05, 95% CI 0.91-1.20, *P*=0.73; Western: RR 1.05, 95% CI 0.89-1.23, *P*=0.50 Broad definition incident depression: Prudent: RR 1.04, 95% CI 0.95-1.13, *P*=0.79; Western: RR 1.09, 95% CI 0.99-1.21, *P*=0.08

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Rienks, 2013 (30), Australia, Cohort (3 yrs)	The Australian Longitudinal Study of Women's Health cohort, national sample of Australian women (n=6060, age: 45-50 years, cases: n=873 at 3 years follow-up)	FFQ, 80 items, validated against 7-d weighted food records; measured at baseline	Factor analysis: quintiles of dietary factor scores	Cooked vegetables – cauliflower, cabbage, Brussels sprouts, broccoli, green beans Fruit – strawberries, pineapple, melon, apricots, mango Mediterranean – garlic, peppers, mushrooms, salad greens, pasta, red wine Meat & processed meat – pork, bacon, sausages, lamb Dairy – cream cheese, low-fat cheese, yoghurt, skim milk High fat & sugar – sweet biscuits, cakes, jam, meat pies, chocolate	CES-D, 10 items, measured at baseline and 3 years follow-up; depression ≥10	Age, area of residence, ability to manage on available income, occupation, education, marital status, smoking, physical activity, BMI, total energy ntake, history of non-insuline dependent diabetes mellitus, hypertension, heart disease, stroke, mean stress score	Cooked vegetables: OR 0.95, 95% CI 0.85-1.06, *P*=0.32 Fruit: OR 1.04, 95% CI 0.94-1.16, *P*=0.44 Mediterranean: OR 0.83, 95% CI 0.75-0.93 Meat & processed meat: OR 1.06, 95% CI 0.93-1.21, *P*=0.37 Dairy: OR 0.93, 95% CI 0.84-1.04, *P*=0.22 High fat & sugar: OR 1.02, 95% CI 0.92-1.14, *P*=0.73
Sanchez-Villages, 2009 (32), Spain, Cohort (4.4 years)	The Seguimiento Universidad de Navarra' Study cohort, alumni of the University in Spain (n=10 094, age: 21-85 years, gender: 58.5% women, cases: n=480)	FFQ, 136 items, validated against non-consecutive 4-d food records, measured at baseline	Mediterranean-diet score (0-9) – higher scores indicate greater adherence; five categories of adherence (lowest – highest): 0-2; 3; 4; 5; 6-9	High ratio of MUFA/SFA; high intakes of legumes, cereal, fruits and nuts, vegetables, fish; low intake of meat & meat products; moderate intake of dairy products, alcohol	Self-reported physician diagnosis, and/or use of antidepressa nt at baseline and 4.4 years follow-up	Age, sex, marital status, no. of children, employment status, no. of work hours, BMI, energy intake, physical activity, smoking, health consciousness/ proxies of overall healthier lifestyle	Highest compared to lowest adherence: HR 0.5, 95% CI 0.33-0.74

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Skarupski, 2013 (33), USA, Cohort (12 years)	The Chicago Health & Aging Project cohort, Black & White residents in 3 southside Chicago neighbourhoods (n=3,502, age ≥65 years, gender: 41% male, cases: 13.7%, 10.7%, 13.4% at each follow-up respectively)	FFQ, 139 items, validated against multiple 24-hour recalls, measured at baseline	MedDiet Score (0-55) – higher scores indicate greater adherence; tertiles of adherence	Daily: non-refined cereals, vegetables (2-3 serves). fruits (6 serves), olive oil (main added lipid); Weekly: fish (4-5 serves), poultry (3-4 serves), olives, pulses & nuts (3 serves), potatoes, eggs (3-4 serves); Monthly: red meat & meat products (4-5 serves)	CES-D, 10 item, yes/no version, measured at baseline and every 3 years; depression≥4	Age, sex, race, education, yearly personal income, widowhood, total calorie intake, BMI, smoking, alcohol consumption, myocardial infarction, stroke, cancer, diabetes, high blood pressure, Parkinson's disease, shingles, thyroid disease, hip fracture, global cognitive function, physical disability	Highest tertile of MedDietScore compared to lowest tertile: β -0.03, SE 0.01
Tsai, 2012 (35), Taiwan, Cohort (4 years)	The Survey of Health and Living Status of the Elderly in Taiwan cohort, national sample of Taiwanese (n=1609, age: ≥60years, gender: 57.6% men, cases ~21%	FFQ, validated against 14-d food diary, measured at baseline	Food groups analysis – all dietary components examined	Meat & poultry, fish, seafood, eggs, fruits, vegetables, infused camellia tea, grains	CES-D, 10 items, measured at baseline and 4 years follow-up; depression ≥10	Age, gender, years of formal education at baseline, economic status, living setting, smoking status, alcohol drinking, betel-nut chewing, functional status, physical exercise, hypertension, diabetes, heart disease, cancer, stroke, chronic kidney disease, gout, joint pain/arthritis, gallbladder/liver disease, hip fracture, lower-back pain, cognitive status	Consumption of ≥3 times/wk compared to <3 times/wk: Meat & poultry: OR 1.31, 95% CI 0.90-1.91, *P*=0.158; Eggs: OR 0.73, 95% CI 0.50-1.03, *P*=0.069; Seafood: OR 0.92, 95% CI 0.51-1.65, *P*=0.773; Fish: OR 0.91, 95% CI 0.62-1.14, *P*=0.622; Fruits: OR 0.77, 95% CI 0.50-1.17, *P*=0.215; Vegetables: OR 0.40, 95% CI 0.17-0.95, *P*<0.05; Cereal/grains: OR 0.85, 95% CI 0.58-1.26, *P*=0.425; Tea: OR 0.77, 95% CI 0.51-1.16, *P*=0.211

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Beydoun & Wang (18), 2010, USA, Cross-sectional	The NHANES study cohort (n=2217, age: 20-39 years, gender: n=977 men, n=1240 women, cases: 6.4% men, 9.2% women)	One 24-hr recall	Healthy Eating Index-2005 (0-100) – higher scores indicate greater adherence to 2005 dietary guidelines for Americans.	High intakes of fruit, vegetables, legumes, whole grains, low-fat dairy; moderate intakes of lean meat/poultry; low intakes of SFA, sodium, alcohol, added sugars	Composite International Diagnostic Interview for ICD-10	Age, ethnicity, marital status, food insecurity	In men: β -3.29, SEE 2.12, p>0.05; In women: β -2.63, SEE 1.96, *P*>0.05
Beydoun, 2010 (17); Kucmarski, 2010 (51); Beydoun (42), 2009 ; USA, Cross-sectional	The HANDLS Study cohort (n=1681, age: 30-64 years, gender: n=734 men, n=947 women, cases: n=156 men, n=304 women)	Two non-consecutive 24-hr dietary recalls (second recall collected 4-7 days after the first recall)	Healthy Eating Index-2005 (0-100) – higher scores indicate greater adherence to 2005 dietary guidelines for Americans.	High intakes of fruit, vegetables, legumes, whole grains, low-fat dairy; moderate intakes of lean meat/poultry; low intakes of SFA, sodium, alcohol, added sugars	CES-D, 20 items	Age, ethnicity, marital status, education, poverty status, smoking status, illicit drug use, BMI	In women: β -0.083, SE 0.023; In men: β -0.045, SE 0.024, *P*>0.05
Crichton, 2013 (20), Australia, Cross-sectional	Representative sample of South Australian (n=1183, age: 40-65 years, gender: 751 women, 432 men)	FFQ, 215 items, validated against protein and urinary measures	Mediterranean diet score (0-11) – higher scores indicate greater adherence; three categories of adherence: low (0-3), medium (4-7), high (8-11)	High intakes of vegetables, fruits and nuts, legumes, cereals, olive oil, fish; moderate intakes of dairy products, red wine; low intakes of meat, poultry, saturated lipids	CES-D, 20 items	No adjustment of confounders – no significant differences for all measures of socioeconomic status between categories of Mediterranean diet	Average depression score for each category of diet score (mean±SD): low 33.4±9.7, medium 32.9±9.9, high 32.6±9.9
Feart, 2009 (21), France, Cross-sectional	The Three-City Study, community-dwelling adults (n=1410, age ≥65 years, gender: 60% women)	FFQ, 40 item, validated against diet recalls	Mediterranean-diet score (0-9) – higher scores indicate greater adherence; three categories of adherence (lowest to highest): 0-3; 4-5; 6-9	High ratio of MUFA/SFA; high intakes of legumes, cereal, fruits and nuts, vegetables, fish; low intakes of meat & meat products; moderate intakes of dairy products, alcohol	CES-D, 20 items	No adjustment for confounders	Depression score for each category of adherence (mean±SD): low 8.2±7.4, middle 7.5±7.5, high adherence 7.3±6.8

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Jacka, 2010 (23), Australia, Cross-sectional	Geelong Osteoporosis Study cohort of women (n=1046, age: 20-94 years, cases: n=60)	FFQ, 74 foods & beverages, validated against 7-day weighed food record	Factor analysis, standardised dietary factor score – higher factor scores indicate greater consumption Australian Recommended Food Score (0-74) – higher scores indicate greater adherence	Western – meat pies, processed meats, pizza, chips, hamburgers, white bread, sugar, flavoured milk drinks, beer Modern – fruits & salads, fish, tofu, beans, nuts, yoghurt, red wine Traditional – vegetables, fruit, beef, lamb, fish, whole grain foods ARFS – ≥2 serves fruit and ≥4 serves vegetable daily; red meat 1-5 serves/wk, use low fat dairy, wholegrain	The Structured Clinical Interview for DSM-IV-TR Research Version, Non-Patient Edition	Age, socio-economic status, physical activity, alcohol consumption smoking, energy intake, BMI	Western diet: OR 1.52, 95% CI 0.96-2.41, p>0.05 Modern: OR 1.29, 95% CI 0.96-1.73, p>0.05 Traditional dietary pattern: OR 0.65, 95% CI 0.43-0.98, p<0.05 ARFS: OR 0.85, 95% CI 0.62-1.13

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Jacka, 2011 (22), Norway, Cross-sectional	The Hordaland Health Study cohort, community-dwelling adults (n=5731, age: 46-49 years and 70-74 years, gender: n=2477 men, n=3254 women, cases: n=240 men, n=281 women)	FFQ, 169 items, validated against weighed food records	Principal component analysis, standardised dietary factor score – higher factor scores indicate greater consumption Self-developed diet quality score (6-18) – higher scores indicate a more healthy diet	Western – liver, processed meats, pizza, salty snacks, chips, sugars & sweets, soft drinks, cake, ice-cream Traditional – fish & shellfish, potatoes, fruits, vegetables, milk & yoghurt, bread, pasta, rice, meat spreads, legumes, eggs Healthy – vegetables, fruits, rice, pasta, cereals, fish, wine, non-processed meats Diet quality score - high intakes of vegetables, fruit, low-fat dairy, whole grain, fish; moderate intakes of red meat	HADS, 7 items: Depression ≥8	Gender, age group (47-49, 70-74 years), income, education, physical activity, smoking, alcohol & energy intake	Western diet: men OR 0.87, 95% CI 0.68-1.11); women OR 1.25, 95% CI 0.93-1.68) Traditional diet: men OR 0.77, 95%CI 0.61-0.96; women OR 0.99, 95% CI 0.76, 1.29 Healthy diet: men OR 1.02, 95% CI 0.87-1.19; women OR 0.68, 95%CI 0.57-0.82 Diet quality score: men OR 0.83, 95% CI 0.7-0.99; women OR 0.71, 95% CI 0.59-0.84
Klassen (24), 2009, USA, Cross-sectional	African-American women, residing in 11 public housing communities (n=156, age: 20-50 years, cases: n=116)	Three non-consecutive 24-hr dietary recalls (2 weekdays/1 weekend), across 21 days	Self-developed cancer prevention index based on dietary recalls	No alcoholic beverage intake; moderate caloric intake (1600-2200kcal); moderate fat intake (<30% calories); ≥5 servings of fruits and vegetables; ≥ 65 on the Healthy Eating Index-2005	CES-D, 20 items; depression >15	Age, depression, life events, smoking, expected future health, food from other sources, shopping transportation, meal planning	OR 0.45, 95% CI 0.22-0.95, *P*<0.05

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Krauchi (25), 1988, Switzerland. Case-control	Female outpatients with SAD; Controls: hospital staff without psychiatric history (n=28 cases, n=24 controls, age: 27-73 years)	FFQ at each season, 33 food/drink items & 13 meal items, validation method not reported	Food and Drink Scores	Starch-rich foods; sugar-rich foods; protein-rich foods; fiber-rich foods; dairy products; alcohol; caffeine containing drinks	A seasonal screening questionnaire	Age – analysis performed with SAD and control subjects matched for age	Food/Drink scores (mean±SD): Starch-rich foods: Cases = 61.7±15.5 vs Control = 50.3±15.1; Fiber-rich foods: Cases = 82.8±27.9 vs Controls = 61.6±12.7
Kronish, 2012 (26), USA, Cross-sectional	The REGARDS study cohort, population study of white and African-American adults residing in 8 Southern US states (n=20,093, age: ≥45 years, gender: 56% women, cases: 9.8%)	FFQ, 109 items, validated against multiple diet records	Self-developed dietary criteria	Fish ≥2 serves/week; Fruit and vegetables ≥4.5 cups/day; Sodium <1500mg/day; Sugar <450kcal/week; Fiber :carbohydrate ratio >0.1	CES-D, 4 items; depression ≥4points	Age, race, sex, geographic region of residence, education, income	Adjusted prevalence ratios comparing with and without depressive symptoms: Diet (<2 out of 5 healthy diet criteria) 1.08, 95% CI 1.06-1.10
Mamplekou, 2010 (27); Bountziouka, 2009 (43), Greek Islands & Cyprus, Cross-sectional	The MEDIS Study cohort, community-dwelling adults (n=595, age ≥65 years, gender: n=553 men, n=637 women, cases: n=161 mild depression, n=246 severe depression)	FFQ, 15 food groups, validation method not described.	MedDietScore (0-55) – higher scores indicate greater adherence	Daily: non-refined cereals, vegetables (2-3 serves). fruits (6 serves), olive oil (main added lipid); Weekly: fish (4-5 serves), poultry (3-4 serves), olives, pulses & nuts (3 serves), potatoes, eggs (3-4 serves); Monthly: red meat & meat products (4-5 serves)	GDS (0-15); depression: mild (6-10), severe (11-15)	Age, sex, education status, BMI, physical activity status, the presence and management of hypertension, hypercholesterolemia and diabetes	OR 1.03, 95% CI 0.976-1.09), *P*=0.99

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Meyer, 2013 (28), Australia, Cross-sectional	The Australian National Nutrition and Health Surveys cohort, national sample of community-dwelling adults (n=10,986, age ≥18 years, gender = 52% women, cases: n=224	24-hour recall	Food groups analysis – all dietary components examined	Meat, poultry, game; milk products and dishes; vegetables (food groups found to be significant predictors of the logistic regression model)	Self-reported physician diagnosis	Age, gender	Meat, poultry, game: β -29.9, 95% CI 9.64-9.6; milk products: β 10.1, 95% CI 3.87-6.8; vegetables: β -15.7, 95% CI 6.48, 5.9
Nanri, 2010 (29), Japan, Cross-sectional	Full-time municipal employees (n=521, age: 21-67 yrs, gender: 59.1% men, cases: n=186)	Diet history questionnaire, 67 items, validated against 16-day weighed dietary records and biomarkers	Factor analysis - tertile of factor scores	Healthy Japanese – fruit, vegetables, soy products, mushrooms, green tea Animal food – fish & shellfish, meat, processed meat, mayonnaise, egg Westernised breakfast – bread, milk & yoghurt, confectioneries, mayonnaise & egg, low intakes of rice, alcohol, fish	CES-D, 20 items; depression ≥16	Age, education, income, marital status	Healthy Japanese: OR 0.4, 95% CI 0.22-0.71 Animal food: OR 0.97, 95% CI 0.61-1.55 Westernised breakfast: OR 1.27, 95% CI 0.77-2.1

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Samieri, 2008 (31), France, Cross-sectional	The Three-City Study cohort Subsample, community-dwelling adults (n=1724, age: ≥65 yrs, gender: n=647 males, n=1077 females)	FFQ, 40 categories of food, validated against dietary recalls	Cluster analysis	Biscuits & snacking – biscuits & cakes, and high energy intake Healthy – high intakes of fish in men vs fruit & vegetable in women Charcuterie, meat, alcohol in men vs charcuterie, starchy foods in women Pasta eaters (men) vs pizza, sandwich eaters (women)	CES-D, 20 items	Age, education, income, marital status	Men 'biscuits & snacking' β -0.06, 95% CI -0.35-0.23; Women 'biscuits & snacking' β 0.13, 95% CI -0.07-0.02 Men 'healthy' β -0.12, 95% CI -0.31-0.07; Women 'healthy' β -0.16, 95% CI -0.33-0.007 Men 'charcuterie, meat, alcohol' β 0.03, 95% CI -0.20-0.26; Women 'charcuterie, starchy foods' β -0.15, 95% CI 0.32-0.02, *P*=0.06 Men 'pasta-eaters' β 0.26, 95% CI 0.06-0.46; Women 'pizza, sandwich' β 0.21, 95% CI -0.11-0.53

Table 2.3 *(Continued)*

Author, Year, Country, Study design	Subjects (*n*)	Dietary assessment	Methods defining dietary patterns	Dietary patterns identified	Depression assessment	Adjustment for confounders	Main findings
Sugawara, 2012 (34), Japan, Cross-sectional	Residents of Iwaki district, Japan (n=791, age: 22-86 years, gender: n=488 females, cases: n=97	Diet history questionnaire, 65 items, validated against 16-day dietary records	Principal component analysis – tertiles of dietary pattern scores	Healthy – vegetables, seaweeds, tofu, fruits, fish Western – beef/pork, processed meats, mayonnaise/dressing, ice cream, bread, spaghetti and macaroni Bread and confectionery – confectioneries and bread, low intakes of vegetables Alcohol and accompanying – noodles, squid/ octopus/ shrimp/ shellfish, alcoholic beverages	CES-D, 20 items; depression ≥16	Age, gender, exercise habits, BMI, education, marital status, current smoking, history of hypertension and diabetes mellitus	Healthy: OR 1.03, 95% CI 0.57-1.88, *P*=0.920 Western: OR 0.71, 95% CI 0.39-1.27, *P*=0.246 Bread and confectionery: OR 1.02, 95% CI 0.59-1.78, *P*=0.941 Alcohol and accompanying: OR 0.94, 95% CI 0.55-1.59, *P*=0.807

[1]CES-D, Centre for Epidemiologic Depression Scale; CVD, cardiovascular disease; FFQ, food frequency questionnaire; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HANDLS, Healthy Aging in Neighbourhoods of Diversity across the Life Span; MEDIS, Mediterranean Islands Elderly; MUFA, monounsaturated fatty acid; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fatty acid; REGARDS, REasons for Geographic and Racial Differences in Stroke; SAD, seasonal affective disorder; SCID, Structured Clinical Interview for DSM-IV; SFA, saturated fatty acid.

2.4.4 Meta-analysis results

Meta-analyses included a total of 13 observational studies (*n*=4 cohort; *n*=9 cross-sectional). For the remaining studies (*n*=1 case-control; *n*=3 cohort; *n*=7 cross-sectional), definitions of dietary patterns were not directly comparable with those included in meta-analysis.

Healthy diet

Figure 2.2 presents the results for all studies examining the association between higher versus lower consumption of the Healthy diet and odds of depression. Subjects with higher consumption of the Healthy diet were shown to have a lower odds of depression (OR = 0.84; 95% CI: 0.76, 0.92; *P*<0.001). There was strong evidence of heterogeneity (I^2 = 81.8%, *P*<0.001), which was further explored in meta-regression. All covariates investigated in the meta-regression provided a poor explanation of the heterogeneity (i.e. negative adjusted R^2, *P*>0.05) (**Table 2.4**). In addition, the analysis was repeated stratified according to each covariate. The results were consistent with that observed in meta-regression. The odds ratio for each subgroup did not significantly change compared to the combined estimate of 0.84 (OR 0.78-0.92), indicating that the estimate is fairly robust. The confidence intervals were largely overlapping for the subgroups compared. Considerable heterogeneity remained even after stratification (I^2_{res} >70%).

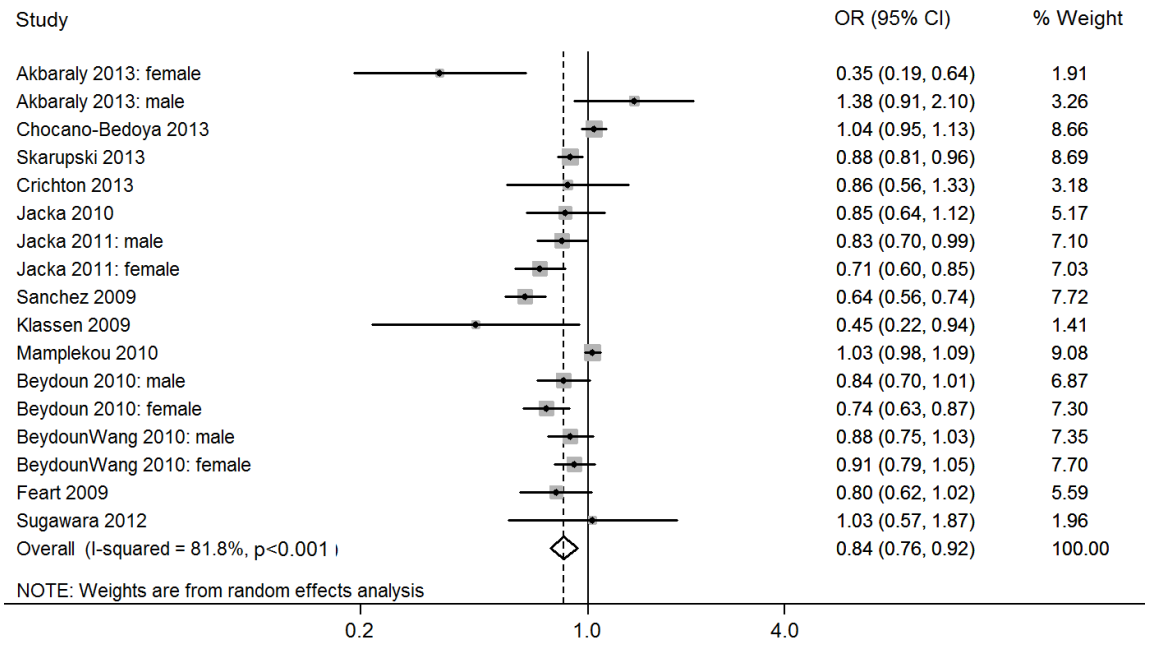

Figure 2.2: Meta-analysis of observational studies quantifying the association between the Healthy dietary pattern and the risk of depression

Table 2.4: Summary of meta-regression and subgroup analysis results

Covariate	I^2_{res}	Adjusted R^2	*P*	OR	95% CI	I^2
None				0.84	0.76-0.92	81.8%
Age group	79.4%	1.04	0.408			
18-65 years				0.82	0.73-0.92	78.5%
≥65 years (ref)				0.92	0.80-1.07	83.9%
Gender	78.1%	-54.7%	0.380			
Male				0.89	0.78-1.01	41.0%
Female (ref)				0.78	0.64-0.93	83.3%
Country	86.4%	-3.07%	0.454			
European countries				0.80	0.63-0.99	92.4%
USA (ref)				0.88	0.79-0.97	70.6%
Study design:	82.6%	-13.7%	0.980			
Cross-sectional				0.84	0.76-0.93	72.4%
Cohort (ref)				0.83	0.66-1.05	91.4%
Dietary assessment tool:	81.6%	-12.4%	0.732			
Dietary recalls				0.83	0.75-0.93	38.8%
FFQ (ref)				0.85	0.75-0.96	85.3%
Depression assessment tool:	82.8%	-13.6%	0.784			
Diagnostic				0.83	0.74-0.94	87.9%
Symptom Inventory (ref)				0.86	0.76-0.92	79.7%
% depression cases	82.7%	-18.0%	0.946			
<20%				0.84	0.74-0.95	81.3%
≥20% (ref)				0.83	0.65-1.04	86.2%
Methodological quality	80.7%	-1.0%	0.462			
Moderate				0.78	0.70-0.87	0.0%
High (ref)				0.86	0.77-0.96	85.1%

[1]FFQ, food frequency questionnaire; ref, reference group

Western diet

Results from the meta-analysis of the Western diet are presented in **Figure 2.3**. There was a trend towards a positive association between higher consumption of the Western diet and the odds of depression, but this relationship did not reach significance (OR = 1.17; 95% CI: 0.97, 1.41; *P*=0.094). Further studies examining this dietary pattern are needed to allow a robust interpretation of these results. Sources of heterogeneity were not investigated in studies examining the Western diet because they are essentially the same studies investigating the Healthy diet.

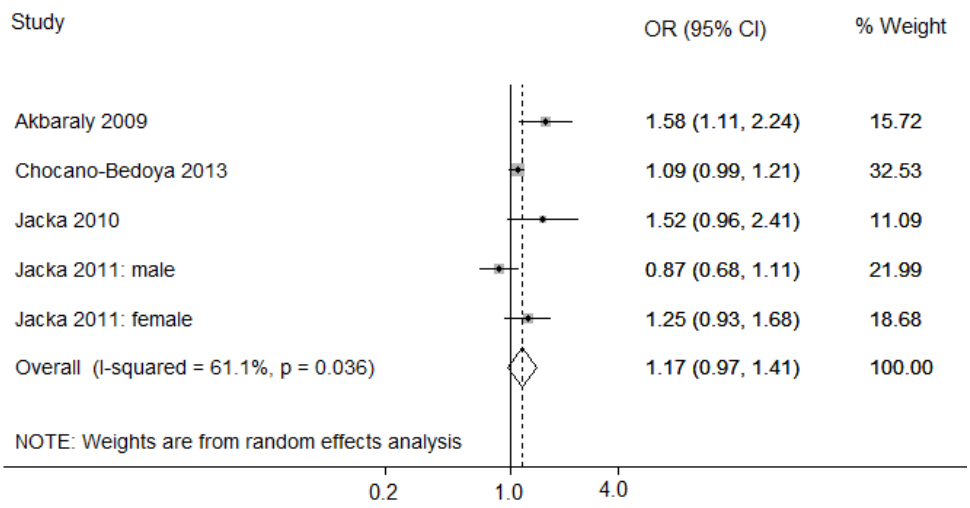

Figure 2.3: Meta-analysis of observational studies quantifying the association between the Western dietary pattern and the risk of depression.

Publication bias

Figure 2.4 displays the contour enhanced funnel plot of studies examining the Healthy diet with the corresponding meta-analysis pooled estimate (OR = 0.84). Visual inspection of the plot suggests little evidence of publication bias. Study estimates were equally distributed in the middle and the left of the plot, indicating that studies of high statistical significance and non-significant studies were included. There is a suggestion of missing studies to the right of the plot, mainly in the area of statistical significance. It is unlikely that studies of statistical significance with results in the opposite direction (i.e. a Healthy diet increasing the risk of depression) would not be published, if methodologically sound (15).

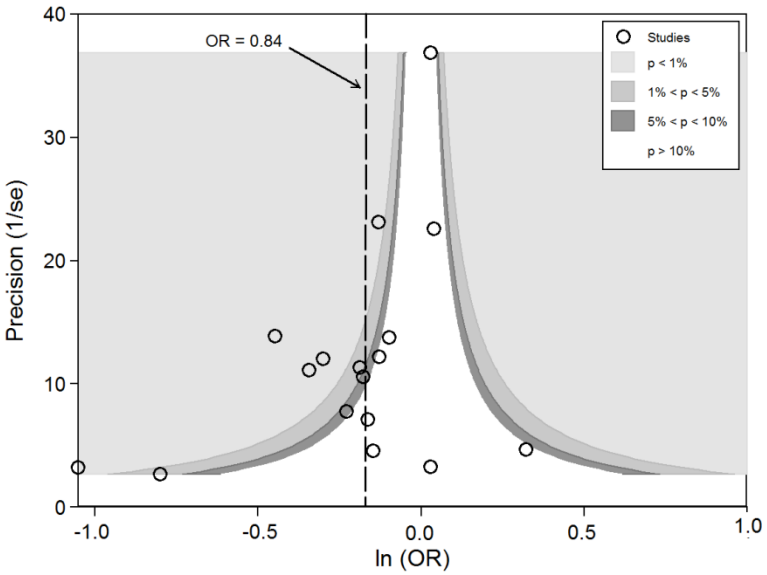

Figure 2.4: Contour-enhanced funnel plot of the observational studies examining the association between the Healthy dietary pattern and the risk of depression.

2.4.5 Narrative review

Data from eight observational studies could not be pooled and thus are included in this narrative section (25, 26, 28-31, 34, 35). One study found that participants with lower intakes of fruit and vegetables have higher odds of depression, which is consistent with the meta-analysis finding (26). Similarly, one study found an inverse association between high intakes of fruits and vegetables and depression but this association was only significant among women (31). Two Japanese studies observed an inverse association between the healthy Japanese diet (which includes high intakes of green tea, soy products, fruit and vegetables) and depression (29, 34). Another study found that high intakes of vegetables were inversely associated with depression, but found no significant association between consumption of fruits, fish, or grains and depression (35). An Australian study found that in addition to vegetables consumption, intakes of meat and poultry, and dairy products are inversely associated with odds of depression (28), but another Australian study found no significant association between consumption of fruits , cooked vegetables or dairy products with depression (30).

There were conflicting results for studies investigating foods similar to the Western diet: one study showed that consumption of processed meat was associated with decreased odds of depression among women (31), but three studies found no significant association between

processed meats, or sweet biscuits, cakes and meat pies, or confectioneries, and depression (29, 30, 34).

In addition, there may be an association between frequent consumption of starch-rich foods and odds of depression. Samieri *et al.* found that high intakes of starchy foods in women and pasta among men were associated with higher depressive symptoms (31). Another study also found that patients with seasonal affective disorder had higher consumption of starch rich foods including pasta, rice, bread and potatoes (25). This suggests a possibility that other types of dietary patterns are also relevant to depression. More research is needed for defining the effect of other dietary patterns.

2.5 Discussion

This systematic review and meta-analysis provides a comprehensive evaluation of current evidence investigating the association between dietary patterns and depression. The results indicate that the Healthy dietary pattern is associated with reduced odds of depression. On the other hand there is no association between the Western dietary pattern and odds of depression, but this may be the result too few studies.

The Healthy diet is consistent with current dietary guidelines recommending high intakes of fruits, vegetables, whole grains, poultry, fish, and reduced fat dairy products (62). A number of reviews confirm that dietary patterns similar to the Healthy diet found in this study are associated with reduced morbidity and all-cause mortality (63, 64). Several potential mechanisms underlying this association have been discussed in other studies. The anti-inflammatory properties of foods in the Healthy diet were shown to influence concentrations of monoamines which are thought to play a role in regulations of emotions and cognition (65). The antioxidant compounds in fruits and vegetables could reduce oxidative-stress induced neuronal damage, particularly neurons in the hippocampus (66, 67). There is also evidence suggesting that high consumption of long-chain omega-3 polyunsaturated fatty acids (68), which is found in high concentrations in oily fish, reduces depression risk. It could also be the cumulative effect of all these nutrients and their biochemical properties that influence depression risk (7, 69).

It should be noted, however, that most of the evidence presented here are cross-sectional in nature, which poses limitations in determining causality. With cross-sectional designs, it is not known whether a poor dietary pattern precedes the development of depression or if depression causes poor dietary intake. Indeed, some studies have shown that depressed individuals seek to self-medicate with high-fat and high sugar food (70, 71). However, the subgroup analysis by study design showed that the cohort studies (n=4) have a remarkably similar odds ratio to cross-sectional studies (n=9) and overlapping 95% CIs, which suggests this is a robust finding. While the association with cohort studies did not reach significance, this is likely due to the lack of studies. All cohort studies tested the possibility of reverse causality of the diet-depression relationship by excluding from the analysis participants who reported depressive symptoms at baseline, or through other statistical methods, and excluded this as an explanation. In addition, two cohort studies used repeated measures of dietary intakes which provided a stronger test of cumulative dietary exposures on depression. Further longitudinal studies assessing the incidence of depression using repeated measures of dietary intakes and depression are required to confirm this finding.

The inclusion of RCTs in this review was intended to provide the highest level of evidence regarding the association of dietary patterns and depression. However, only one RCT met our inclusion criteria (37). This RCT used a short intervention period of 2 weeks and had a small sample size (i.e. less than 15 participants per group).

When investigating possible reasons for heterogeneity, several factors were identified and further explored using meta-regression and subgroup analysis. Dietary habits may be culturally-related and location specific. The use of different dietary measurements could potentially influence the association between dietary patterns and depression. The 24-hour recall has higher precision in assessing diet but only measures actual dietary intake on one or several days instead of long-term intake (72). The FFQ, on the other hand, measures dietary intake over a longer period of time but is subjected to a number of errors introduced as a result of restrictions to a fixed list of foods, memory, and perception of portion sizes (72). Similarly, the strength of the association between dietary patterns and depression may vary depending on whether a diagnostic schedule or whether symptom inventories were used. Symptom inventories generally have poorer criterion validity compared to diagnostic schedules and may result in stronger association (73). The meta-regression and subgroup analysis results,

however, showed that none of the covariates explained the observed heterogeneity. Additional sources of heterogeneity are likely to exist but were not explored due to a lack of studies. Although foods commonly consumed within each dietary pattern were matched as closely as possible, the actual foods within the same dietary pattern were never identical between studies, as these are dependent on the methods used to define dietary patterns. For example, factor analysis involves subjective techniques such as the consolidation of food items into food groups and the number of factors extracted (8). The use of diet quality scores or indices also varied in scoring methods. Likewise, depressive symptoms inventories have different ways of scoring depressive symptoms and classifying depression cases. The inconsistent adjustment for potential confounders among the included studies could also have contributed to heterogeneity. Some of the studies included in our analyses provided crude estimates of association. There are likely to remain potentially important confounding differences that could substantially affect the results. For example, it is also possible that adoption of the Healthy diet is a marker of other healthy lifestyle factors responsible for the lower odds of depression. Some studies found individuals with healthy dietary behaviours are also more likely to be non-smokers, sensible alcohol drinkers, and more physically active (74, 75).

Meta-analyses studies examining the Western diet yielded pooled estimates that suggested a trend towards increased odds of depression but were not statistically significant, likely due to insufficient power as a result of the small number of high-quality studies included. Although we identified three additional cross-sectional studies that could be pooled, these had low methodological quality and were excluded due to the risk of bias. We chose to err on the side of having imprecise but unbiased estimates rather than having precise but potentially misleading estimates.

The present review has systematically identified, appraised and synthesised current evidence and provided a quantification of the association of dietary patterns and depression. The existing literature suggests that consumption of a diet high in fruit, vegetables, whole grains and fish may reduce depression risk, indicating that dietary interventions have the potential to be included as a primary prevention strategy for depressive disorder. However, the limitations mentioned should be considered. Significant heterogeneity is found in our analysis making it difficult to achieve a reliable combined estimate of the association between dietary patterns and depression. However, we have applied strict inclusion criteria to limit heterogeneity to a

minimum. In proceeding with a meta-analysis despite the heterogeneity, it allows the conflicting results between studies to be formally assessed and more accurately quantified (14). We were also able to explore potential sources of heterogeneity through meta-regression and subgroup analysis, which further justified that our study finding is robust. A further issue to consider is that when there are many studies with large sample sizes, the I^2 test may detect heterogeneity that may be statistically significant but clinically unimportant, which could be the case in our study (76). In conclusion, there is a need for more RCTs and prospective cohort studies to clarify whether true causal associations exist between dietary patterns and depression.

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PART 2: METHODS

CHAPTER 3: Overview of Data Sources

This section provides a brief description of the datasets used to form the main study population of this thesis, and most importantly, to highlight the appropriateness of using both datasets in the investigation of the overall aim of this thesis. A detailed description of both datasets have been previously published by Lee et al (1) for the Australian Longitudinal Study on Women's Health (ALSWH) and McEvoy et al (2) for the Hunter Community Study (HCS).

3.1 The Australian Longitudinal Study on Women's Health

The ALSWH is an ongoing longitudinal population-based survey that examines the health of Australian women of various age groups including those over 45 years of age (1). A substantial amount of data has been collected since 1996 on many health and lifestyle factors, providing an excellent opportunity to explore women's mental health and dietary behaviour using longitudinal methods. In depth exploration of the diet-depression relationship in women is necessary as a higher proportion of this gender group is reported to have depressive disorder and to access mental health services (3, 4), and a higher proportion of women are living beyond the age of 65 (5). The study population at baseline is broadly nationally representative, except that they were more likely to have received tertiary education (1), thus the findings produced from studies utilising these data can be cautiously generalised to the Australian female population. Note, however, that the ALSWH sampled women from rural and remote areas at twice the rate of women in urban areas from the beginning of study to ensure sufficient power in statistical comparisons between women living in these two areas (1). The ALSWH dataset was used in Chapters 5 and 6 to examine the diet-depression relationship among middle-aged women, following them since they were 45-50 years of age to when they became 60-65 years old.

Dietary intake was measured from Survey 3 in 2001 and at every 3-year follow-up (except in 2004) using the Dietary Questionnaire for Epidemiology Study, version 2 (DQES v2) (6) or a shortened version. The regularity of data collection has afforded the opportunity to assess changes in dietary intake over time in Chapters 5 and 6. The DQES v2 assesses participants' dietary intake over the past 12 months of seventy-four foods using a ten-point frequency scale

ranging from ‘never’ to ‘three or more times per day’, six types of alcoholic beverages with options ranging from ‘never’ to ‘every day’, and ten questions on the type and amount of core foods: fruit, vegetables, bread, eggs, sugar, dairy products and fat spreads (6). The shortened version assesses the consumption of sixty-eight foods, and used a 3-point frequency scale for majority of food items (‘never’, ‘less than once a week’ or ‘once a week or more’), except for dairy products, meat and fish, which were assessed with five frequency response options (‘never’ to ‘five or more times per week’). Nine questions on the type and amount of core foods were retained but the question on the amount of sugar consumed per day was replaced by a question on the number of servings of vegetables. This questionnaire was first developed to measure dietary intakes among Australian adults taking part in the Melbourne Collaborative Cohort Study, and has been used in numerous other large epidemiological studies in Australia such as the Australian arm of the Breast Cancer Family Registry and the Australian Prostate Cancer Family Study (6). It has demonstrated high reproducibility and reasonable validity in measuring dietary intakes through multiple testing against weighed food records and biochemical indicators, and among population of different ages (7-10). Comparison with reported dietary intakes from weighed food records showed good agreement between both methods for most nutrients and fruits and vegetables intakes ($r \geq 0.40$) (7, 8). In validation studies against nutrient biomarkers, the DQES v2 was found to be useful for ranking individuals according to their antioxidants, fatty acids and fish intakes ($r \geq 0.28$) (9, 10). As such, the ALSWH dietary data as measured by DQES v2 can be considered reliable in capturing respondent’s dietary intake.

The association of diet quality and depression were examined in Chapters 5 and 6. Diet quality was assessed using the Australian Recommended Food Score (ARFS) (11), and the scores were calculated based on DQES v2 items. The ARFS was previously validated for use among the ALSWH 1946-51 cohort (the study population for Chapters 5 and 6) and was shown to reasonably rank these women according to their diet quality and nutrient intake, and higher scores were associated with better self-rated health and lower health service use (11). A shortened DQES v2 was used in a few of ALSWH surveys to minimise participant burden, but this did not affect the calculation of diet quality scores. From the original version, the scores were calculated based on the consumption of 63 food items, two questions on alcoholic

beverages, and nine questions on the type and amount of core foods. All these questionnaire items were retained in the shortened version. Likewise, the use of a shortened frequency scale ('never', 'less than once a week' or 'once a week or more') did not affect the calculation as scoring is independent of the total amounts of each food item, that is, points are given as long as participants consumed that food item 'once a week or more' (11). The shortening of the frequency scale, however, severely limits precise estimation of actual amounts of nutrient and food intakes. Therefore, this thesis focused on diet quality assessed with the ARFS method as the main exposure for Chapters 5 and 6, rather than estimates of nutrient and food intakes, which also precluded the use of dietary pattern analysis or indices that rely on the availability of these data.

Depression status, like diet, was measured at multiple time-points using the 10-item Centre for Epidemiologic Studies-Depression (CES-D) scale and/or self-reported clinical diagnosis. The CES-D was originally developed as a 20-item scale (12), and remains one of the most common screening tests for identifying depressive symptoms in the general population. The reliability and validity of this tool in assessing clinical and non-clinical depressive symptoms have been well-established (12). However, when embedded in large-scale surveys, the 20-item version can result in substantial response burden. A briefer 10-item CES-D was thus developed (13), and studies have demonstrated that this shorter version produced results comparable in reproducibility and validity to the 20-item version (14, 15). The use of valid and reliable measure in the investigation of the association between diet and depression is important to minimise misclassification bias. In addition, there are comprehensive data collected on sociodemographic, health behaviours, and medical conditions, allowing for adequate adjustment for potential confounders in the analyses of the diet-depression relationship.

3.2 The Hunter Community Study

The HCS is an ongoing, population based study collecting information on factors affecting health and wellbeing and social functioning of ageing in a cohort of men and women aged 55 to 85 years residing in Newcastle, New South Wales, Australia (2). The baseline data collection started in 2004-05, and the first 5-year follow-up was completed in 2010. The HCS included adults of more than 65 years at baseline, providing an important perspective on dietary

behaviours and depression in older Australians. In addition, the inclusion of both men and women allows the examination of gender difference in the association between dietary intakes and depression. One further advantage of the HCS is the availability of blood samples from over 90% of participants that can be used for biochemical analysis.

Similar to ALSWH, the HCS utilised a prospective cohort study design, which is most appropriate in determining the temporal relationship between diet and depression. The HCS also used validated instruments in measuring dietary intake and depression (i.e. 20-item CES-D and self-reported clinical diagnosis), and included measurements for a range of socio-demographic, health behaviours and medical factors. However, unlike the DQES v2 which has been validated many times, the FFQ used in HCS had only been validated against weighed food records in a cohort of men and women participating in the Blue Mountain's Eye Study (16). The validity of the FFQ in measuring the dietary intakes of the HCS study subjects had not been ascertained. Therefore, a validation study of the FFQ against biochemical indicators among a sub-sample of HCS participants was carried out as part of this thesis, described in Chapter 4. The HCS dataset was also used in Chapter 7 to examine inflammation as a potential mediator of the diet-depression relationship.

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CHAPTER 4: Biochemical validation of the Older Australian's food frequency questionnaire using carotenoids and Vitamin E

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Reference:

Lai JS, Attia J, McEvoy M, Hure AJ. Biochemical Validation of the Older Australian's Food Frequency Questionnaire Using Carotenoids and Vitamin E. Nutrients. 2014;6(11):4906-17.

4.1 Abstract

Background

Validation of a food frequency questionnaire (FFQ) is important, as inaccurate and imprecise information may affect the association between dietary exposure and health outcomes.

Objective

This study assessed the validity of the Older Australian's FFQ against plasma carotenoids and Vitamin E.

Methods

A random subsample (*n*=150) of 2420 participants in the Hunter Community Study, aged 55–85 years, were included. Correlations between crude and energy-adjusted FFQ estimates of carotenoids, Vitamin E, and fruit and vegetables with corresponding biomarkers were determined. Percentages of participants correctly classified in the same quartile, and in the same or adjacent quartile, by the two methods were calculated.

Results

Significant correlations ($P<0.05$) were observed for α-carotene (r=0.26-0.28), β-carotene (r=0.21-0.25), and β-cryptoxanthin (r=0.21-0.23). Intakes of fruits and vegetables also showed similar correlations with these plasma carotenoids. Lycopene was only significantly correlated with fruit and vegetable intakes (r=0.19-0.23). Weak correlations were observed for lutein + zeaxanthin (r=0.12-0.16). For Vitamin E, significant correlation was observed for energy-adjusted FFQ estimate and biomarker (r=0.20). More than 68% of individuals were correctly classified within the same or adjacent quartile, except for lutein + zeaxanthin.

Conclusion

With the exception of lutein + zeaxanthin, the Older Australian's FFQ provides reasonable rankings for individuals according to their carotenoids, Vitamin E, fruit and vegetable intakes.

4.2 Introduction

A number of methods are used to measure dietary intake in epidemiological research including dietary recalls, food records, and food frequency questionnaires (FFQs) (1). Of these, dietary recalls and food records are considered more precise, but they are limited in that they only measure short-term dietary intake. However, FFQs provide dietary data over a longer period of time (1), which in nutritional epidemiologic research is more important than intake on a few specific days. A number of FFQs have been developed to measure dietary intake among Australian adults (2-4). Considering the fact that older people may differ in dietary habits and food patterns from younger adults (5), existing FFQs should be adapted to reflect these differences, and/or validated in older populations.

Food Frequency Questionnaires are often criticised for having a large number of measurement errors (1). Consequently, much research has been concerned with the relative performance of FFQs in estimating dietary intake. Most studies have validated FFQs against food records or dietary recalls (2, 3), but self-reporting bias remains. Alternatively, biochemical indicators (or biomarkers), can act as objective measures in the validation of nutrient intake, as the errors recorded are assumed to be independent of self-report (1). The body of literature on the performance of FFQs in older populations is relatively small, and validation against biochemical indicators is scarce. To date, we identified only one FFQ, developed by the Blue Mountains Eye Study (BMES), to measure dietary intake among older community-dwelling adults in Australia, which has been previously validated against 4-day food records (3). In this study, we will further assess the validity of this FFQ against more objective biochemical indicators, using a sub-population of older Australian adults from the Hunter Community Study (HCS).

With increasing evidence that high intakes of fruits and vegetables are associated with better health outcomes (6, 7), it is important that the FFQ used adequately captures these foods among the population of interest. The protective effects of fruit and vegetables may be due to their antioxidant properties. Nutrients such as carotenoids and Vitamin E have the ability to reduce inflammation and prevent free radical damage, all of which have been shown to play important functions in the biology of ageing (8, 9). Furthermore, concentrations of carotenoids and Vitamin E in blood are considered reliable markers of dietary intake (1) and have been

previously used in a number of dietary validation studies (10-12). Hence, this study aims to compare the dietary intakes of carotenoids and Vitamin E, estimated by the Older Australian's FFQ, against plasma biomarkers, in a sample of 150 HCS participants.

4.3 Methods

4.3.1 Validation quality

This study was developed based on the EURopean micronutrient RECommendations Aligned Network of Excellence (EURRECA) scoring system of a good quality validation study (13), scoring a total of 4 out of 7 points. The allocation of points was as follows: 1) 0.5 points for non-homogenous sample, and 0.5 points for a sample size of >50; 2) 1.5 points for reporting crude and energy-adjusted correlation coefficients, and including statistics to assess classification; and 3) 1.5 points for including supplements intake.

4.3.2 Subjects

The study subjects were drawn from the HCS. The HCS is a population based cohort study of adults aged 55-85 years residing in Newcastle, New South Wales state, randomly selected from the state's electoral roll (14). Recruitment began in December 2004 and ended in December 2007. A total of 3253 individuals participated in the study. All participants were required to attend a clinical assessment, provide a blood sample and complete a series of self-administered questionnaires including the Older Australian's FFQ (14). Full methodological details have been published previously (14). The HCS has received ethics approval from the University of Newcastle Research Ethics Committee (H-820-0504), and all participants provided written informed consent.

To be included in this study, participants needed to have completed the FFQ (*n*=3022) and provided a blood sample at baseline with enough volume for analysis (*n*=2534). Participants with more than 25 missing values or an entire blank page in their FFQ (*n*=132) were excluded from the final dataset. A subset of 150 subjects was selected from the remaining 2420 HCS participants. Stratified random sampling using computer-generated sequence was used to select 30 participants from each quintile of total energy intake, and ensuring an equal

representation across gender and age groups (<65, 65+). A participant selection flow diagram is presented in **Figure 4.1**.

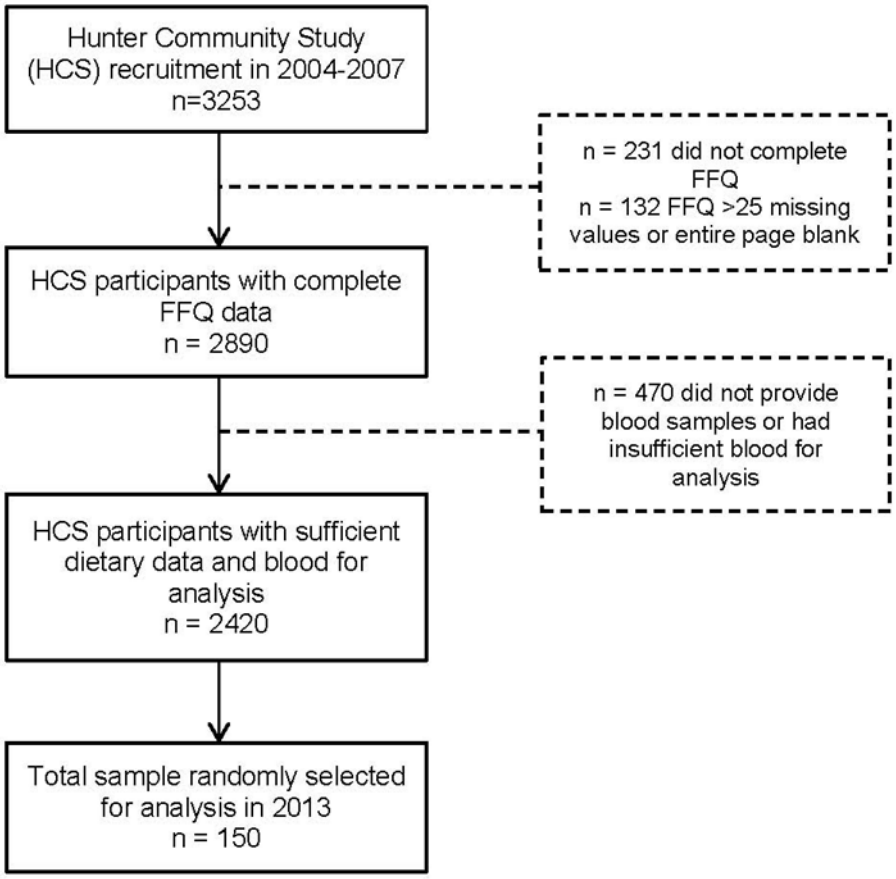

Figure 4.1: Participant flow diagram for a validation study of FFQ estimated intakes against biomarkers

4.3.3 Food frequency questionnaire

Dietary intake was assessed by a self-administered, 145-item semi-quantitative FFQ (3), modified from the version developed by Willett (15), specifically for use with older Australians participating in the BMES (3). The BMES previously validated this FFQ against 4-day weighed food records and demonstrated reasonable validity (i.e. $r \geq 0.5$ for most nutrients including $r=0.49$ for β-carotene; and ≥70% correctly classified within same±1 quintile) (3). Participants were required to indicate their usual frequency of foods consumed in the past year, with nine categorical frequency options, ranging from never to four or more times per day. Open-ended questions were included on the type of fruit juices, breakfast cereal, and other frequently

consumed foods that were not included in the list. The FFQ also assessed dietary supplements usage. Participants completed the FFQ within three months of their blood collection. Dietary intake of carotenoids and Vitamin E was calculated using the US Department of Agriculture (USDA) data (16), and other nutrient intakes were derived from NUTTAB 2006, an Australian nutrient composition database (17). Servings of fruits and vegetables were defined based on the Australian Dietary Guidelines (e.g. one serving of fruit = 150g or 1 medium-sized fruit; one serving of vegetables = 75g or ½ cup cooked vegetables) (18). Nutrient supplement information was obtained from manufacturers and added to the database. Approximately 2% of all FFQs were re-entered into the FoodWorks 2009, version 6 (19), by an Accredited Practising Dietitian who was blinded to the original FFQ data entry to check for errors. Only minor discrepancies were observed and rectified prior to data analysis.

4.3.4 Biomarkers assays

The biomarkers included in this study were plasma concentrations of *α*-carotene, *β*-carotene, *β*-cryptoxanthin, lycopene, lutein + zeaxanthin, and Vitamin E (*α*-tocopherol). The plasma and FFQ estimates of lutein and zeaxanthin are shown combined (lutein + zeaxanthin) because both the nutrient database and biochemical analysis combine lutein and zeaxanthin. Fasting venous blood was obtained using standard venepuncture techniques. All blood samples were centrifuged and stored in approximately 1 ml aliquots, cryopreserved in dimethyl sulfoxide (DMSO) at -80^{o}C immediately after collection (14). These blood samples had been stored at -80^{o}C for approximately seven years at the time of assay, and were thawed immediately prior to analysis. Plasma carotenoids concentrations were determined using the high performance liquid chromatography method (20). Measurements of red blood cell (RBC) folate concentration was carried out using the chemiluminescent immunoassay analyser (Access® Immunoassay Systems, Beckman Coulter, Inc. CA, USA) (21). However, it was subsequently determined that DMSO had likely affected the integrity of RBC membrane, reducing the accuracy of the folate concentration. Therefore, subsequent results and discussion will focus on carotenoids and Vitamin E only.

4.3.5 Statistical analysis

Dietary intakes were expressed as absolute amounts and as energy-adjusted intakes. Energy-adjusted intakes were computed for individual carotenoids, Vitamin E, servings of fruits and vegetables, using the residual method (22). Adjusting for total energy intake accounts for between-person variation in total energy intake as a result of physiological differences such as body size and physical activity (22), thus reducing the potentially confounding effects of total energy intake. As the distribution of dietary intakes and biomarkers were skewed, Spearman rank correlation coefficients were used in all correlation analyses, unless otherwise specified. The significance level was set at $P<0.05$. Aside from comparing individual dietary intakes of carotenoids and Vitamin E to their respective plasma biomarkers, fruit and vegetable intakes were also compared to each plasma carotenoid. Intakes of fruits and vegetables were restricted to those that contributed ≥5% of daily mean intake for each carotenoid (e.g. carrot and pumpkin intakes to plasma *α*-carotene). We did not compare intakes of fruits and vegetables to plasma Vitamin E, because Vitamin E comes from more diverse sources than each of the carotenoids.

Linear regression analyses were performed to identify potential confounders. Plasma carotenoids and Vitamin E were modelled as the dependent variables and the corresponding FFQ estimated intakes as the independent variables. This was performed using log-transformed values to comply with the assumptions for normality. The following variables were tested as potential confounders: age groups, gender, smoking status, body mass index (BMI) categories, medication use, supplement use and alcohol consumption. The significance level was set at $P<0.05$.

Dietary intakes estimated by the FFQ and biomarkers were classified into quartiles to determine the ability of both methods to rank individuals. Percentages were calculated for participants correctly classified into the same quartile and within the adjacent quartile. All statistical analyses were performed using Stata, version 11 (23).

4.4 Results

Characteristics of the sampled subjects, along with their average daily nutrient intake values from the FFQ and measured biomarkers are presented in **Table 4.1**. The participants' ages ranged from 55-85 years. Stratified random sampling ensured a similar proportion of males and females. Mean BMI was 28.5 kg/m^2 indicating a high proportion of overweight and obesity, which is consistent with the broader Australian population of this age (24). Only 6% of the sample currently smoked but many more were former smokers (41.3%). A large proportion of the sample (78.6%) was taking at least one prescription medication, which is not surprising for an older population. Approximately 12% of the subjects reported taking supplements containing vitamin A (including carotenoids) and/or vitamin E. Approximately 63% of participants reported consuming alcoholic beverages at least once a week.

Carrots and pumpkins were the main contributors to *α*-carotene intake. Sources of *β*-carotene included apricots or peaches, cantaloupe, broccoli, carrots, spinach or silverbeet, lettuce, peas, pumpkin, sweet potato. Intake of *β*-cryptoxanthin was from paw-paw, orange, pumpkin, apricots or peaches, carrots and corn. Lycopene was predominantly from tomato and tomato products, but also included watermelon and grapefruit. Lutein and zeaxanthin were mainly from dark green vegetables such as broccoli, brussel sprout, spinach or silverbeet, lettuce, and beans, peas, corn and pumpkin.

Results from linear regression showed that age, gender, smoking status, BMI, medication use, supplement use and alcohol consumption had little effect on correlation coefficients. As such, the correlation coefficients were only reported for crude intakes and energy-adjusted intakes.

Table 4.1: Characteristics of Hunter Community Study participants (*n*=150) in a dietary validation study

Characteristics	
Age (years), mean ± SD	66.2 ± 7.3
Gender, *n* (%)	
Male	77 (51.3%)
Female	73 (48.7%)
Body Mass Index, kg/m^2	28.5 ± 4.8
Smoking status[a], *n* (%)	
Non-smoker	73 (48.7%)
Ex-smoker	62 (41.3%)
Current smoker	9 (6%)
Current use of medication, *n* (%)	118 (78.6%)
Supplement use, *n* (%)	
Multivitamin[b]	15 (10%)
Vitamin E only	3 (2%)
Alcohol intake, *n* (%)	
None	55 (36.7%)
≥1 drink/week	95 (63.3%)
FFQ estimated nutrient intake, mean ± SD	
α-carotene, µg/day	1810 ± 1499
β-carotene, µg/day	8449 ± 5005
β-cryptoxanthin, µg/day	590 ± 372
Lycopene, µg/day	6457 ± 6276
Lutein + zeaxanthin, µg/day	4026 ± 2538
Vitamin E, mg/day	5.8 ± 2.3
FFQ estimated fruit + vegetable intakes, mean ± SD	
α-carotene sources, servings/day	0.8 ± 0.6
β-carotene sources, servings/day	2.8 ± 1.4
β-cryptoxanthin sources, servings/day	2.2 ± 1.3
Lycopene sources, servings/day	0.8 ± 0.6
Lutein + zeaxanthin sources, servings/day	2.2 ± 0.9
Plasma concentration, mean ± SD	
α-carotene, mg/L	0.07 ± 0.06
β-carotene, mg/L	0.35 ± 0.40
β-cryptoxanthin, mg/L	0.14 ± 0.12
Lycopene, mg/L	0.29 ± 0.14
Lutein + zeaxanthin, mg/L	0.47 ± 0.27
Vitamin E, mg/L	13.61 ± 4.08

[a] *n*=6 did not report smoking status; [b] Multivitamin supplements containing carotenoids and vitamin E.

Correlations between FFQ estimated intakes of individual carotenoids, vitamin E, fruit and vegetables, and plasma concentrations are presented in **Table 4.2**. Both crude and adjusted correlations were significant for *α*-carotene (*r*=0.26 and 0.28), *β*-carotene (*r*=0.21 and 0.25) and *β*-cryptoxanthin (*r*=0.21 and 0.23). Energy-adjusted vitamin E intake yielded a stronger correlation with plasma concentration (*r*=0.20) compared to crude intake (*r*=0.08). In contrast, weak correlations were observed for lycopene and lutein + zeaxanthin. Intakes of fruits and vegetables showed significant correlations with plasma *α*-carotene (*r*=0.23 and 0.25) and *β*-carotene (*r*=0.20 and 0.25), respectively. Interestingly, correlations between fruit and vegetable intakes, and plasma *β*-cryptoxanthin (*r*=0.31 and 0.36) and lycopene (*r*=0.19 and 0.23) were much higher than the corresponding nutrient intakes. Plasma lutein + zeaxanthin was weakly correlated with fruit and vegetable intakes (*r*=0.11 and 0.14).

Table 4.2: Correlations and 95% CI between FFQ estimated intakes and biomarkers

	Individual nutrient intakes				**Fruit and Vegetable intakes**			
	r_{crude}[a]	**95% CI**	**r_{adj}[b]**	**95% CI**	**r_{crude}[a]**	**95% CI**	**r_{adj}[b]**	**95% CI**
α-carotene	0.26[c]	0.10, 0.38	0.28[c]	0.12, 0.42	0.23[c]	0.07, 0.38	0.25[c]	0.08, 0.39
β-carotene	0.21[d]	0.04, 0.35	0.25[c]	0.08, 0.39	0.20[d]	0.04, 0.36	0.25[c]	0.08, 0.38
β-cryptoxanthin	0.21[d]	0.04, 0.36	0.23[c]	0.07, 0.38	0.31[c]	0.16, 0.45	0.36[c]	0.21, 0.50
Lycopene	0.13	-0.04, 0.27	0.17	-0.01,0.32	0.19[d]	0.02, 0.34	0.23[c]	0.07, 0.38
Lutein + zeaxanthin	0.12	-0.05, 0.25	0.16	-0.01, 0.31	0.11	-0.01, 0.30	0.14	-0.03,0.27
Vitamin E	0.08	-0.07, 0.24	0.20[d]	0.04, 0.36	n/a[e]			

[a] Spearman rank correlation using crude intakes and plasma biomarkers; [b] Spearman rank correlation using energy-adjusted intakes and plasma biomarkers; [c] P <0.01; [d] P <0.05; [e] No comparison made between plasma vitamin E and fruit and vegetables because vitamin E had more diverse sources.

Quartile agreements between individual nutrient intakes and their respective blood concentrations were in the range of 24-31% for correctly classified within the same quartile and 62-72% for correctly classified within the same or adjacent quartile (**Table 4.3**). Extremely low quartile agreements were observed for lutein + zeaxanthin. For fruit and vegetable intakes, quartile agreements were similar to those comparing individual carotenoid intakes. However, quartile agreements for fruit and vegetable intakes and *β*-cryptoxanthin were much higher (>34% within same quartile and >74% within the same/adjacent quartile).

Table 4.3: Agreement (%) between quartiles of FFQ estimated intakes and biomarkers

	Individual nutrient intakes				**Fruit and Vegetable intakes**			
	Crude[a]		**Energy-adjusted[b]**		**Crude[a]**		**Energy-adjusted[b]**	
	Same	Adjacent	Same	Adjacent	Same	Adjacent	Same	Adjacent
α-carotene	30	70	30	72	30	68	32	69
β-carotene	28	69	31	72	29	70	30	72
β-crytoxanthin	30	68	28	71	34	74	40	75
Lycopene	29	68	30	72	34	71	32	74
Lutein + zeaxanthin	24	62	24	65	22	62	21	62
Vitamin E	28	67	28	70	n/a[c]			

[a] Percentage correctly classified using crude intakes and plasma biomarkers; [b] Percentage correctly classified using energy-adjusted intakes and plasma biomarkers; [c] No comparison made between plasma vitamin E and fruit and vegetables because vitamin E had more diverse sources.

4.5 Discussion

This study determined the relative validity of the Older Australian's FFQ used in the BMES and HCS by comparing self-reported dietary carotenoid and vitamin E intakes with more objective plasma biomarkers. Overall, we found that this FFQ performed reasonably well in assessing intakes of carotenoids, vitamin E, and fruit and vegetables. Although all correlations presented were modest in magnitude (≤0.36), they were comparable to those noted by other validation studies conducted in populations across Australia (10, 11) and other countries (12, 25-27). More than 68% of individuals were correctly classified within the same or adjacent quartile, based on all nutrients assessed, with the exception of lutein + zeaxanthin.

We identified two other recent FFQ and biomarker validation studies conducted in Australia (10, 11). One of these studies was the validation study for the commercially available Dietary Questionnaire for Epidemiological Study used in a number of large epidemiological studies, including the Melbourne Collaborative Cohort Study, the Australian Prostate Cancer Family Study, and the Australian Longitudinal Study of Women's Health (28). The correlations between dietary and plasma *α*-carotene and lycopene in our study were only slightly lower compared to these other two studies where correlations for *α*-carotene ranged between 0.35-0.47 and for lycopene ranged between 0.19-0.28 (10, 11). Our correlations for *β*-carotene, *β*-cryptoxanthin and lutein + zeaxanthin were within the ranges reported in the two Australian studies (*β*-carotene: 0.22-0.28; *β*-cryptoxanthin: -0.002-0.46; lutein + zeaxanthin: 0.03-0.29).When we compared our results to four other FFQ-biomarker validation studies conducted in the United States of America, similar correlations were observed, although *β*-cryptoxanthin showed a stronger correlation in the American studies (12, 25-27). These studies reported correlations as follows: *α*-carotene 0.18-0.35, *β*-carotene 0.25-0.36, *β*-cryptoxanthin 0.32-0.45, lycopene 0.002-0.37, lutein + zeaxanthin 0.10-0.47. A stronger correlation between energy-adjusted vitamin E intake and plasma concentration was observed in our study (r=0.20), compared to these other six studies which reported correlations of 0.05-0.07 for vitamin E (10-12, 25-27).

Plasma levels of carotenoids were significantly correlated with fruit and vegetable intakes except for lutein + zeaxanthin. The observed correlation coefficients were also similar to other studies (*α*-carotene: 0.23-0.25; *β*-carotene: 0.13-0.29; *β*-cryptoxanthin: 0.17-0.35; lycopene: 0.06-0.21; lutein + zeaxanthin: 0.05-0.18) (12, 29), indicating that fruit and vegetable intakes are reasonably well measured by the Older Australian's FFQ and comparable to other FFQs (12, 29). In fact, plasma *β*-cryptoxanthin and lycopene were more strongly correlated with fruit and vegetable intakes than with individual nutrients. A similar pattern was observed in another study that examined the correlation between plasma carotenoids and fruit and vegetable intakes (12). Tucker et al. found that correlations were strongest for *β*-cryptoxanthin followed by lycopene, and the lowest correlation was observed for lutein + zeaxanthin (12).

Our study did not identify any important confounding variables. However, the study may have been under-powered for sub-group analyses and there could be other factors not accounted for,

such as cholesterol levels in blood, which other studies have adjusted for (10-12). Adjusting for these factors could potentially improve the correlations.

Quartile agreements between dietary intakes and plasma concentrations further demonstrated that the Older Australian's FFQ performed well in ranking individuals according to their carotenoid and vitamin E intakes. As biomarkers are not a measure of absolute intake, the ability to rank individuals according to their consumption is more important (1). Apart from lutein + zeaxanthin, the percentages of participants correctly classified within the same quartile, and within the same or adjacent quartile for carotenoids and vitamin E were comparable to those observed in other studies (>25% within same quartile or >65% within same or adjacent quartile) (12, 29). A much lower quartile agreement was observed for lutein + zeaxanthin. Quartile agreement comparing fruit and vegetable intakes rather than individual carotenoid intakes showed similar results, indicating that simply measuring fruit and vegetable intakes provides a reasonable ranking. Subsequent studies examining the effects of nutrition on health outcomes can be confident that this FFQ not only has the ability to accurately capture individual carotenoid intakes but it is also a good measure of fruit and vegetable intakes.

The advantage of this validation method is that the error associated with biomarkers is unlikely to be associated with the error in self-report measures, thus offering an objective measure of nutrient intake (1). Furthermore, our study methods comply with that of the EURRECCA scoring system, meeting the criteria of a good quality validation study (13). The strength of this FFQ is that it is developed specifically for an older population and twice validated; firstly against weighed food records in the BMES (3) and now against nutritional biomarkers in the HCS. Validation against weighed food records demonstrated acceptable reproducibility and validity. The current study further demonstrates reasonable validity in reference to nutritional biomarkers, showing that this FFQ is useful in ranking individuals according to their consumption. However, due to the weaker correlation and low quartile agreements for lutein + zeaxanthin, we are less confident of the ability of this FFQ to measure intake of this nutrient.

Conclusions

In conclusion, results from the current study, together with findings from previous validation against weighed food records indicate that the Older Australian's FFQ can reasonably rank

individuals according to their consumption of carotenoids (with the exception of lutein + zeaxanthin), Vitamin E, fruit and vegetables. Future studies can use this FFQ to collect dietary data from the older population knowing that it has acceptable validity.

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PART 3: RESULTS

CHAPTER 5: Prospective study on the association between diet quality and depression in mid-aged women over 9 years

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Reference

Lai JS, Hure AJ, Oldmeadow C, McEvoy M, Byles J, Attia, J. Prospective study on the association between diet quality and depression in mid-aged women over 9 years. European Journal of Nutrition. 2015 Oct 17. [Epub ahead of print] doi:10.1007/s00394-015-1078-8

5.1 Abstract

Purpose

To examine the longitudinal association between diet quality and depression using prospective data from the Australian Longitudinal Study on Women's Health.

Methods

Women born in 1946-51 (*n*=7877) were followed over nine years starting from 2001. Dietary intake was assessed using the Dietary Questionnaire for Epidemiological Studies (version 2) in 2001 and a shortened form in 2007 and 2010. Diet quality was summarised using the Australian Recommended Food Score. Depression was measured using the 10-item Centre for Epidemiologic Depression Scale and self-reported physician diagnosis. Pooled logistic regression models including time-varying covariates were used to examine associations between diet quality tertiles and depression. Women were also categorised based on changes in diet quality during 2001-2007. Analyses were adjusted for potential confounders.

Results

The highest tertile of diet quality was associated marginally with lower odds of depression (OR: 0.94, 95% CI: 0.83, 1.00, *P*=0.049) although no significant linear trend was observed across tertiles (OR: 1.00; 95% CI: 0.94, 1.10; *P*=0.48). Women who maintained a moderate or high score over six years had a 6-14% reduced odds of depression compared to women who maintained a low score (Moderate vs Low score – OR: 0.94; 95% CI: 0.80, 0.99; *P*=0.045; High vs Low score – OR: 0.86; 95% CI: 0.77, 0.96; *P*=0.01). Similar results were observed in analyses excluding women with prior history of depression.

Conclusion

Long term maintenance of good diet quality may be associated with reduced odds of depression. Randomised controlled trials are needed to eliminate the possibility of residual confounding.

5.2 Introduction

Depression is a common mental health disorder, which is associated with severe disability, decreased physical function, and poor quality of life and wellbeing (1). According to the World Health Organization (WHO), depression is expected to become the world's second leading cause of disease burden in the year 2020 (2). Depression is most prevalent during early adulthood then decreases with increasing age (1). However, the prognosis of depression deteriorates with age (3), and depression experienced in later life is more likely to be severe and persist for longer (4). With a progressively ageing population worldwide, prevention and treatment of depression in later life becomes increasingly important (5).

Population-based epidemiological research, as well as research focused on prevention and early intervention techniques have not received much attention until recent years (4). An emerging area of preventative research suggests that nutrients have the potential to modulate many physiological factors involved in the aetiology of depression (6). A recent meta-analysis by our group showed that consumption of a diet high in fish, fruits and vegetables and whole-grains, is associated with a reduced odds of depression (7). However, this finding was mainly based on cross-sectional studies. Thus, it remains unclear whether there is a temporal relationship between diet and depression.

Four prospective cohort studies were included in our meta-analysis, but only two of them used repeated measure of dietary intakes (8, 9) . The ability to measure dietary intake repeatedly allows the examination of dietary trends over time, and the impact of these dietary changes in relation to health outcomes (10). This is important especially when there is evidence suggesting dietary intakes changes with increasing age (11), and older adults tend to show better diet quality (12). Furthermore, repeated assessments of dietary intake allows one to examine whether the effect of diet on depression changes over time, and also provides a stronger test of cumulative dietary exposures on depression (10). If diet is indeed associated with depression, it would be expected that a change in diet would result in a change in depression risk.

In this study, we used prospective data from a cohort of women that has been followed over a 20 year period. Women are twice as likely as men to be diagnosed with depression, and a higher proportion of women are living beyond the age of 65 (13). The study by Rienks, Dobson

(14) has previously demonstrated that the Mediterranean style dietary pattern (identified via factor analysis) may reduce depression risk. In the same cohort, we aimed to examine the association of long-term diet quality (based on national dietary recommendations) on depression risk among Australian women for whom repeated assessments of both diet and depression were obtained over a period of nine years.

5.3 Methods

5.3.1 Study population

Data were drawn from the Australian Longitudinal Study on Women's Health (ALSWH), an ongoing prospective cohort study of over 40, 000 Australian women from three age groups – 1973-78 cohort, 1946-51 cohort, and 1921-26 cohort. (15). Women from these three age cohorts were randomly selected from the Medicare health insurance database, which includes all Australian citizens and permanent residents, with over-representation of women living in rural and remote areas (15). Participants completed a self-administered questionnaire at the study's induction in 1996 (Survey 1), and at follow up of approximately three year intervals. Further details of this study have been described elsewhere (15). This research was approved by the Human Research Ethics Committees of the University of Newcastle and the University of Queensland. Written informed consent was obtained after the study was described to the participants.

Our sample was obtained from the 1946-51 cohort (women aged 45-50 years in 1996) and included data from Surveys 3-6 (2001-2010). A total of 11,226 women responded to Survey 3 in 2001. Retention rate was high at each survey cycle, and more than 81% of the initial study sample remained at Survey 6 in 2010. Among those lost to follow-up, 4% were due to deaths or frailty, 7% actively withdrew and 7% did not return the questionnaires. Women who were lost to follow-up did not differ in their diet quality scores but a slightly larger proportion of them had depression (31.5% lost to follow-up vs 25.9% completed follow-up) at Survey 3. The respondents have been shown to be broadly representative of the national population of women at baseline (15). Of the 11,226 women at Survey 3, women who reported having depression in the three years prior to Survey 3 (*n*=2928) were excluded (i.e. those having depression in 1998-

2001). The final analyses included women with measures of both diet and depression at Survey 3 (*n*=7877).

5.3.2 Assessment of dietary Intake

Dietary intake was first measured at Survey 3 (2001), and then at Surveys 5 (2007) and 6 (2010). At Survey 3, the Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2) (16) was administered to all participants. This semi-quantitative food frequency questionnaire was developed by the Cancer Council Victoria to assess the dietary intakes in Australian adults. Both the development of the DQES v2 (17) and its validation in mid-aged Australian women have been published previously (18). The DQES v2 requires participants to report their usual consumption of 74 foods and six alcoholic beverages over the past 12 months using a 10-point frequency scale ranging from 'never' to 'three or more times per day' (16). In addition, there are 10 questions on the amount of fruit, different types of vegetables, milk, bread, sugar and eggs consumed, and on the type of milk, bread, fat spreads and cheese used. Further details of the DQES v2 are presented elsewhere (17).

The participants' completed a shortened version of the DQES v2 at Survey 5 and 6. This version assesses the frequency of usual consumption of 68 foods instead of 74 foods in the original version. A shortened frequency scale was also used for majority of the food items ('never', 'less than once a week' or 'once a week or more'), except dairy products, meat and fish which were assessed on a 5-point frequency scale ranging from 'never' to '5 or more times per week'. Nine questions on the amount of fruit, different types of vegetables, milk, bread, sugar and eggs consumed, and the type of milk, bread, fat spreads and cheese used were retained. The question on the amount of sugar consumed per day was removed, and a question on the number of servings of vegetables consumed per day was included in its place. The shortened DQES v2 was designed to minimise participant burden whilst still facilitating a summary of diet quality, using the Australian Recommended Food Score (ARFS) method (described below).

5.3.3 Assessment of diet quality

Diet quality was assessed using the ARFS method by Collins, Young (19), which was modelled on the Recommended Food Score by Kant and Thompson (20). The ARFS was previously validated using the ALWSH cohort and provides reasonable rankings for middle-age women

according to their diet quality and nutrient intake (19). The scores were calculated based on DQES v2 items consistent with national recommendations in the Dietary Guidelines for Australian Adults (21) and the core foods given in the Australian Guide to Healthy Eating (22). The scoring method assigns points for the consumption of desirable foods at the recommended levels (19). Desirable food items consumed at least once a week were assigned one point. For questions assessing the type and amount of core foods, points were assigned for consuming at least two servings of fruit a day, at least four servings of vegetables per day, at least four slices of bread per day, use of polyunsaturated or monounsaturated spreads or no fat spread, use of low-fat dairy products, and consuming at least 500mL of milk per day. In addition, a maximum of two points were assigned for alcohol consumption: one point for frequency (up to four days per week), and one point for quantity (not more than two drinks on days when alcohol was consumed). The maximum ARFS score is 74, with higher values corresponding to a healthier diet. Missing values were recoded to zero for up to four items. Participants with greater than four missing values were considered as having incomplete data and excluded during statistical analyses. The scores were calculated in the same manner for the shortened version of DQES v2 used in Surveys 5 and 6. Further details on the scoring system are described elsewhere (19).

5.3.4 Assessment of depression

At each survey, participants were asked “In the PAST THREE YEARS, have you been diagnosed or treated for depression”. In addition, participants were asked to complete the 10-item Centre for Epidemiologic Studies Depression (CES-D) scale assessing the presence of depressive symptoms. The 10-item CES-D has been previously demonstrated to have high reliability and validity, and comparable to the 20-item version (23, 24). Possible scores range from 0-30 where higher scores indicate higher levels of depressive symptoms. A cut-off score of ≥10 was used to indicate the presence of depressive symptoms, as suggested by Andresen, Malmgren (23), to produce results consistent with the 20-item version. Participants who answered ‘Yes’ to being diagnosed or treated for depression in the past three years, and/or scored ≥10 on CES-D at Surveys 4, 5 or 6 were categorised as those with depression.

5.3.5 Assessment of covariates

A number of potential confounding variables were considered. Socio-demographic variables included area of residence (urban, rural and remote), marital status (married/*de facto*, separated/divorced, widowed, never married), average household income ($0-25,999 annually, $26,000-51,999 annually, $52,000 or more annually), and education (no formal education/school certificate, higher school or trade certificate/diploma, university degree). Health behaviours were smoking status (never smoked/former smoker, light smoker, heavy smoker), and physical activity (sedentary/low, moderate/high). Anxiety or nervous disorder was the only comorbid condition included. These variables were reported at all surveys except that education was obtained from Survey 1 (1996) and average income was reported at Survey 3 (2001) only. The covariates were selected based on a theoretical framework in the form of a directed acyclic graph (**Figure 5.1**) developed *a priori*.

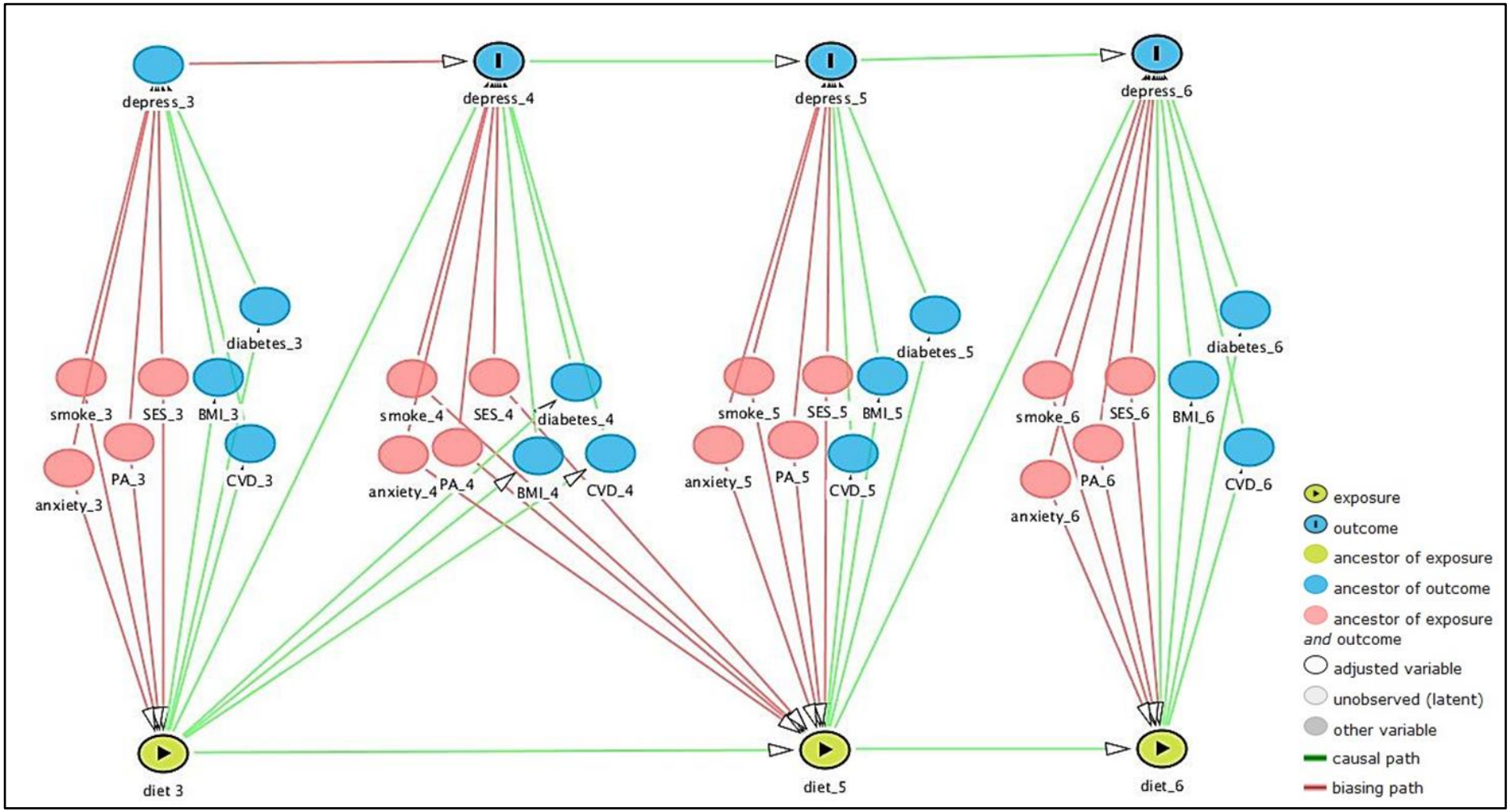

Figure 5.1: Theoretical framework for the association between diet quality and depressive symptoms for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health, where diet quality (diet) at one survey predicts odds of depression (depress) at the following survey. Confounding variables were: socioeconomic (SES) indicators which include area of residence, average household income, marital status, and education; physical activity (PA); smoking status (smoke); and anxiety disorder. BMI, diabetes and cardiovascular disease (CVD) were mediators and not adjusted for in statistical analyses. Numbers represent survey wave.

5.3.6 Statistical analyses

Characteristics of participants according to depression status were compared using the chi-square test for categorical covariates and two independent samples t-test for normally distributed continuous covariates. In order to examine temporal relationships between diet quality and depression, where diet quality at one survey predicts the odds of depression at the following survey, pooled logistic regression models were used including time-varying covariates (25). Diet quality score was categorised into tertiles, and coded as a lagged time-varying variable. Tests of linear trend across increasing tertiles were also conducted where diet quality was treated as continuous.

Participants were followed until they experienced depression or loss to follow-up. Observations recorded after the participant had depression were excluded. If there were missing values for any of the included variables, the observations with missing value(s) were excluded, but all other observations with complete data were kept in the statistical model. The final analyses included 11,856 observations for a total of 7877 participants. All models were adjusted for baseline values of all potential confounders (described above), except that smoking status and physical activity were coded as time-varying categorical variables. A survey-wave indicator was also included to explicitly model the effects of time.

In addition, changes in diet quality from Survey 3 to 5 (6 years) were examined in relation to changes on depression. First, ARFS at each Surveys 3 and 5 were categorised into tertiles. Then, participants were grouped into five categories based on changes in tertile groups from Survey 3 to 5. Participants remaining in the lowest ARFS tertile at both Surveys 3 and 5 were categorised as “maintained low score”. Participants who moved from a lower tertile at Survey 3 to a higher tertile at Survey 5 were categorised as “increased score”, or “decreased score” if the situation were reversed. Participants who remained in the middle tertile at both surveys were categorised as “maintained moderate score”, or “maintained high score” if they remained in the highest tertile.

All analyses were conducted using Stata, version 11 (26). The significance level was set at $P<0.05$.

Sensitivity analyses

Most depressive episodes experienced in later life are recurrence rather than the first episode (4). In order to preclude the possibility of reverse causation, all analyses were repeated excluding participants who reported having depression prior to Survey 2 in 1998 (*n*=1366). These were women who experienced depression prior to 1998 but did not have depression during 1998-2001, thus were not excluded at initial analyses. At Survey 2, participants were asked for the first time “Have you EVER been told by a doctor that you have depression”, with response options of “Yes, in the last 2 years” and/or “Yes, more than 2 years ago”. Participants were excluded if they answered ‘Yes’ to either option.

The use of long or short versions of DQES v2 at different time points may have affected diet quality scoring although the effect was very small. As such, analyses were repeated excluding dietary data at Survey 3. Changes in diet quality from Survey 5 to 6 (3 years change) were examined instead.

5.4 Results

Participant characteristics by depression status at Surveys 4-6 are shown in **Table 5.1**. Approximately 36% (*n*=2841) of participants reported experiencing depression in at least one of the follow-up surveys. Of these, 697 women reported a history of depression at Survey 2. Compared to women without depression, those who were depressed had lower household income, were more likely to be a current smoker, were less physically active, and more frequently had a comorbid anxiety disorder. The ARFS for women with depression were slightly lower at both Surveys 3 and 5.

Table 5.1: Participants characteristics in 2001 according to their depression status at follow-up (2004-2010) in women born in 1946-51 from the Australian Longitudinal Study on Women's Health (*n*=7877)

	Depression at Surveys 4-6 (2004-2010)		
Characteristics at Survey 3 (2001)[a]	**No (*n*=5036)**	**Yes (*n*=2841)**	***P***
	***n* (%)**	***n* (%)**	
Area of Residence			0.60
Urban	1887 (37.5)	1049 (36.9)	
Rural	2863 (56.9)	1617 (56.9)	
Remote	263 (5.2)	163 (5.7)	
Marital status			0.38
Married /de facto	4241 (84.2)	2393 (84.2)	
Separated / divorced	483 (9.6)	293 (10.3)	
Widowed	153 (3.0)	75 (2.6)	
Never married	141 (2.8)	68 (2.4)	
Average household income			0.003
Low ($0-25,999 annually)	2106 (41.8)	1286 (45.3)	
Middle ($26,000-51,999 annually)	1554 (30.8)	797 (28.1)	
High ($52,000 or more annually)	748 (14.9)	386 (13.6)	
Smoking status			0.01
Never smoked / Ex-smoker	4415 (87.7)	2426 (85.4)	
Light smoker	217 (4.3)	131 (4.6)	
Heavy smoker	379 (7.5)	266 (9.4)	
Physical activity			0.03
Sedentary / low	2531 (50.3)	1467 (51.6)	
Moderate / high	2340 (46.5)	1222 (43.0)	
Health status			
Anxiety / nervous disorder	107 (2.1)	102 (3.6)	<0.001
Diet quality[b] at Survey 3 (2001)	33.4 ± 8.7	32.6 ± 8.7	0.02
Diet quality[b] at Survey 5 (2007)	33.3 ± 8.4	32.5 ± 8.5	0.007

[a] Number of participants varies for some variables because of missing data; [b] Summarised by the Australian Recommended Food Score. Values in mean ± SD.

The associations between time-varying ARFS at Surveys 3 and/or 5 and depression at subsequent follow-up are presented in **Table 5.2**. Analyses in which ARFS was treated as time-varying continuous variable showed no significant dose-response relationship between diet quality tertiles and depression after adjustment for confounders. The highest tertile of diet quality appears to be associated with a 6% reduced odds of depression compared to the lowest tertile (OR: 0.94; 95% CI: 0.83, 1.00). Analyses examining the 6-year change in ARFS and depression showed women who maintained a high or moderate score had 14% and 6% lower odds of depression respectively, compared to women who maintained a low score. There was no significant association observed for categories of women who increased or decreased their score.

Table 5.2: Odds ratios (OR) and 95% confidence intervals (CI) for the association between diet quality[a] and depression in women born in 1946-51 from the Australian Longitudinal Study on Women's Health (*n*=7877)

	n	Crude OR (95% CI)	*P*	Adjusted OR[b] (95% CI)	*P*
Diet quality score[c]	7877	0.96 (0.89, 0.99)	0.045	1.00 (0.94, 1.10)	0.48
Tertile 1		(reference)		(reference)	
Tertile 2		0.94 (0.83, 1.04)	0.21	1.04 (0.92, 1.18)	0.53
Tertile 3		0.89 (0.78, 0.99)	0.04	0.94 (0.83, 1.00)	0.049
6-year change in diet quality[d]					
Maintained low score	1132	(reference)		(reference)	
Increased score	1648	0.89 (0.78, 1.02)	0.08	0.90 (0.76, 1.06)	0.21
Decreased score	1345	0.90 (0.79, 1.02)	0.11	1.02 (0.87, 1.20)	0.82
Maintained moderate score	941	0.85 (0.75, 0.95)	0.01	0.94 (0.80, 0.99)	0.045
Maintained high score	1572	0.82 (0.64, 0.78)	0.01	0.86 (0.77, 0.96)	0.01

[a] Summarised by the Australian Recommended Food Score (ARFS); [b] All models adjusted for baseline values of area of residence, marital status, average household income, education, smoking status, physical activity, presence of anxiety/nervous disorder; [c] Test of linear trend across tertiles of diet quality; [d] Data only available for 6638 women (*n*=1239 no complete data for ARFS at Survey 5)

5.4.1 Changes in diet quality

In both surveys, women who maintained a low score (*n*=1132) had a mean of 22 points, those who maintained a moderate score (*n*=941) had a mean of 33 points, and those who maintained a high score (*n*=1572) had a mean of 43 points. From Survey 3 to 5, a total of 1648 women increased their score by a mean of 9 points, while 1345 women decreased their score by a mean of 8 points. Among women who increased their score, 579 increased from lowest to middle tertile, 800 from middle to highest tertile, and 269 from lowest to highest tertile. Among women who decreased their score, 587 decreased from highest to middle tertile, 574 from middle to lowest tertile, and 184 from highest to lowest tertile.

Compared to women in other ARFS categories, more points were contributed by meat and alternatives, dairy and alcohol components for women maintaining a low score, while fruit and vegetables contributed the least. In contrast, fruit contributed a much higher proportion of total ARFS for women maintaining a high score, and less were contributed by dairy, fat and alcohol components. The breads and cereals component contributed equally for all ARFS categories. Those who increased or decreased their score mainly recorded changes in fruit (±3 points) and

vegetable (±5 points) components while other ARFS components remain largely the same (±1 point) between Surveys 3-5.

5.4.2 Sensitivity analysis

The study estimates were similar even after the exclusion of women with a history of depression prior to Survey 2 (1998) but the results became non-significant (**Table 5.3**). The inverse association between the category of women who maintained a high score and odds of depression remained significant (OR: 0.90; 95% CI: 0.79, 0.99). In addition, the analyses excluding dietary data at Survey 3 showed similar results to the initial analyses (**Table 5.4**) – no significant linear association between diet quality tertiles and depression. The highest tertile of diet quality was no longer associated with reduced odds of depression. The study estimates for 3-year change in diet quality were also similar to those of 6-year change.

Table 5.3: Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association between diet quality[a] and depression in women born in 1946-51 from the Australian Longitudinal Study on Women's Health, excluding those with a history of depression prior to Survey 2 (1998) (*n*=6511)

	n	Crude OR (95% CI)	*P*	Adjusted OR[b] (95% CI)	*P*
Diet quality score[c]	6511	0.97 (0.88, 1.00)	0.047	1.00 (0.99, 1.05)	0.54
Tertile 1		(reference)		(reference)	
Tertile 2		0.96 (0.83, 1.06)	0.34	1.03 (0.90, 1.10)	0.64
Tertile 3		0.92 (0.77, 1.01)	0.13	0.97 (0.85, 1.08)	0.30
6-year change in diet quality[d]					
Maintained low score	891	(reference)		(reference)	
Increased score	1315	0.93 (0.79, 1.07)	0.32	0.94 (0.78, 1.08)	0.69
Decreased score	1070	0.92 (0.79, 1.06)	0.24	1.04 (0.87, 1.15)	0.40
Maintained moderate score	751	0.90 (0.80, 1.10)	0.50	0.95 (0.82, 1.03)	0.56
Maintained high score	1276	0.85 (0.73, 0.98)	0.03	0.90 (0.79, 0.99)	0.045

[a] Summarised by the Australian Recommended Food Score; [b] All models adjusted for baseline values of area of residence, marital status, average household income, education, smoking status, physical activity, presence of anxiety/nervous disorder; [c] Test for linear trend across tertiles of diet quality; [d] Data only available for 5303 women (*n*=1208 no complete data for ARFS at Survey 5)

Table 5.4: Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association between diet quality[a] during 2007-2010 and depression in women born in 1946-51 from the Australian Longitudinal Study on Women's Health (*n*=7646)

	n	Crude OR (95% CI)	*P*	Adjusted OR[b] (95% CI)	*P*
Diet quality score[c]	7646	0.98 (0.87, 1.03)	0.52	0.99 (0.88, 1.11)	0.97
Tertile 1		(reference)		(reference)	
Tertile 2		0.99 (0.68, 1.04)	0.97	1.03 (0.71, 1.12)	0.85
Tertile 3		0.95 (0.66, 0.98)	0.83	0.96 (0.68, 1.03)	0.09
3-year change in diet quality[d]					
Maintained low score	1231	(reference)		(reference)	
Increased score	1142	0.88 (0.80, 0.98)	0.02	0.92 (0.75, 1.13)	0.18
Decreased score	1490	0.89 (0.81, 0.98)	0.02	1.04 (0.89, 1.25)	0.56
Maintained moderate score	1658	0.83 (0.76, 0.90)	0.01	0.95 (0.81, 0.98)	0.04
Maintained high score	984	0.84 (0.77, 0.93)	0.01	0.88 (0.71, 1.00)	0.046

[a] Summarised by the Australian Recommended Food Score; [b] All models adjusted for baseline values of area of residence, marital status, average household income, education, smoking status, physical activity, presence of anxiety/nervous disorder; [c] Test of linear trend across tertiles of diet quality; [d] Data only available for 6505 women (*n*=1141 no complete data for ARFS at Survey 6).

5.5 Discussion

The present study aimed to examine the longitudinal association between diet quality and depression, using repeated assessments of dietary intake and depression outcomes. Over the nine years of follow-up, a reduction in risk of 6% was observed for highest tertile of diet quality, although the linear trend across diet quality tertiles was not significant. When the analyses were repeated using categories of ARFS, women who maintained good diet quality (moderate or high score) had a significantly lower odds of depression compared to those with poor diet quality. Those who improved their diet quality showed lower risk of depression, similar in magnitude to those who maintained good diet quality, and those who worsened their diet quality showed an increased risk of depression; neither of these results reached statistical significance.

The results are in line with the findings from a recent meta-analysis of dietary patterns and depression by our group (7). While there are two approaches used to define dietary patterns, the general consensus is that healthy eating habits are associated with a lower likelihood of developing depression. Studies which derived dietary patterns from statistical modelling found that a diet high in fish, and fruit and vegetables is associated with lower risk of depression (9, 27, 28). Similarly, studies using dietary indices or scores based on dietary recommendations have

also demonstrated an inverse association between diet quality scores and depression (8, 29, 30). Our study found that the association between diet quality and depression is only apparent for the highest tertile of diet quality, and among women who maintained a moderate or high score over six years than women who maintained a low score. Given the small detectable effect of dietary factors on chronic diseases (31), consuming a very high quality diet or maintaining moderate-high diet quality for long periods of time (e.g. scoring at least 33 points in ARFS for six years), is necessary to achieve a difference in depression outcomes. Likewise, categories of increased or decreased ARFS did not achieve significance, although point estimates showed similar magnitude effects and in the expected directions. The ARFS placed greater emphasis on whether a food is consumed rather than a measure of absolute amount (17), contributing less to between-person variation (32). Hence, it is more likely to observe an association between extreme categories of ARFS (highest versus lowest tertiles; maintaining versus increasing/decreasing scores) where there is greater variation among groups rather than as a continuous variable. On the other hand, while the associations between women who maintained a moderate or high score and depression are significant, it is modest in magnitude, indicating that ARFS may not have captured the aspect of diet most closely linked to depression. Furthermore, we are not certain of the ability of ARFS at predicting the risk of chronic diseases as it has only been used in one study to predict type 2 diabetes risk and showed no significant association (33). Residual confounding is also likely to exist, which also affects the strength of the association observed.

The ARFS assessed diet diversity in addition to the recommended number of serves for all food groups (19). Aside from meeting the recommended amount for each food group, it is also important to increase the diversity of foods consumed to achieve the highest score possible. The results from our study suggest that those found to have lower odds of depression adhered to a diet quality that is better than average, achieving a total of ≥33 points (mean) in ARFS. To achieve this, individuals should aim to meet the recommended serves for each food group (giving a minimum of 7 points), and consume at least 26 different core food items per week (i.e. different types of vegetables, fruits, lean meats and alternatives, breads and cereals, and dairy products), with a larger proportion of consumption from fruit and vegetables. It is likely that antioxidants and phytochemicals in fruits and vegetables drives the association between diet

and depression, as these compounds have been found to reduce levels of inflammation and oxidative-stress induced damage (34, 35), suggested to play an important role in the pathophysiology of depression (36).

In order to address the temporality of long term dietary intake and subsequent development of depression, we used repeated measures of dietary intakes over a long period of time (6-9 years), and a latency period of three years between dietary assessments and depression at follow-up. As mentioned, only two studies have attempted to establish the temporality of this association using multiple measures of diet and depression (8, 9). Furthermore, the analyses were repeated excluding women who reported a history of depression to further address the possibility of reverse causation. This has not been adequately examined as most evidence presented to date is cross-sectional in nature (7). The results were no longer significant except that maintaining a high diet quality score was still significantly associated with lower odds of depression, thus this finding is considered robust. Although most associations were not significant, the odds ratios estimated in the sensitivity analyses were not very different from the main analyses, indicating that this could be a result of decreased sample size rather than a true null association.

In this study, we employed both self-reported physician diagnosis of depression and the use of CES-D to assess depression. This approach ensures that we are capturing women with undiagnosed depression. We estimated about 36% of the ALSWH women were experiencing depression compared to other studies that found a much lower prevalence of depression among a similar group of individuals (9, 29), although it should be noted that 697 of these women had depression prior to Survey 2, but did not experience depression three years before Survey 3. A recent review found that in Australia, the reported depression rates can range from 1-44% depending on depression measures used (37). Due to the large number of people in this age group with undiagnosed depression, studies using depressive symptoms inventories including our study are likely to report higher numbers of depression cases. Misclassification of depression cases is possible because the data for depression are mainly self-reported, which in general leads to bias toward null (38). However, this is unlikely as CES-D has good sensitivity (75-93%) and specificity (73-87%) in detecting depression in later life (39).

Dietary intakes were not measured at Survey 4 (2004), which may have affected the magnitude of the association observed between diet quality and depression. It is likely that the odds ratio would have recorded a stronger association between ARFS and depression if dietary data at Survey 4 had been available. Surveys 5 and 6 used a shortened version of DQES v2, but the calculation of ARFS was not affected. Any non-differential misclassification that might have resulted from the format change would again bias the odds ratios toward the null (38). We found similar study estimates when the analyses were repeated excluding dietary data at Survey 3 where the long version of DQES v2 was used, which further confirms the robustness of our initial findings. The reduction in sample size and use of dietary data at only two time points may have resulted in a decrease in power, thus the association between highest tertile of diet quality and depression was lost.

Although retention in the study was high (>81%), there were some missing data. Instead of imputing the values for each missing data item, we excluded observations with incomplete data on any of the variables. Imputing values for missing items would allow more observations to be included, and may strengthen the magnitude of the association observed. The statistical analyses did not adjust for body mass index and a number of medical conditions (e.g. type 2 diabetes and cardiovascular disease) which other studies have included as potential confounders (8, 9). However, the selection of confounders was based on background knowledge of the causal structure connecting diet to depression, and as shown in the directed acyclic graph, these variables were mediators rather than confounders.

Conclusion

The use of the ALSWH data allowed us to investigate the association between diet quality and depression in a nationally representative population of Australian women aged 50-65 years, using repeated measurements of diet and depression over a period of 9 years. This is one of the few studies to examine the longitudinal association between diet quality and depression prospectively, and the first in Australia. We observed a significant inverse association between maintenance of good diet quality and subsequent depression. This finding, however, needs to be confirmed by quality randomised controlled trials of interventions to improve nutrition as a component of depression management, and to ensure that the association observed is not affected by residual confounding. Future studies should also consider examining depression as

a time-varying continuous variable rather than a categorical model because depression is characterised by fluctuating symptom levels over time, and a large proportion of cases are likely to present with sub-clinical depression (40). Finally, it is important to identify nutrients and food groups that are most relevant to depression to allow specific diet quality scores to be developed, which can better predict depression risk.

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CHAPTER 6: Longitudinal diet quality is not associated with depressive symptoms in a cohort of mid-aged Australian women

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6.1 Abstract

Background

There is increasing evidence for the role of nutrition in the prevention of depression. This study aims to describe changes in diet quality over 12 years among participants in the Australian Longitudinal Study on Women's Health, in relation to changes in depressive symptoms.

Methods

Women born in 1946-51 were followed for 12 years (2001-2013). Dietary intake was assessed using the Dietary Questionnaire for Epidemiological Studies (version 2) in 2001, 2007 and every 2-3 years after that until 2013. Diet quality was summarised with the Australian Recommended Food Score (ARFS). Depressive symptoms were measured using the 10-item Centre for Epidemiologic Depression Scale at every 2-3 year intervals during 2001-2013. Linear mixed models were used to examine trends in diet quality and its sub-components. The same model including time-varying covariates was used to examine associations between diet quality and depressive symptoms adjusting for confounders. Sensitivity analyses were conducted using the Mediterranean Dietary Pattern (MDP) index to assess diet quality.

Results

Minimal changes in overall diet quality and its sub-components over 12 years were observed. There was a significant association between baseline diet quality and change in baseline depression (β=-0.24, P=0.001), but this was lost when time-varying covariates were added (β=-0.04, P=0.10). Sensitivity analyses showed similar performance for both ARFS and MDP in predicting depressive symptoms.

Conclusions

Initial associations seen when using baseline measures of diet quality and depressive symptoms disappear when using methods that handle time-varying covariates, suggesting that previous studies indicating a relationship between diet and depression may have been affected by residual confounding. More high quality randomised controlled trials are necessary to confirm the role of diet in depression.

6.2 Introduction

Depression is a common mental health disorder, which can lead to severe disability and poor quality of life (1). Current interventions used to manage depression include both psychological interventions and medications, but they are only partially adequate in reducing symptom burden, with medications showing minimal benefit in subthreshold depression (2) and psychological interventions only reducing incidence rate by 20%–25% (3). Considering the high burden of this disorder, preventive strategies are also needed to reduce the public health consequences and costs. A multidisciplinary approach to depression prevention is important to reflect the multiple factors affecting the development and course of depression (4), with particular attention given to modifiable behaviours, like diet, that can potentially prevent this disorder.

In recent years, research into the relationship between dietary patterns and the risk of depression has expanded (5, 6). There are two main approaches to defining dietary patterns: the use of statistical exploratory methods derived from reported dietary intakes, and the use of dietary scores or indices (7). The use of dietary scores or indices may be more useful in public health practice as it allows the assessment of the population's adherence to current dietary recommendations based on empirical evidence (8).

It is also important to consider how diet may change for individuals and populations over time to guide future health promotion policy. There is evidence suggesting that the dietary intakes of Australians have changed in the past decade. In particular, cross-sectional surveys of the Australian population showed reductions in the overall percent energy from sugar and saturated fat (9). A number of cohort studies examining longitudinal changes in dietary intakes have been reported. The Blue Mountain Eye Study found an increase in intakes of omega-3 fatty acid and fish but also a decrease in wholemeal/grain bread consumption from 1992-2004 among older adults living in Sydney, Australia (10). The Nambour Skin Cancer Study found an overall improvement in diet quality from 1992-2007 among residents of Queensland (11). Despite the long-standing recognition that a variety of dietary dimensions are important for the prevention of chronic diseases, a limited number of studies have explored trends in overall diet quality in relation to chronic diseases.

Monitoring dietary trends and their association with chronic diseases in middle-aged women is of considerable interest because this group of individuals has a higher prevalence of chronic diseases compared to their younger counterparts (12). While depression prevalence decreases with age, episodes experienced later in life are more likely to persist if untreated (13). Prognosis of depression also deteriorates with age mainly due to the presence of co-morbidities and the many cases of depression that goes undiagnosed because of that. Furthermore, women are twice as likely as men to be diagnosed with depression (12).

Previously we have shown that maintaining good diet quality over a six year period is associated with reduced odds of incident depression among middle-aged women participating in the Australian Longitudinal Study on Women's Health (Chapter 5). This previous study examined the diet-depression link from a prevention perspective, while the current analyses aimed to explore whether good diet quality relieves existing depressive symptoms, making it a potential therapeutic strategy for depression. Evidence from prospective studies on a healthy diet in effectively relieving existing depressive symptoms is scarce. Furthermore, we recognised that depression is often characterised by fluctuating symptom levels over time instead of a continuum of severity (14). Therefore, in this study, we aim to (1) describe changes in diet quality over 12 years in the same group of women; and (2) examine how a change in diet relates to depressive symptoms longitudinally, whereby depressive symptoms are treated as a continuous variable rather than a categorical variable (i.e. with or without depression).

6.3 Methods

6.3.1 Study sample

The Australian Longitudinal Study on Women's Health (ALSWH) is an ongoing prospective cohort study of over 50, 000 Australian women from four age cohorts – women born in 1989-95, 1973-78, 1946-51, and 1921-26 (15, 16). A total of 40392 women from 1973-78 cohort, 1946-51 cohort, and 1921-26 cohort were recruited in 1996, and followed for almost 20 years (15). In 2012, a new cohort of 17069 women born in 1989-95 was recruited (16). Women from these age cohorts were randomly selected from the Medicare health insurance database, which includes all Australian citizens and permanent residents, with over-representation of women

living in rural and remote areas. The respondents have been shown to be broadly representative of the national population of women at baseline. Further details of this study have been described elsewhere (15, 16). This research was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Human Research Ethics Committees of the University of Newcastle and the University of Queensland, Australia. Written informed consent was obtained from all participants prior to inclusion in the study.

Our sample was obtained from the 1946-51 cohort. Women aged 45-50 years completed a self-administered questionnaire at the baseline survey in 1996 (Survey 1), and at each follow up at approximately three year intervals. Studying the characteristics of women from this cohort will provide useful perspectives on the profile of depression and dietary behaviour for this middle-aged group. For this study, only data from Surveys 3-7 (2001-2013) were used because dietary information was included in the questionnaires starting in 2001. A total of 11,226 women responded to Survey 3 in 2001. Retention rate was high at each survey cycle, and >80% of the initial study sample remained at Survey 7 in 2013. Participants were included in the present analyses if they had data for dietary intakes for at least one of Surveys 3, 5-6 and depressive and depressive symptoms for any subsequent follow-ups (**Figure 6.1**). The statistical analyses included a total of 11,046 women.

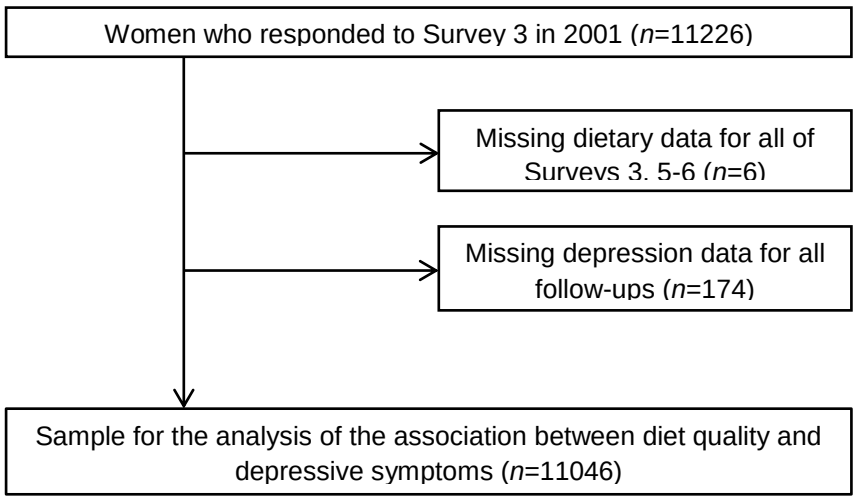

Figure 6.1 Study sample selection flow diagram for analysis of the association between diet quality and depressive symptoms among women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health.

6.3.2 Dietary Intake

Dietary intake was first measured at Survey 3 (2001), and then at Surveys 5, 6 and 7 (in 2007, 2010 and 2013). At Surveys 3 and 7, the Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2) (17) was administered to all participants. This questionnaire was developed by the Cancer Council Victoria for assessing dietary intakes among Australian adults in epidemiological studies. The DQES v2 requires participants to report their usual consumption over the past 12 months of 74 foods using a 10-point frequency scale ranging from 'Never' to 'three or more times per day', and six types of alcoholic beverage with options ranging from 'never' to 'every day'. In addition, there are 10 questions on the amount of fruit, different types of vegetables, milk, bread, sugar and eggs consumed, and on the type of milk, bread, fat spreads and cheese used. Further details of the DQES v2 are presented elsewhere (17). The performance of the DQES v2 has been evaluated in multiple studies against weighed food records, and correlation coefficients for most nutrient intakes were comparable with those reported for other food frequency questionnaires (18, 19).

A shortened version of the DQES v2 was administered to participants at Surveys 5 and 6. This version assesses the consumption of 68 foods instead of the 74 foods in the original version. A shortened frequency scale was also used for majority of the food items ('never', 'less than once a week' or 'once a week or more'), except dairy products, meat and fish which were assessed with five frequency response options ranging from 'never' to 'five or more times per week'. Nine questions on the amount of fruit, different types of vegetables, milk, bread, sugar and eggs consumed, and the type of milk, bread, fat spreads and cheese used were retained. The question on the amount of sugar consumed per day was removed, and a question on the number of servings of vegetables consumed per day was included in its place. The shortened DQES v2 was designed to minimise participant burden whilst still facilitating a summary of diet quality, using the Australian Recommended Food Score (ARFS) method (described below).

6.3.3 Diet quality

Diet quality scores were calculated based on DQES v2 items using the ARFS method by Collins et al. (20), which was modelled on the Recommended Food Score by Kant and Thompson (21). The ARFS was previously validated using the ALWSH cohort and provides reasonable rankings

for middle-age women according to their diet quality and nutrient intake (20). The scoring method assigns points for the consumption of desirable foods at the recommended levels consistent with national recommendations in the Dietary Guidelines for Australian Adults (22) and the core foods given in the Australian Guide to Healthy Eating (23). Desirable food items consumed at least once a week were assigned one point (20). For questions assessing the type and amount of core foods, points were assigned for consuming at least two servings of fruit a day, at least four servings of vegetables per day, at least four slices of bread per day, use of polyunsaturated or monounsaturated spreads or no fat spread, use of low-fat dairy products, and consuming at least 500mL of milk per day. In addition, a maximum of two points was assigned for alcohol consumption: one point for frequency (up to four days per week), and one point for quantity (not more than two drinks on days when alcohol was consumed). The maximum ARFS score is 74, with higher values corresponding to a healthier diet. There are seven sub-components to the ARFS: vegetables (22 points), fruit (14 points), protein foods (14 points), grains (14 points), dairy (7 points), fats (1 point), and alcohol (2 points). Missing values were recoded to zero for up to four items. Participants with greater than four missing values were considered as having incomplete data. The scores were calculated in the same manner for the shortened version of DQES v2 used in Surveys 5 and 6. Further details on the scoring system are described elsewhere (20).

6.3.4 Depressive symptoms

Participants were asked to complete the 10-item Centre for Epidemiologic Studies Depression (CES-D) scale assessing depressive symptoms during the past week at each survey. Each item was rated on a 4-point scale, ranging from “none of the time” to “most of the time” (24). Possible scores range from 0-30 where higher scores indicate greater severity of depressed mood. The 10-item CES-D has high levels of reliability and validity against a set of reference measures assessing life satisfaction, self-rated health and social support (25), and produces results consistent with those measured with the 20-item version (24).

6.3.5 Covariates

A number of potential confounding variables were considered. Socio-demographic variables included area of residence (urban, rural and remote), marital status (married/de facto,

separated/divorced, widowed, never married), average household income ($0-25,999 annually, $26,000-51,999 annually, $52,000 or more annually), and education (no formal education/school certificate, higher school or trade certificate/diploma, university degree). Health behaviours were smoking status (never smoked/former smoker, light smoker, heavy smoker), and physical activity – measured using minutes of metabolic equivalents of task (MET.mins) based on self-reported walking, and moderate and strenuous physical activity (nil/sedentary, 0-40 MET.min/week; low, 40-600 MET.min/week; moderate, 600-1200 MET.min/week; high, ≥1200 MET.min/week). Self-reported physician diagnosis of depression and use of antidepressants were also included as potential confounders. These variables were reported at all surveys except that education was obtained from Survey 1 (1996), average income from Survey 3 (2001), and information on the use of antidepressants was obtained from data linkage with the Pharmaceutical Benefit Scheme database.

6.3.6 Statistical analyses

Characteristics of participants at Survey 3 (2001) according to quintiles of ARFS were compared using the chi-square test. A linear mixed model was used to examine changes in diet quality between 2001 and 2013. Diet quality (ARFS) at each survey was the outcome variable, and year of observation was included in the model as fixed effect and a random subject-specific intercept to account for serial correlations with a compound symmetric variance-covariance error structure. The estimated coefficient for year corresponded to the yearly change in diet score. The analysis was repeated for each sub-component of ARFS: vegetables, fruit, protein foods, grains, dairy, fats and alcohol.

A similar model was used to examine the longitudinal association between ARFS and depressive symptoms. A theoretical model in the form of a directed acyclic graph was set up in which diet quality at one survey predicts change in depressive symptoms at the following survey (**Figure 6.2**). Depressive symptoms at each survey were treated as the continuous outcome variable, and ARFS was categorised into quintiles and included in the model as a lagged time-varying variable. The models included adjustment for all potential confounders described above. Smoking status and physical activity were coded as time-varying categorical variables, while the

remaining variables were considered as time-independent variables. A survey-wave indicator was also included to explicitly model any secular trends in depressive symptoms.

We used all available data from each participant under the missing-at-random assumption. All analyses were conducted using Stata, version 13 (StataCorp, College Station, TX, USA). The significance level was set at $P<0.05$.

Sensitivity analyses

The analyses examining the association between diet quality and depressive symptoms were repeated using diet quality scores calculated with the Mediterranean Dietary Pattern (MDP) index by Trichopoulou et al (26). Considering the fact that diet quality indices have not been tested extensively in their ability to predict the risk of depression (27), comparing results from multiple indices can help ascertain the robustness of our study findings. Further details of the scoring method are described elsewhere (26). Briefly, the MDP index assigns a score of 0 or 1 based on daily intake of nine components. One-point was assigned if the participant's intake was over the sample median for each of the following: ratio of mono-unsaturated fat to saturated fat intake, legumes, cereal, fruit and nuts, vegetables, and fish. Participants received 1-point if intake was below sample median for meat and meat products, and dairy products. For the alcohol component, 1-point was scored if consumption was 5-25g/day. The scores were categorised into five quintiles (0-2, 3, 4, 5, and 6-9 points). The MDP index could only be calculated for Surveys 3 and 7 when the full version of DQES v2 was used; results from this analysis will only be compared to that of the ARFS at the two surveys. All variables in the sensitivity analyses were treated as time-independent due to only having data at two time points.

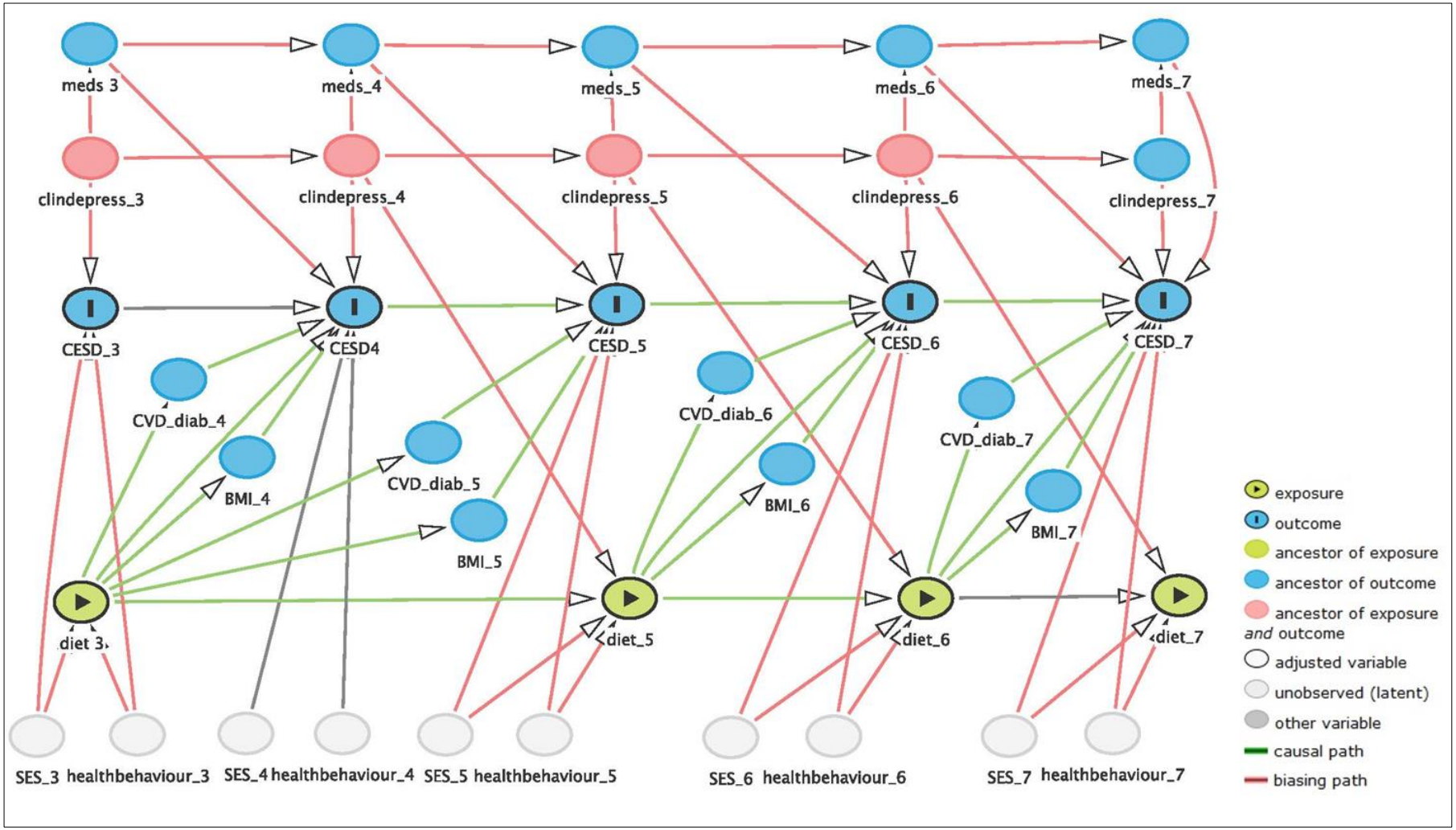

Figure 6.2: Theoretical framework for the association between diet quality and depressive symptoms for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health. Diet quality (diet) was summarised using the Australian Recommended Food Score. Depressive symptoms were measured using the 10-item Centre for Epidemiologic Studies Depression Scale (CESD). Confounding variables were: socioeconomic (SES) indicators which include area of residence, average household income, marital status, and education; health behaviour (healthbehaviour) indicators which include physical activity and smoking status; self-reported physician diagnosis of depression (clindepress) and use of antidepressants (meds).

6.4 Results

Characteristics of participants by quintiles of ARFS are presented in **Table 6.1**. Women with higher diet quality scores were more likely to be married or in a de facto relationship, have higher household income, received higher education, were physically active, and less likely to smoke.

Table 6.1: Participant characteristics in 2001 by diet quality quintiles for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health (n=11046)

Characteristics in 2001[a]	**Quintiles of diet quality**										
	Q1		**Q2**		**Q3**		**Q4**		**Q5**		***P***
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Diet quality[b]	19.6	4.2	27.7	1.6	32.4	1.3	36.9	1.6	44.1	3.8	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	
Area of residence											0.098
Urban	699	35.9	817	36.1	728	38.3	822	39.1	917	38.6	
Rural	1155	59.3	1324	58.6	1053	55.5	1177	56.0	1331	56.1	
Remote	93	4.8	119	5.3	118	6.2	101	4.8	125	5.3	
Marital status											0.006
Married / de facto	1463	74.9	1854	82.0	1578	83.0	1755	83.6	1991	84.0	
Separated / divorced	331	16.9	289	12.8	204	10.7	230	11.0	246	10.4	
Widowed	78	4.0	60	2.7	56	2.9	64	3.0	66	2.8	
Never married	82	4.2	58	2.6	64	3.4	50	2.4	66	2.8	
Average household income											0.001
Low	1006	59.4	1056	52.8	872	51.7	893	48.5	1003	47.0	
Middle	490	28.9	648	32.4	553	32.8	646	35.1	761	35.7	
High	198	11.7	294	14.7	262	15.5	303	16.4	369	17.3	
Education											0.001
No formal qualification	1144	58.6	1158	51.4	899	47.4	907	43.4	960	40.7	
Higher school or trade certificate/ diploma	623	31.9	777	34.5	690	36.4	834	39.9	977	41.3	
University degree	184	9.4	319	14.2	306	16.1	351	16.8	423	17.9	
Smoking status											0.001
Never smoked / ex-smoker	1521	78.2	1899	84.0	1642	86.4	1846	88.1	2153	90.8	
Light smoker	86	4.4	117	5.2	87	4.6	97	4.6	108	4.6	
Heavy smoker	339	17.4	244	10.8	171	9.0	153	7.3	109	4.6	
Physical activity											0.001
None/sedentary	568	31.0	468	21.3	309	16.9	255	12.5	213	9.3	
Low	657	35.8	834	38.0	753	41.2	770	37.9	779	34.0	
Moderate	277	15.1	418	19.1	365	20.0	451	22.2	552	24.1	
Heavy	332	18.1	474	21.6	399	21.9	557	27.4	748	32.6	
Self-reported depression	245	12.6	258	11.5	219	11.6	207	9.9	242	10.3	0.054
Use of antidepressants	268	13.7	320	14.1	260	13.6	303	14.4	344	14.4	0.908

[a] Number of participants varies for some variables because of missing data; [b] Summarised by the Australian Recommended Food Score.

6.4.1 Trends in diet quality 2001-2013

Total diet quality was found to remain stable throughout the follow-up period (**Table 6.2**). Similarly, the score for the fruit component did not change significantly over time. There were significant decreasing trends in scores for vegetables, grains, and fats components. For protein foods, dairy, and alcohol components, significant upward trends in scores were observed. However, these changes were negligible (β= ±0.05, 95% CI= ±0.01-0.06).

Table 6.2: Scores for each component of the Australian Recommended Food Score between 2001-2013 for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health (n=11046)

	Diet quality scores								Diet quality change, units/year		
	2001		2007		2010		2013				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	β	95% CI	*P* trend
Total	32.6	8.8	32.5	8.8	31.9	8.5	33.1	8.6	0.01	-0.02, 0.03	0.089
Sub-components											
Vegetables	13.6	4.4	12.2	4.6	12.0	4.5	13.8	4.5	-0.03	-0.04, -0.02	0.001
Fruits	5.6	3.2	5.7	3.2	5.4	3.0	5.6	3.1	0.01	-0.01, 0.01	0.842
Protein foods	5.2	2.0	6.0	2.0	6.0	2.0	5.7	2.0	0.05	0.05, 0.06	0.001
Grains	4.0	1.8	3.8	1.8	3.7	1.8	3.8	1.8	-0.03	-0.03, -0.02	0.001
Dairy	2.1	1.0	2.9	1.2	2.9	1.1	2.2	1.0	0.03	0.02, 0.03	0.001
Fats	0.7	0.5	0.6	0.5	0.6	0.5	0.5	0.5	-0.01	-0.01, -0.01	0.001
Alcohol	1.4	0.6	1.3	0.8	1.3	0.8	1.5	0.6	0.01	0.01, 0.01	0.001

6.4.2 Diet quality and depressive symptoms

The initial univariate model showed a significant association between diet quality and depressive symptoms (β=-0.13, *P*-trend=0.001). There is a gradual reduction in depressive symptoms across quintiles of diet quality with the highest quintile showing greatest reduction in depressive symptoms (**Table 6.3**). Further adjustment for indicators of socioeconomic status (Model 2) attenuated the association observed, and adjustments for health behaviours (Model 3) reduced the magnitude of the association even further. The final adjustment for self-reported physician diagnosis of depression and use of antidepressants (Model 4) did not change the study estimates and significance level substantially. There were no significant associations between each sub-component of the diet quality score and depressive symptoms (data not shown).

Table 6.3: Associations between diet quality[a] quintiles and depressive symptoms for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health (n=11046) [b, c]

		Diet quality quintiles				
		Q2	Q3	Q4	Q5	
	n[d]	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***P***
Model 1	11046	-0.31 (-0.53, -0.09)	-0.43 (-0.65. -0.20)	-0.43 (-0.65, -0.20)	-0.59 (-0.81, -0.37)	0.001
Model 2	9122	-0.12 (-0.36, 0.12)	-0.24 (-0.49, 0.01)	-0.19 (-0.43, 0.05)	-0.36 (-0.60, -0.11)	0.005
Model 3	8923	-0.06 (-0.30, 0.19)	-0.12 (-0.37, 0.14)	-0.08 (-0.32, 0.18)	-0.20 (-0.45, 0.05)	0.147
Model 4	8880	-0.06 (-0.31, 0.15)	-0.05 (-0.29, 0.19)	-0.05 (-0.29, 0.18)	-0.23 (-0.47, 0.01)	0.104

[a] Summarised by the Australian Recommended Food Score as time-varying variable; [b] Model 1 was the univariate analysis including only diet quality and depressive symptoms. Model 2 was adjusted for indicators of socioeconomic status: area of residence, marital status, average household income, and education. Model 3 was adjusted as for model 2 and for smoking status and physical activity as time-varying variables. Model 4 was adjusted as for model 3 and self-reported physician diagnosis of depression and use of antidepressants; [c] Coefficients and 95% CI for depressive symptoms in each diet quality quintiles compared to the lowest quintile; [d] Number of participants varies because of missing data for the covariates.

6.4.3 Sensitivity analyses

When analyses were repeated with ARFS and MDP scores at Surveys 3 and 7, a significant inverse association between diet quality and depressive symptoms was observed, after adjusting for all potential confounders (**Table 6.4**). Diet quality assessed with the ARFS (*β*= -0.20, *P*-trend=0.001) produced a greater reduction in depressive symptoms compared to the MDP index (*β*=-0.08, *P*-trend=0.007). To determine if this is a result of using time-independent variables instead of time-varying, we repeated the model using ARFS at Surveys 3, and Surveys 5-7 coding all variables as time-independent. Contrary to the results in Table 3, a significant inverse association between ARFS and depressive symptoms remained (*β*= -0.24, *P*-trend=0.001) after adjusting for all potential confounders (**Table 6.5**).

Table 6.4: Sensitivity analyses examining associations between diet quality quintiles and depressive symptoms for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health (n=9280) [a, b]

		Diet quality quintiles				
		Q2	Q3	Q4	Q5	
	n	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***P***
Model 1-ARFS[c]	9280	-0.25 (-0.51, -0.01)	-0.42 (-0.68, -0.17)	-0.62 (-0.87, -0.36)	-0.84 (-1.10, -0.59)	0.001
Model 2-MDP[d]	9280	-0.17 (-0.45, 0.10)	-0.24 (-0.51, 0.03)	-0.36 (-0.63, -0.08)	-0.48 (-0.74, -0.21)	0.007

[a] Examined using diet quality data at two time points – 2001 and 2013. All models adjusted for area of residence, marital status, average household income, education, smoking status, physical activity, self-reported physician diagnosis of depression and use of antidepressants; [b] Coefficients and 95% CI for depressive symptoms in each diet quality quintiles compared to the lowest quintile; [c] Summarised by the Australian Recommended Food Score. [d] Summarised by the Mediterranean Dietary Pattern index.

Table 6.5: Associations between diet quality[a] quintiles and depressive symptoms for women in the 1946-51 cohort of the Australian Longitudinal Study on Women's Health (n=11046)[b, c]

		Diet quality quintiles				
		Q2	Q3	Q4	Q5	
	***n*[d]**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***P***
Model 1	11046	-0.80 (-0.96, -0.64)	-1.18 (-1.34, -1.02)	-1.45 (-1.61, -1.29)	-1.70 (1.87, -1.56)	0.001
Model 2	9710	-0.69 (-0.87, -0.52)	-0.96 (-1.14, -0.78)	-1.24 (-1.42, -1.06)	-1.52 (-1.71, -1.34)	0.001
Model 3	9656	-0.51 (-0.69, -0.33)	-0.68 (-0.87, -0.50)	-0.90 (-1.09, -0.72)	-1.13 (-1.32, -0.94)	0.001
Model 4	9647	-0.44 (-0.61, -0.27)	-0.60 (-0.78, -0.42)	-0.81 (-0.98, -0.63)	-1.01 (-1.19, -0.83)	0.001

[a] Summarised by the Australian Recommended Food Score[(1)] as time-independent variable.; [b] Model 1 was the univariate analysis including only diet quality and depressive symptoms. Model 2 was adjusted for indicators of socioeconomic status: area of residence, marital status, average household income, and education. Model 3 was adjusted as for model 2 and for smoking status and physical activity as time-independent variable. Model 4 was adjusted as for model 3 and self-reported physician diagnosis of depression and use of antidepressants; [c] Coefficients and 95% CI for depressive symptoms in each diet quality quintiles compared to the lowest quintile; [d] Number of participants varies because of missing data for the covariates.

6.5 Discussion

This study described the trends in diet quality over a period of 12 years, and examined how these changes relate to depressive symptoms longitudinally. Results suggest that overall diet quality among this group of middle-aged women remained stable throughout the follow-up period. While statistical tests revealed significant temporal trends in the sub-components of diet quality score, the changes in score were minimal (<0.1 point change/year). These findings are

similar to those in the study by Arabshahi et al. (11) reporting an overall improvement in diet quality among a sample of Australian adults but found that women in the older age group (≥45 years) showed minimal improvement in diet quality than their younger counterparts.

We did not observe a significant association between diet quality and depressive symptoms, contrary to findings from two other cohort studies that evaluated the association using dietary indices (28, 29). The previous two studies used the Alternative Healthy Eating Index (AHEI) and MDP index to assess diet quality, which have been constructed differently to the ARFS and have different scoring methods. To allow direct comparison, we repeated the analyses using the MDP index to assess diet quality. While we were only able to compare results for ARFS and MDP index at two time-points and treating all variables as time-independent, results suggest that both scores affect depressive symptoms in a similar direction (inverse association) with ARFS resulting in greater reduction in depressive symptoms.

Interestingly, as a result of the sensitivity analyses, we found that models including time-independent variables produced very different study estimates and significance levels to models including time-varying variables. This is an important finding as it justifies why our study findings differ from the previous two studies. The fact that previous studies are showing significant associations between diet quality and depression could be a result of not adequately accounting for variables that change over time, and thus are biased by residual confounding (30, 31). We believe that our approach of using a mixed-model including time-varying variables provides a more valid and precise study estimate for the association of diet quality and depressive symptoms, as it accounts for the effects of time, and estimates change within each subject in addition to the average change in study sample, while adjusting for time-varying confounding (32).

The meta-analysis by our group showed that consumption of a healthy diet is associated with reduced odds of depression (5). However, our meta-analysis only included four prospective cohort studies, and the subgroup analysis based on cohort studies suggests no significant association although the study estimate was in the direction of an inverse association (OR: 0.83, 95% CI: 0.66, 1.05). More studies have been published since, arriving at a similar conclusion. One cohort study in Australia found no predictive effect of a prudent dietary pattern on

depressive symptom incidence in middle-aged men and women (33). The PREDIMED Study randomised 7447 community-dwelling men and women aged 60-80 years at high risk of cardiovascular disease to two Mediterranean diets and a low-fat diet (control group), and showed no significant difference in depression risk among participants assigned to a Mediterranean diet compared to the control group (34). Note, however, that these studies focused on overall diet at predicting new cases of depression rather than reducing depressive symptoms among individuals with depressive disorder or subthreshold depression.

Conversely, studies have demonstrated that unhealthy eating habits increased the likelihood of developing depression. In a French cohort study, high snacking habits was associated with elevated depressive symptoms (35). The results from the Women's Health Initiative study suggest that high glycaemic index diets were associated with increased odds of depression (36). The Nurse's Health Study found a positive association between an inflammatory dietary pattern and depression (37). These studies provided useful information regarding which unhealthy foods to avoid for a lower likelihood of developing depression, in addition to existing literature on healthy eating habits.

The current study is an extension to our previous investigation of diet quality and incident depression (Chapter 5), by examining the influence of diet quality on depressive symptoms, to explore the role of diet in effectively relieving depressive symptoms in individuals with depressive disorder or subthreshold depression. Our previous study found that maintaining good diet quality for at least six years has a borderline significance with lower odds of incident depression compared to maintaining poor diet quality (Chapter 5). The conflicting findings between the studies can be explained by the fact that the previous study made comparisons between extreme groups (i.e. long term exposure to high or low quality diet), resulting in high between-subject variability in adherence, thus allowing an effect to be detected. That study also focused on a clinical diagnosis of depression, and it is possible that a dietary effect may not be detectable for sub-clinical depression or depressive symptoms.

The strength of the current study is that the data is drawn from a prospective study conducted among a large number of middle-aged community-dwelling women that are nationally representative of the Australian population. This study has a 12-year follow-up period with a

high retention rate. We were able to carry out multiple assessments of diet quality and depressive symptoms using well-validated tools, and using the mixed-model approach allows inclusion of subjects with incomplete data across time. All these contribute to increased statistical power.

Several limitations were noted. First, it is debatable whether the ARFS is the best tool to use to capture the aspect of diet most closely linked to depression. In fact, we are not certain of the ability of the ARFS at predicting other chronic diseases as only one other study has used this score to predict type 2 diabetes, and that study showed no association between ARFS and diabetes, but found an association between diet quality, measured by the Dietary Guideline Index, and diabetes (38). To date, studies showing most consistent results are in relation to CVD risk because the diet quality score items were derived from epidemiological associations with reduced CVD risk and its risk factors (27). Hence, the null association in our study may be because the ARFS was not specifically designed based on current evidence for reduced depression risk. The lack of difference in diet quality over time may be a result of repeated assessments of diet using the same instruments, as participants may remember and repeat the same answers each time (39). While the sensitivity analyses showed similar performance in both ARFS and MDP index, the results are not directly comparable to our initial model (time-varying ARFS at four time points) thus we cannot be sure of the ability of ARFS in predicting depression outcomes. Second, the CES-D measures depressive symptoms in the past four weeks. It is possible that participants completed the questionnaire when depressive symptoms were less severe (i.e. a form of healthy respondent bias). As such, the number of participants with depressive symptoms may be underestimated. Third, we included participants with self-reported physician diagnosis of depression and/or were using antidepressants, thus reverse causation is possible. However, we aimed to examine whether good diet quality relieves existing depressive symptoms and not on its association with incident depression. Additionally, including participants with existing depression diagnosis may confound the association, but we have adjusted for these in our analysis. While adjusting for these variables may contribute to unnecessary attenuation of the association, we have demonstrated that adjustment made little difference to the study estimates. Results may also be biased by unmeasured factors, for

example, dieting alters dietary intake and was associated with higher symptoms of emotional disorders (40).

Conclusion

Study results suggest no significant association between diet quality, assessed using ARFS, and depressive symptoms among middle-aged Australian women over a period of 12 years. Our results are concordant with randomised controlled trials and suggest that previous positive associations may have been due to residual confounding. It would be useful if similar analyses could be carried out using other diet quality indices to explore the association between diet quality and depressive symptoms to determine how robust the findings are. This study also highlights the need for more high quality randomised controlled trials with longer follow-up time to definitively assess the role of diet in relieving existing depressive symptoms.

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CHAPTER 7: Inflammation mediates the association between fatty acid intake and depression in older men and women

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*****_The following sentence was added to this chapter (Page 164) following thesis examiner's comment but does not appear in the published version:_

"The cross-sectional nature of the Japanese study meant that the observed association may reflect the influence of depression on nutritional status rather than a true causal association since reduced appetite and poor eating habits have been reported in individuals with depression."

7.1 Abstract

Background

Antioxidants and fatty acids are associated with depression and inflammation, and inflammation appears to predict depression risk, hence the association between these nutrients and depression may be mediated by inflammation. We hypothesised that inflammatory markers – interleukin (IL)-6 and C-reactive protein (CRP) mediate the associations between antioxidant and fatty acid intakes, and depression.

Methods

Participants were from the Hunter Community Study, a longitudinal cohort of adults aged 55-85 years. Dietary intakes were assessed using the Older Australian's Food Frequency Questionnaire. Fasting blood samples were drawn for analysis of nutrient and inflammatory biomarkers. Depressive symptoms were assessed using the 20-item Centre for Epidemiologic Studies – Depression scale at baseline and at 5-years follow-up. Linear mixed models were used to investigate longitudinal associations between dietary intakes and depression, and mediation analysis carried out to determine if IL-6 and/or CRP were the mediators. Analyses were conducted on males and females separately, and adjusted for potential confounders.

Results

Fruits and mono-unsaturated fat intakes were negatively associated with depression, whereas total fat and saturated fat intakes were positively associated with depression in both genders. Omega-3 polyunsaturated fat was inversely associated with depression in males only. IL-6 was a significant mediator of the association between fruits with low carotenoid content and depression in females. CRP significantly mediated the relationship between total fat, saturated fat and mono-unsaturated fat intakes and depression in females, and saturated fat intake and depression in males.

Conclusion

Our findings raise the possibility that the association between fatty acid intake and depression is partially mediated by inflammatory markers.

7.2 Introduction

Depression is a highly prevalent mental health disorder that results in substantial disability (1). Much work has been devoted to understanding the cause of depression to allow for development of prevention and treatment strategies. The pathophysiology of depression is understood to be influenced by endocrine, immunological and metabolic mediators, and cellular, molecular and epigenetic forms of plasticity (2). In particular, several lines of research have implied that systemic, low-grade inflammation may have a causative role in the onset of depression (2, 3). Inflammatory markers such as interleukin (IL)-6, tumor-necrosis-factor-α, interferon-α, and C-reactive protein (CRP) may modulate the synthesis, release and reuptake of neurotransmitters which are involved in mood regulation (2). Inflammatory cytokines may also exert effects on the hypothalamic-pituitary-adrenal-axis hormones where high levels of corticotrophin-releasing-hormone and cortisol are suggested to contribute to the signs and symptoms of depression (2). Administration of low doses of pro-inflammatory cytokines to rodents resulted in depression-like behavior including social withdrawal, and decreased exploratory and sexual behavior (4). High concentrations of inflammatory markers have also been found in depressed patients (3, 5). Thus, the causal connection between inflammation and depression is plausible.

Emerging evidence from epidemiological studies has shown how various dietary components are associated with inflammation and depression. Studies have found high intakes of omega-3 polyunsaturated fat (n-3 PUFA) to be associated with lower inflammatory cytokine production (6). Likewise, consumption of fish or n-3 PUFA supplements may be associated with lower depression risk (7). Antioxidants and phytochemicals (usually found in fruits and vegetables) may be beneficial in reducing levels of inflammation (8), and a diet high in fruits and vegetables has been demonstrated to be associated with reduced depression (9). Conversely, foods with a high glycemic index (10) and high saturated fat (SFA) content (11) may be associated with elevated levels of inflammatory markers. This nutrient profile is typical of a Western diet that includes high amounts of refined grains, red and processed meat, and fast food, which is potentially associated with an increased risk of depression (9). In other words, foods with anti-inflammatory properties may reduce the risk of depression while pro-inflammatory diets could fuel depressive symptoms.

Current large scale epidemiological evidence suggests consumption of a diet high in fish, fruits and vegetables, and wholegrains may reduce depression risk (9). However, these results have been somewhat inconsistent. This may be due to the fact that many studies examining diet and depression do not incorporate existing knowledge of nutrient-disease associations or the underlying mechanisms that drive the diet-depression relationship, and may not capture the aspects of diet most relevant to depression. There is therefore a need to identify the mechanism underlying the anti-depressive or depressive properties of everyday diets to allow more tailored dietary advice as a population-based strategy for reducing the burden of depression.

A number of studies have examined the association of dietary factors and inflammation (6, 8, 11) or the association of inflammation and depression (3). Others have examined the association of dietary factors with depression (7). However, it is not known whether inflammatory markers mediate the relationship between diet and depression. Based on available evidence, we hypothesised that nutrients with anti- or pro-inflammatory properties such as antioxidants and fatty acids would be associated with depressive symptoms; and that inflammatory markers – IL-6 and CRP would mediate these associations. Therefore, we aimed to (1) explore the prospective associations between carotenoids, Vitamin E, fatty acids, fruit and vegetables, and depressive symptoms among a group of older Australian adults, and (2) test the potential mediating effects of inflammatory markers using mediation analyses.

7.3 Methods

7.3.1 Study sample

Data for this study were drawn from the Hunter Community Study (HCS), which is a population based cohort of adults aged 55-85 years at recruitment residing in Newcastle, New South Wales, Australia (12). Study participants were randomly selected from New South Wales State Electoral Roll, and recruited between December 2004 and December 2007. A total of 3254 individuals participated in the study. The HCS participants provide a population profile approximately reflecting that of the national profile in terms of gender and marital status but are slightly younger in age (12). At baseline, all participants were required to attend a face-to-face

clinical assessment at the HCS clinic with trained study assessors, provide a fasting blood sample and complete a series of self-administered questionnaires which included assessment of dietary intake and depressive symptoms (for detail on measures see McEvoy et al., 2010) (12). In 2010, participants were invited to complete follow-up questionnaires, and 2250 participants completed the follow-up. Full methodological details have been published previously (12). The present study was restricted to participants who had complete dietary data, provided a blood sample, and completed the assessment for depressive symptoms (*n*=2035).The HCS has received ethics approval from the University of Newcastle Research Ethics Committee (H-820-0504). Written informed consent was obtained before participants were enrolled in the study.

7.3.2 Assessment of dietary intake

Dietary intake was assessed at baseline with the Older Australian's Food Frequency Questionnaire (FFQ). This self-administered, 145-item semi-quantitative FFQ was developed by the Blue Mountain Eye Study (BMES) specifically for use with older Australians (13). Participants were required to indicate their usual frequency of foods consumed in the past year, with nine categorical frequency options: 'never' to 'four or more times per day'. Open-ended questions were included on the types of fruit juices, breakfast cereal, and other frequently consumed foods that were not included in the list. The FFQ also assessed dietary supplement usage. The FFQ was validated twice, against 4-day weighed food records in the BMES (13), and against plasma biomarkers in the HCS (14). This FFQ demonstrated reasonable validity against both self-reported and objective biochemical measures. The correlation coefficient for most nutrients was ≥0.5 when assessed against reported intakes from weighed food records (13). In addition, this FFQ provides reasonable rankings (≥70% correctly classified within the same ±1 quartile) according to carotenoids, Vitamin E, and fruit and vegetable intakes when validated against plasma biomarkers (14).

For the current analyses, dietary intakes of carotenoids, Vitamin E, fatty acids, fruits and vegetables were of interest. Carotenoids, Vitamin E, and fruits and vegetables have well-established anti-inflammatory properties (15-17), and different types of fatty acids have been shown to exert pro-inflammatory (e.g. SFA) (11) and anti-inflammatory properties (e.g. n-3

PUFA) (6). Estimates of carotenoids and Vitamin E were calculated using the U.S. Department of Agriculture Nutrient Database for Standard Reference, Release 19 (18) as it is the most comprehensive in regard to these nutrients. Intakes of other nutrients including fatty acids were derived from NUTTAB 2006 – an Australian nutrient composition database (19). Dietary supplement information was obtained from manufacturers and added to the database. Fruit and vegetable intakes were calculated in servings based on the definition set by the Australian Dietary Guidelines (e.g. one serving fruit = 1 medium-sized fruit; one serving of vegetables = ½ cup cooked vegetables) (20). Fruit and vegetable intakes were also categorized into "carotenoid-rich" or "other". Carotenoid-rich fruits or vegetables were defined as those that contributed ≥10% of total carotenoid intakes (fruits: apricots, peaches, melons, citrus fruits, plums or prunes and paw-paw; vegetables: broccoli, spinach or silver beets, carrots, pumpkins, sweet potatoes, peas, corns and tomatoes). Other types of fruits included grapes, berries, mangoes, pineapple, apples, and banana. Other types of vegetables included potatoes (not fried), green beans, eggplant or zucchini, mushrooms, cabbages, Brussel sprouts, lettuces, celery and bean sprouts.

7.3.3 Assessment of nutrient biomarkers

Data for nutrient biomarkers were available for 150 subjects, as part of the validation study of the Older Australian's FFQ (14). Plasma concentrations of carotenoids and Vitamin E (α-tocopherol) were included as they are reliable markers of dietary intake (21). At baseline, blood samples were collected from 2534 participants at the HCS clinic after an overnight (12-hour) fast. Venipuncture of the left antecubital vein was performed with tourniquet. All blood samples were collected into EDTA tubes and centrifuged at 4^{o}C and 3000g for 10 minutes, which was stored in approximately 1mL aliquots, cryopreserved in dimethyl sulfoxide at -80^{o}C immediately after collection (12), and thawed just prior to analysis. This subset was randomly selected from 2420 participants with complete FFQ data and provided sufficient volume of blood sample, with equal representation across gender, age groups (<65, 65+), and quintiles of energy intake. Plasma carotenoids concentrations were determined using the high performance liquid chromatography method (22) at the University of Newcastle's Priority Research Centre for Asthma and Respiratory Diseases laboratory (New South Wales, Australia).

7.3.4 Assessment of inflammatory markers

Blood samples were collected and stored as described above. High sensitivity CRP was analyzed via CRP Flex System on Dimension Vista System immunonephelometry (Siemens Health care Diagnostics, Newark, DE, USA). The limit of detection was 0.16mg/L and coefficient of variation was 4.8%. High sensitivity IL-6 was analyzed via Access IL-6 magnetic bead/chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA, ref A16369), performed on a Beckman Dxl. The lower limit of detection was 0.5pg/mL and coefficient of variation was 12%. All assays were performed by the Hunter Area Pathology Service – a National Association of Testing Authorities accredited laboratory.

7.3.5 Assessment of depressive symptoms

Depressive symptoms were measured at baseline and at follow-up using the Centre for Epidemiologic Studies-Depression scale (CES-D) – a self-reported measure of depressive symptoms in the general population (23). The criterion and construct validity of CES-D has been well established (23). Participants were asked to score the frequency of occurrence of specific symptoms during the previous week on a four-point scale, ranging from less than 1 day to 5-7 days. These were summed to yield a total score between 0-60 with higher scores indicating greater depressive symptoms.

7.3.6 Assessment of covariates

A number of potential confounding variables were identified. Socio-demographic variables included: age, marital status (never married, married/de facto, widowed, divorced/separated), annual household income ($0-19, 999, $20 000-39 999, $30 000-69 999, ≥$70 000), and education (primary/secondary schooling only, trade qualification or TAFE, University or other tertiary study). Health behavior indicators were smoking status (current smokers, former smokers, never smoked), physical activity (defined as mean pedometer step counts/day), and body mass index (BMI). Medical conditions included were self-reported diabetes, stroke, heart attack and depression/anxiety disorder. Use of antidepressants was also included as a potential confounder. In addition, all analyses were performed separately for males and females to account for gender differences in inflammatory markers and depressive symptoms as observed in a previous study (24).

7.3.7 Statistical analyses

Dietary intakes of carotenoids, fatty acids, fruits and vegetables were energy-adjusted using the residual method (21). Adjusting for total energy intake accounts for between-person variation in total energy intake as a result of physiological differences (e.g. body size and physical activity), thereby reducing the potentially confounding effects of total energy intake. Each dietary variable (nutrient or food intake and nutrient biomarkers) was categorized into quartiles, and for all further analyses, they were entered into the models as quartiles (using the lowest quartile as reference) and as ordinal variables (tests of linear trend across quartiles). As for inflammatory markers and depressive symptoms, they were treated as continuous variables.

Baseline demographics, dietary and clinical characteristics were compared between genders to account for gender differences in inflammatory markers and depression prevalence, using chi-square tests for categorical variables and t-tests for continuous variables. Data are presented as means ± standard deviations, or number of participants and percentages.

Cross-sectional and longitudinal analyses were undertaken to determine if inflammatory markers were related to the exposure (diet) and outcome (depressive symptoms). Cross-sectional diet-inflammation associations were examined using linear regression models with the respective dietary variable as the predictor and inflammatory marker as outcome, adjusting for baseline values of age, smoking status and physical activity. Longitudinal inflammation-depression associations were examined using linear mixed models in which baseline inflammatory marker predicts follow-up depressive symptoms, with random subject level effects and fixed effects, adjusting for baseline values of age, smoking status, physical activity, BMI, use of antidepressants and all medical conditions.

The total effects of quartiles of each dietary variable on depressive symptoms (study aim 1) were examined using linear mixed models, with random subject level effects and fixed effects, adjusting for baseline values of age, marital status, income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.

To explore the potential mediating effects of inflammatory markers (study aim 2), when significant associations between dietary intake and depressive symptoms were identified, the total effect were partitioned into direct (dietary intake on depressive symptoms independent of

inflammation) and indirect effect (mediation via inflammatory markers) using parametric simulations (25, 26) with the Stata Mediation package (27). The models included baseline dietary variables as predictors, baseline inflammatory markers as mediators, and depressive symptoms at follow-up as the outcome.

All analyses were conducted using Stata version 13 (StataCorp LP, TX, USA). Data are presented as coefficients and 95% confidence intervals (unless otherwise specified). Distributions of CRP, IL-6 and CES-D were skewed thus were long-transformed before all analyses to comply with modelling assumptions. We used all available data from each participant under the missing-at-random assumption. Due to the large number of hypothesis tests carried out, the significance level was set at $P<0.01$, and $P<0.05$ were considered as suggestive evidence.

Sensitivity analyses were conducted excluding participants with high concentrations of inflammatory markers (CRP>10mg/L based on cut-off points suggested by Clyne and Olshaker (28) and IL-6>23 pg/L which is more than 3 standard deviations above the mean) as concentrations of inflammatory markers are highly influenced by acute illness. No participants in the subgroup with nutrient biomarkers had unusually high IL-6, thus sensitivity analyses were only carried out for nutrient biomarkers and CRP. In addition, for analyses examining the association between dietary intake and CES-D, stratified analyses were performed according to use of vitamins or fish oil supplements to examine if intake of dietary supplements influences the initial associations observed.

7.4 Results

7.4.1 Sample characteristics

Table 7.1 describes the baseline characteristics of 2035 participants included in this study. A greater proportion of participants was females (52%), married (74.8%), low-to-middle income earners (75.0%), and most received education up to trade qualification. Females were less likely to smoke, have lower physical activity level and BMI but had higher CESD score, and a lower proportion of them suffered from diabetes, stroke, heart attack, or depression and/or

anxiety. For dietary intakes, females had lower energy intake, higher total and individual carotenoids (except lycopene) and fruit and vegetable intakes, and lower total and individual fatty acid intakes compared to males.

Table 7.1: Baseline participant characteristics of the Hunter Community Study included in analyses examining inflammatory markers as mediators of associations between diet and depression (*n*=2035)

Participant characteristics	**Males (*n*=970)**	**Females (*n*=1065)**	***P***
Age, mean ± SD	66.7 ± 7.7	65.9 ± 7.3	0.007
Marital status, *n* (%)			<0.001
Married/de facto	805 (85.2)	719 (69.3)	
Divorced/separated	75 (7.9)	136 (13.1)	
Widowed	35 (3.7)	156 (15.0)	
Never married	30 (3.2)	27 (2.6)	
Annual household income, *n* (%)			<0.001
$0-19, 999	191 (20.8)	294 (30.4)	
$20 000-39 999	300 (32.7)	296 (30.6)	
$30 000-69 999	225 (24.5)	220 (22.8)	
≥$70 000	201 (21.9)	157 (16.2)	
Highest Education, *n* (%)			<0.001
Primary/secondary schooling	324 (34.4)	551 (53.2)	
Trade qualification or TAFE	327 (34.8)	187 (18.1)	
University or other tertiary study	248 (26.4)	227 (21.9)	
No education	42 (4.5)	71 (6.9)	
Smoking status, *n* (%)			<0.001
Never smoke	395 (41.6)	698 (66.9)	
Ex-smoker	478 (50.4)	277 (26.6)	
Current smoker	68 (7.2)	57 (5.5)	
Physical activity – movement counts, mean ± SD	75.1 ± 73.6	72.8 ± 72.8	0.538
Body mass index, mean ± SD	28.8 ± 4.1	28.6 ± 5.4	0.284
Centre for Epidemiologic Studies-Depression scale, mean ± SD	6.5 ± 8.1	7.5 ± 7.9	0.005
Diabetes, *n* (%)	100 (10.7)	83 (8.1)	0.05
Stroke, *n* (%)	36 (3.8)	27 (2.6)	0.131
Heart attack, *n* (%)	92 (9.8)	26 (2.5)	<0.001
Depression/anxiety, *n* (%)	143 (15.3)	270 (26.4)	<0.001
Interleukin-6, mean ± SD	4.9 ± 32.3	4.7 ± 32.6	0.906
C-reactive protein, mean ± SD	3.3 ± 6.0	3.7 ± 5.4	0.133
Nutrient intakes, mean ± SD			
Energy, kJ/day	8648 ± 2781	7810 ± 2606	<0.001
Total carotenoids, µg/day	20816 ± 13899	23117 ± 13380	<0.001
α-carotene, µg/day	1845 ± 2324	1972 ± 2110	0.209
β-carotene, µg/day	7996 ± 6170	9343 ± 6274	<0.001
β-cryptoxanthin, µg/day	575 ± 404	609 ± 412	0.067
Lycopene, µg/day	233 ± 7008	177 ± 5646	0.567
Lutein + zeaxanthin, µg/day	3889 ± 2623	4517 ± 3075	<0.001
Vitamin E, mg/day	6 ± 3	6 ± 3	<0.001
Total fat, g/day	62 ± 24	56 ± 25	<0.001
Saturated fat, g/day	24 ± 10	22 ± 11	<0.001
Monounsaturated fat, g/day	21 ± 8	19 ± 9	<0.001
Polyunsaturated fat, g/day	9 ± 4	9 ± 4	<0.001
Long-chain Omega-3 fat, mg/day	59 ± 25	56 ± 29	0.031

Table 7.1 *(Continued)*

Participant characteristics	Males (*n*=59)	Females (*n*=52)	*P*
Fruits and vegetables intakes, mean ± SD			
Total fruits, servings/day	3 ± 2	4 ± 3	<0.001
Carotenoid-rich fruits, servings/day	1 ± 1	1 ± 1	<0.001
'Other fruits', servings/day	2 ± 1	2 ± 2	<0.001
Total vegetables, servings/day	5 ± 2	5 ± 2	<0.001
Carotenoid-rich vegetables, servings/day	3 ± 2	4 ± 2	<0.001
'Other vegetables', servings/day	2 ± 1	2 ± 1	<0.001
Nutrient biomarkers (n=111), mean ± SD			
Plasma carotenoids	1.23 ± 0.66	1.36 ± 0.75	0.312
Plasma *α*-carotene	0.07 ± 0.06	0.08 ± 0.07	0.404
Plasma *β*-carotene	0.28 ± 0.25	0.36 ± 0.32	0.116
Plasma *β*-cryptoxanthin	0.15 ± 0.15	0.14 ± 0.10	0.738
Plasma Lycopene	0.29 ± 0.21	0.27 ± 0.22	0.620
Plasma Lutein + zeaxanthin	0.44 ± 0.20	0.51 ± 0.34	0.191
Plasma *α*-tocopherol	12.71 ± 3.23	14.46 ± 4.08	0.013

7.4.2 Diet-Inflammation relationship

Figure 7.1 summarizes the significant cross-sectional associations between dietary variables and nutrient biomarkers as ordinal variables, and inflammatory markers (further details including study estimates for each quartile of dietary variables compared to the lowest quartile are included in **Supplementary Table 7.6.1 and Supplementary Table 7.6.2**).

For females, total dietary carotenoids, α-carotene (suggestive evidence), lutein + zeaxanthin intakes were negatively associated with IL-6. Intake of Vitamin E was not linearly associated with IL-6, but reduced IL-6 concentration was associated with the highest quartile of intake compared to the lowest quartile (*β*= -0.190, 95% CI= -0.361, -0.019). None of the dietary carotenoids were linearly associated with IL-6 in males, but there was suggestive evidence that Vitamin E intake was negatively associated with IL-6. There was suggestive evidence that vegetables and 'other fruits' intakes were negatively associated with IL-6 in females, but none of the associations observed were significant in males. No significant associations between fatty acid intakes or nutrients biomarkers and IL-6 were observed in either males or females, except that the highest quartile of plasma Vitamin E was associated with reduced IL-6 concentration.

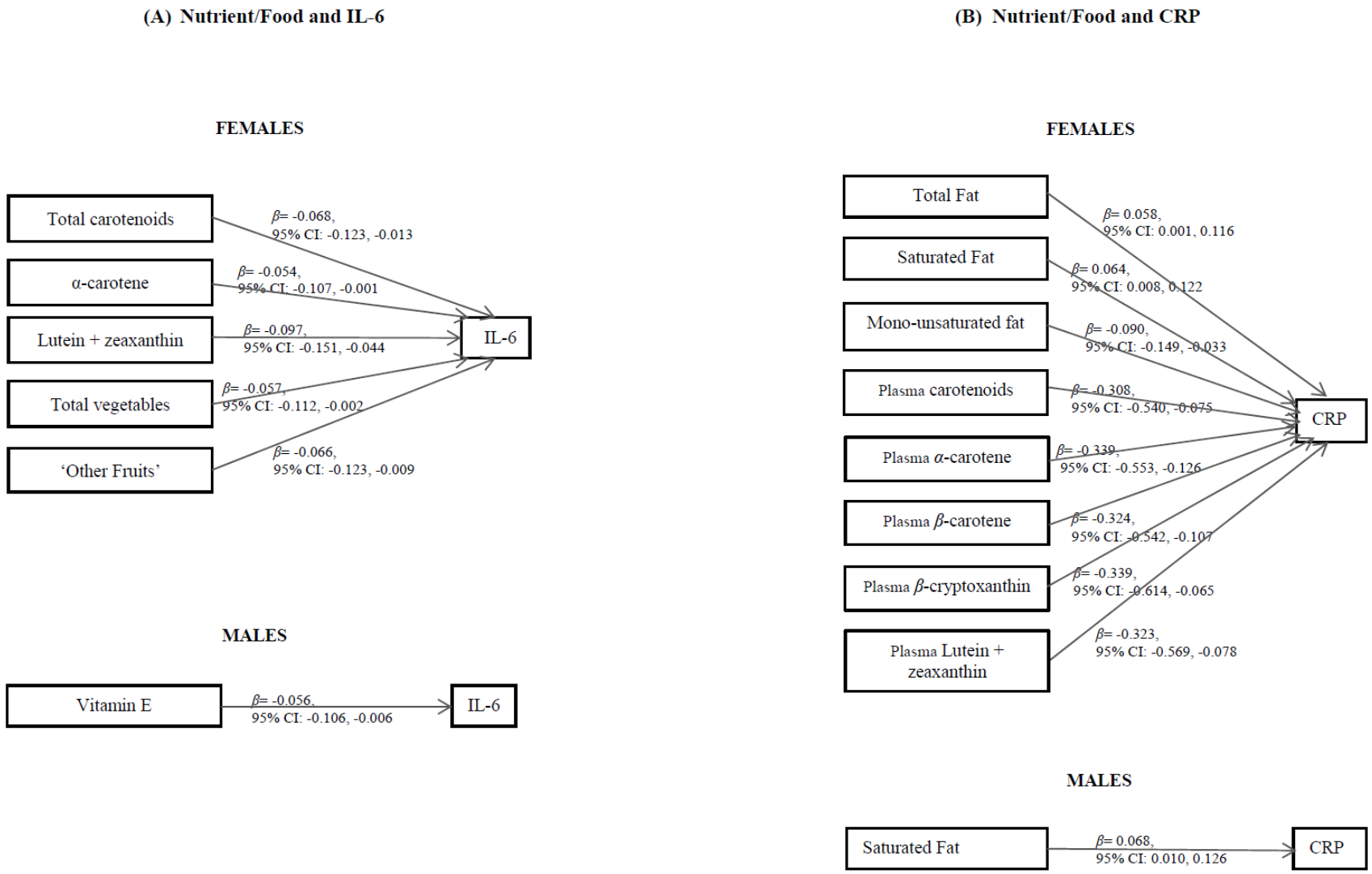

Figure 7.1: Coefficients (β) and 95% Confidence Intervals (CI) showing significant associations (P<0.05) between baseline dietary intakes or nutrient biomarkers, and (A) interleukin (IL)-6 or (B) C-reactive protein (CRP) in females and males. Further details are included in the online supplementary files to the article (Supplementary Tables 7.6.1 and 7.6.2).

No significant associations between carotenoids and Vitamin E intakes, and CRP were observed for either gender. Total fat intake was positively associated with CRP (suggestive evidence), whereas mono-unsaturated fat (MUFA) was inversely related to CRP in females. Saturated fat showed suggestive evidence of a positive association with CRP in both genders. All plasma carotenoids were inversely associated with CRP in females except lycopene. The highest quartile of lycopene was significantly associated with lower CRP levels compared to the lowest quartile (*β*= -0.840, 95% CI= -1.629, -0.051) although the linear trend with CRP was non-significant.

7.4.3 Inflammation-Depression relationship

Both IL-6 (*β*= 0.124, 95% CI= 0.043, 0.205, *P*= 0.003) and CRP (*β*= 0.098, 95% CI= 0.028, 0.168, *P*= 0.006) were significantly associated with CES-D in females, and CRP showed suggestive evidence of a positive association with CES-D in males (*β*= 0.061, 95% CI= 0.007, 0.139, *P*= 0.048).

7.4.4 Diet-Depression relationship

No significant associations were observed between dietary carotenoids and Vitamin E, and depressive symptoms for either males or females (**Table 7.2**). There was suggestive evidence that fruit intake was negatively associated with depressive symptoms (females: *β*= -0.060, *P*-trend= 0.047; males: *β*= -0.027, *P*-trend= 0.025) but when carotenoids-rich fruits and 'other fruits' were examined separately, only 'other fruits' showed a suggestive evidence of a negative association with depressive symptoms (females: *β*= -0.061, *P*-trend= 0.042; males: *β*= -0.068, *P*-trend= 0.023).

Total fat and SFA intakes showed suggestive evidence of a positive association with depressive symptoms in females (Total fat: *β*= 0.074, *P*-trend= 0.019; SFA: *β*= 0.067, *P*-trend= 0.027), whereas in males a significant positive association were observed (Total fat: *β*= 0.098, *P*-trend= 0.001; SFA: *β*= 0.104, *P*-trend<0.001). Mono-unsaturated fat was inversely associated with depressive symptoms in both genders (females: *β*= -0.091, *P*-trend= 0.003; males: *β*= -0.111, *P*-trend<0.001). Among males, n-3 PUFA were inversely associated with CES-D (*β*= -0.101, *P*-trend= 0.003).

No significant linear trends were observed between total plasma carotenoids and plasma *β*-carotene and CES-D score, but there was suggestive evidence that highest concentrations of these nutrient biomarkers were associated with greatest reduction in CES-D score in males. Plasma lutein + zeaxanthin showed suggestive evidence of an inverse association with CES-D score in males (*β*= -0.239, *P*-trend= 0.020). No associations between nutrient biomarkers and CES-D score were observed in females.

Table 7.2: Longitudinal associations between quartiles of baseline dietary intake or nutrient biomarkers, and Centre for Epidemiologic Studies-Depression scale (CES-D), stratified by sex, in the Hunter Community Study (n=1466) [a, b].

	β (95% CI) for CES-D			
	Q2	Q3	Q4	*P*
Females (n=729)				
Dietary Intakes				
Total carotenoids	-0.013 (-0.194, 0.169)	0.093 (-0.089, 0.275)	-0.069 (-0.245, 0.107)	0.620
Alpha-carotene	-0.093 (-0.269, 0.084)	-0.040 (-0.213, 0.133)	-0.104 (-0.276, 0.068)	0.351
Beta-carotene	0.097 (-0.087, 0.280)	0.039 (-0.141, 0.220)	-0.054 (-0.231, 0.123)	0.331
Beta-cryptoxanthin	0.088 (-0.086, 0.263)	-0.018 (-0.194, 0.157)	-0.051 (-0.227, 0.125)	0.327
Lycopene	0.088 (-0.095, 0.271)	0.009 (-0.163, 0.182)	0.115 (-0.059, 0.289)	0.344
Lutein+zeaxanthin	-0.088 (-0.269, 0.094)	-0.039 (-0.223, 0.144)	-0.049 (-0.225, 0.127)	0.800
Vitamin E	0.006 (-0.173, 0.184)	-0.028 (-0.205, 0.148)	-0.011 (-0.187, 0.164)	0.810
Total Fruits	-0.084 (-0.270, 0.101)	-0.144 (-0.321, 0.033)	**-0.189 (-0.369, -0.009)**	**0.047**
Carotenoids-rich fruits	0.081 (-0.101, 0.263)	-0.155 (-0.331, 0.021)	0.002 (-0.168, 0.172)	0.503
Other fruits	-0.072 (-0.257, 0.113)	-0.121 (-0.300, 0.058)	**-0.166 (-0.312, -0.049)**	**0.042**
Total Vegetables	0.049 (-0.133, 0.231)	0.055 (-0.133, 0.243)	0.020 (-0.155, 0.195)	0.889
Carotenoids-rich vegetables	0.133 (-0.053, 0.318)	0.033 (-0.158, 0.224)	0.050 (-0.131, 0.230)	0.978
Other vegetables	-0.105 (-0.280, 0.071)	-0.125 (-0.304, 0.054)	-0.100 (-0.270, 0.070)	0.280
Total fat	0.028 (-0.127, 0.182)	0.172 (-0.008, 0.335)	**0.198 (0.009, 0.388)***	**0.019**
Saturated fat	0.054 (-0.101, 0.210)	0.107 (-0.058, 0.271)	**0.173 (0.010, 0.356)***	**0.027**
Mono-unsaturated fat	-0.007 (-0.161, 0.148)	**-0.213 (-0.377, -0.048)**	**-0.218 (-0.306, -0.030)***	**0.003***
Poly-unsaturated fat	0.018 (-0.143, 0.179)	-0.115 (-0.279, 0.050)	0.081 (-0.097, 0.259)	0.201
Long-chain Omega-3	0.081 (-0.097, 0.259)	-0.020 (-0.191, 0.151)	-0.039 (-0.213, 0.135)	0.420
Nutrient Biomarkers (n=75)				
Total carotenoids	0.357 (-0.447, 1.161)	0.247 (-0.412, 0.905)	-0.409 (-1.137, 0.318)	0.318
α-carotene	0.079 (-0.653, 0.811)	0.009 (-0.670, 0.687)	-0.263 (-0.910, 0.384)	0.446
β-carotene	0.279 (-0.458, 1.016)	-0.138 (-0.833, 0.557)	-0.039 (-0.700, 0.621)	0.684
β-cryptoxanthin	-0.576 (-1.339, 0.187)	-0.095 (-0.803, 0.614)	-0.512 (-1.420, 0.395)	0.832
Lycopene	-0.182 (-0.957, 0.594)	0.563 (-0.055, 1.180)	-0.172 (-0.845, 0.501)	0.727
Lutein+zeaxanthin	-0.140 (-0.834, 0.554)	0.124 (-0.658, 0.905)	-0.765 (-1.535, 0.005)	0.084
Vitamin E	1.242 (-0.100, 1.784)	0.533 (-0.078, 1.144)	0.653 (-0.004, 1.310)	0.304

Table 7.2 *(Continued)*

	β (95% CI) for CES-D			
	Q2	Q3	Q4	*P*
Males (n=737)				
Dietary Intakes				
Total carotenoids	0.021 (-0.137, 0.179)	-0.014 (-0.180, 0.153)	-0.039 (-0.212, 0.135)	0.620
α-carotene	-0.071 (-0.232, 0.151)	-0.017 (-0.144, 0.208)	0.032 (-0.009, 0.010)	0.642
β-carotene	-0.087 (-0.245, 0.071)	0.024 (-0.139, 0.188)	-0.008 (-0.184, 0.168)	0.806
β-cryptoxanthin	-0.003 (-0.168, 0.162)	-0.008 (-0.177, 0.160)	-0.018 (-0.196, 0.159)	0.834
Lycopene	-0.122 (-0.283, 0.038)	-0.144 (-0.317, 0.029)	-0.120 (-0.289, 0.048)	0.149
Lutein+zeaxanthin	0.027 (-0.134, 0.188)	0.049 (-0.117, 0.215)	0.003 (-0.171, 0.176)	0.863
Vitamin E	-0.087 (-0.247, 0.073)	0.109 (-0.058, 0.277)	0.088 (-0.082, 0.259)	0.114
Total Fruits	-0.042 (-0.215, 0.131)	-0.070 (-0.228, 0.087)	**-0.204 (-0.370, -0.037)***	**0.025**
Carotenoids-rich fruits	-0.007 (-0.166, 0.152)	-0.104 (-0.269, 0.061)	-0.055 (-0.235, 0.124)	0.316
Other fruits	-0.075 (-0.246, 0.095)	-0.200 (-0.368, 0.003)	**-0.205 (-0.365, -0.046)***	**0.023**
Total Vegetables	-0.025 (-0.186, 0.137)	-0.137 (-0.298, 0.025)	-0.133 (-0.316, 0.049)	0.063
Carotenoids-rich vegetables	0.066 (-0.096, 0.228)	-0.134 (-0.293, 0.025)	-0.037 (-0.219, 0.146)	0.217
Other vegetables	0.023 (-0.138, 0.184)	-0.072 (-0.237, 0.092)	0.007 (-0.167, 0.181)	0.741
Total fat	0.115 (-0.076, 0.305)	0.155 (-0.036, 0.347)	**0.303 (0.125, 0.482)***	**0.001***
Saturated fat	0.156 (-0.031, 0.344)	**0.247 (0.065, 0.428)**	**0.279 (0.102, 0.455)***	**0.002***
Mono-unsaturated fat	-0.021 (-0.210, 0.167)	-0.074 (-0.263, 0.114)	**-0.324 (-0.502, -0.146)***	**<0.001***
Poly-unsaturated fat	-0.004 (-0.186, 0.180)	-0.107 (-0.288, 0.074)	0.091 (-0.081, 0.263)	0.175
Long-chain Omega-3	-0.105 (-0.269, 0.059)	-0.109 (-0.279, 0.061)	**-0.276 (-0.447, -0.105)***	**0.003***
Nutrient Biomarkers (n=75)				
Total carotenoids	-0.571 (-1.106, 0.036)	0.162 (-0.531, 0.856)	**-0.695 (-1.257, -0.134)**	0.082
α-carotene	0.101 (-0.510, 0.711)	-0.118 (-0.838, 0.602)	-0.159 (-0.808, 0.491)	0.538
β-carotene	-0.346 (-0.928, 0.236)	0.069 (-0.510, 0.679)	**-0.939 (-1.730, -0.149)**	0.184
β-cryptoxanthin	-0.094 (-0.730, 0.541)	-0.165 (-0.836, 0.507)	-0.290 (-0.941, 0.360)	0.365
Lycopene	-0.301 (-1.001, 0.398)	-0.635 (-1.374, 0.105)	-0.611 (-1.238, 0.017)	0.339
Lutein+zeaxanthin	-0.514 (-1.084, 0.552)	**-0.662 (-1.309, -0.016)**	**-0.815 (-1.502, -0.127)***	**0.020**
Vitamin E	-0.344 (-0.883, 0.196)	-0.415 (-1.143, 0.312)	-0.170 (-0.789, 0.449)	0.478

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles. *P*<0.05 in bold. **P*<0.01.

[a] All models adjusted for baseline values of age, marital status, annual household income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.

7.4.5 Inflammatory markers as mediators of diet-depression relationships

IL-6 was a significant mediator of the association between 'other fruits' and CES-D in females (**Table 7.3**), as indicated by a small but significant indirect effect of -0.0006 (i.e. 1% of total effect). Most of the effect of 'other fruits' on CES-D is independent of IL-6 (direct effect: -0.0605). CRP significantly mediated the relationship between total fat, SFA and MUFA intakes and depressive symptoms in females (**Table 7.4**), and the percentage of total effects explained by CRP was approximately 6-7% for each. Among males, CRP was a significant mediator between saturated fat intake and CES-D, but the mediating effect was 2% out of a total effect of 0.122.

Table 7.3: Interleukin-6 as mediator of the associations between dietary intakes or nutrient biomarkers and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study (n=1466)[a, b]

	Females (n=729)			Males (n=737)		
	β (95% CI)	*P*	Direct vs Indirect Effects	*β* (95% CI)	*P*	Direct vs Indirect Effects
Total Fruits	-0.060 (-0.119, -0.001)	0.048	Direct: -0.0591 (-0.1160, -0.0004)	-0.028 (-0.083, -0.008)	0.036	Direct: -0.0269 (-0.0801, -0.0005)
Q4 vs Q1	-0.228 (-0.440, -0.015)	0.036	Indirect: -0.0005 (-0.0047, 0.0026)	-0.146 (-0.336, -0.044)	0.023	Indirect: -0.0015 (-0.0071,
Q3 vs Q1	-0.204 (-0.411, 0.004)	0.055		-0.060 (-0.236, 0.116)	0.505	0.0034)
Q2 vs Q1	-0.139 (-0.356, 0.077)	0.206		-0.028 (-0.219, 0.163)	0.773	
Other fruits	-0.061 (-0.120, -0.002)	0.042	Direct: -0.0605 (-0.1167, -0.0025)	-0.063 (-0.083, -0.002)	0.032	Direct: -0.0645 (-0.0803, -0.0008)
Q4 vs Q1	-0.245 (-0.456, -0.034)	0.023	**Indirect: -0.0006 (-0.0022, -0.0001)**	-0.156 (-0.337, -0.024)	0.010	Indirect: 0.0020 (-0.0026, 0.0075)
Q3 vs Q1	-0.205 (-0.412, 0.002)	0.053	**% total effect mediated: 1%**	-0.155 (-0.342, 0.032)	0.104	
Q2 vs Q1	-0.131 (-0.344, 0.083)	0.230		-0.052 (-0.243, 0.138)	0.589	
Total fat	0.074 (0.012, 0.135)	0.019	Direct: 0.0740 (0.0154, 0.1344)	0.104 (0.041, 0.156)	0.001	Direct: 0.0980 (0.0435, 0.1559)
Q4 vs Q1	0.197 (0.011, 0.383)	0.038	Indirect: 0.0003 (-0.0033, 0.0040)	0.322 (0.117, 0.527)	0.002	Indirect: 0.0059 (-0.0003, 0.0138)
Q3 vs Q1	0.180 (-0.044, 0.404)	0.115		0.161 (-0.056, 0.377)	0.145	
Q2 vs Q1	0.068 (-0.108, 0.243)	0.451		0.161 (-0.098, 0.330)	0.287	
Saturated fat	0.067 (0.008, 0.127)	0.027	Direct: 0.0678 (0.0107, 0.1267)	0.110 (0.058, 0.162)	0.001	Direct: 0.1048 (0.0499, 0.1616)
Q4 vs Q1	0.198 (0.010, 0.386)	0.039	Indirect: 0.0001 (-0.0037, 0.0033)	0.334 (0.132, 0.536)	0.001	Indirect: 0.0047 (-0.0004, 0.0119)
Q3 vs Q1	0.139 (-0.073, 0.351)	0.200		0.262 (0.058, 0.467)	0.012	
Q2 vs Q1	0.062 (-0.112, 0.236)	0.485		0.180 (-0.033, 0.392)	0.097	
Mono-unsaturated fat	-0.092 (-0.152, -0.030)	0.003	Direct: -0.0919 (-0.1521, -0.0336)	-0.118 (-0.169, -0.054)	0.001	Direct: -0.1115 (-0.1683, -0.0564)
Q4 vs Q1	-0.236 (-0.454, -0.017)	0.035	Indirect: -0.0001 (-0.0033, 0.0038)	-0.324 (-0.527, -0.121)	0.002	Indirect: -0.0063 (-0.0004,
Q3 vs Q1	-0.215 (-0.403, -0.026)	0.026		-0.044 (-0.254, -0.015)	0.069	0.0145)
Q2 vs Q1	-0.024 (-0.198, 0.151)	0.792		-0.007 (-0.217, 0.204)	0.494	
Long-chain Omega-3				-0.102 (-0.159, -0.044)	0.001	Direct: -0.1019 (-0.1586, -0.0469)
Q4 vs Q1				-0.339 (-0.537, -0.141)	0.001	Indirect: -0.0002 (-0.0057,
Q3 vs Q1				-0.167 (-0.352, 0.019)	0.079	0.0047)
Q2 vs Q1				-0.126 (-0.379, 0.066)	0.199	
Plasma lutein + zeaxanthin[c]				-0.234 (-0.439, -0.039)	0.020	Direct: -0.2377 (-0.4248, -0.0447)
Q4 vs Q1				-0.936 (-1.613, -0.258)	0.007	Indirect: 0.0033 (-0.0271, 0.0484)
Q3 vs Q1				-0.835 (-1.441, -0.230)	0.006	
Q2 vs Q1				-0.801 (-1.383, -0.219)	0.008	

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles. *P*<0.01 in bold.

[a] Mediation analyses were carried out where there are significant associations between dietary intake or nutrient biomarkers and depressive symptoms. Total effects were partitioned into Direct effects (dietary intake on depressive symptoms independent of inflammation) and Indirect effects (mediation via inflammatory markers).

[b] All models adjusted for age, marital status, annual household income, education, smoking status, physical activity, BMI, use of antidepressants and self-reported depression/anxiety disorder, diabetes, stroke and heart attack.

[c] *n*=59 for males

Table 7.4: C-reactive protein as mediator of the associations between dietary intakes, nutrient biomarkers and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study (n=1466)[a, b]

	Females (n=729)			Males (n=737)		
	β (95% CI)	*P*	Direct vs Indirect Effects	*β* (95% CI)	*P*	Direct vs Indirect Effects
Total Fruits	-0.046 (-0.099, -0.014)	0.014	Direct: -0.0419 (-0.0957, -0.0036)	-0.033 (-0.088, -0.020)	0.025	Direct: -0.0331 (-0.0848, -0.0103)
Q4 vs Q1	-0.216 (-0.414, -0.017)	0.033	Indirect: -0.0040 (-0.0105, 0.0003)	-0.177 (-0.358, -0.005)	0.007	Indirect: 0.0003 (-0.0023, 0.0036)
Q3 vs Q1	-0.164 (-0.369, 0.040)	0.114		-0.053 (-0.225, 0.119)	0.547	
Q2 vs Q1	-0.154 (-0.349, 0.042)	0.123		-0.031 (-0.217, 0.154)	0.741	
Other fruits	-0.055 (-0.108, -0.010)	0.021	Direct: -0.0452 (-0.0990, -0.0014)	-0.031 (-0.085, -0.003)	0.026	Direct: -0.0305 (-0.0821, -0.0027)
Q4 vs Q1	-0.205 (-0.403, -0.007)	0.043	Indirect: -0.0099 (-0.0122, 0.0001)	-0.190 (-0.364, -0.015)	0.033	Indirect: -0.0008 (-0.0045, 0.0017)
Q3 vs Q1	-0.159 (-0.357, 0.038)	0.113		-0.161 (-0.343, 0.020)	0.081	
Q2 vs Q1	-0.132 (-0.334, 0.070)	0.200		-0.067 (-0.252, 0.117)	0.474	
Total fat	0.086 (0.023, 0.138)	0.006	Direct: 0.0812 (0.0262, 0.1382)	0.121 (0.063, 0.174)	0.001	Direct: 0.1191 (0.0657, 0.1741)
Q4 vs Q1	0.226 (0.017, 0.435)	0.034	**Indirect: 0.0047 (0.0003, 0.0127)**	0.385 (0.188, 0.582)	0.001	Indirect: 0.0016 (-0.0014, 0.0067)
Q3 vs Q1	0.150 (-0.027, 0.327)	0.098	**% total mediated effect: 5.8%**	0.222 (0.013, 0.431)	0.037	
Q2 vs Q1	0.021 (-0.147, 0.188)	0.810		0.189 (-0.017, 0.396)	0.072	
Saturated fat	0.082 (0.020, 0.133)	0.008	Direct: 0.0767 (0.0225, 0.1327)	0.122 (0.064, 0.175)	0.001	Direct: 0.1199 (0.0666, 0.1750)
Q4 vs Q1	0.192 (-0.009, 0.394)	0.062	**Indirect: 0.0051 (0.0003, 0.0135)**	0.372 (0.177, 0.566)	0.001	**Indirect: 0.0024 (0.0004, 0.0102)**
Q3 vs Q1	0.158 (-0.021, 0.338)	0.084	**% total mediated effect: 6.7%**	0.315 (0.119, 0.512)	0.002	**% total mediated effect: 2.0%**
Q2 vs Q1	0.053 (-0.114, 0.220)	0.533		0.214 (0.008, 0.419)	0.041	
Mono-unsaturated fat	-0.107 (-0.158, -0.042)	0.001	Direct: -0.1006 (-0.1577,-0.0453)	-0.125 (-0.179, -0.069)	0.001	Direct: -0.1247 (-0.1791, -0.0720)
Q4 vs Q1	-0.271 (-0.476, -0.065)	0.010	**Indirect: -0.0065 (-0.0171, -0.0011)**	-0.370 (-0.564, -0.176)	0.001	Indirect: -0.0001 (-0.0033, 0.0031)
Q3 vs Q1	-0.195 (-0.375, -0.015)	0.034		-0.075 (-0.278, 0.128)	0.470	
Q2 vs Q1	-0.006 (-0.172, 0.160)	0.945	**% total mediated effect: 6.1%**	-0.021 (-0.224, 0.182)	0.840	
Long-chain Omega-3				-0.106 (-0.160, -0.049)	0.001	Direct: -0.1051 (-0.1596, -0.0523)
Q4 vs Q1				-0.348 (-0.537, -0.158)	0.001	Indirect: -0.0008 (-0.0051, 0.0017)
Q3 vs Q1				-0.179 (-0.357, -0.001)	0.050	
Q2 vs Q1				-0.125 (-0.309, 0.059)	0.184	
Plasma lutein + zeaxanthin[c]				-0.219 (-0.415, -0.004)	0.04	Direct: -0.2038 (-0.4003, -0.0011)
Q4 vs Q1				-0.823 (-1.504, -0.143)	0.018	Indirect: -0.0151 (-0.0756, 0.0295)
Q3 vs Q1				-0.579 (-1.157, -0.001)	0.050	
Q2 vs Q1				-0.619 (-1.263, 0.026)	0.060	

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles. *P*<0.01 in bold

[a] Mediation analyses were carried out where there are significant associations between dietary intake or nutrient biomarkers and depressive symptoms. Total effects were partitioned into Direct effects (dietary intake on depressive symptoms independent of inflammation) and Indirect effects (mediation via inflammatory markers).

[b] All models adjusted for age, marital status, annual household income, education, smoking status, physical activity, BMI, use of antidepressants and self-reported depression/anxiety disorder, diabetes, stroke and heart attack.

[c] *n*=59 for males

7.4.6 Sensitivity analyses

Similar results were observed after the exclusion of participants with extreme inflammatory markers concentrations. Associations between total dietary carotenoids, α-carotene, lutein + zeaxanthin, 'other fruits', and IL-6 in females, and dietary Vitamin E and IL-6 in males remained significant (**Supplementary Table 7.6.3**). Similarly, associations between MUFA, plasma carotenoids and CRP in females, and SFA and CRP in both gender groups observed in the initial analyses remained significant (**Supplementary Table 7.6.4**). In addition, a significant association between intake of 'other fruits' and IL-6 in males, that was not initially observed, was demonstrated in the sensitivity analyses. IL-6 remained a significant mediator of the association between 'other fruits' and depressive symptoms but the mediating effect increased from 1% to 6.4% (**Supplementary Table 7.6.5**). Likewise, CRP remained a significant mediator of the associations between total fat, SFA and MUFA intakes and depressive symptoms in females, and between SFA intake and depressive symptoms in males, but the mediating effects were reduced (**Supplementary Table 7.6.6**).

Stratified analyses comparing participants taking dietary supplements to those without, demonstrated that use of dietary supplements had little influence on study estimates and significance of the associations (**Appendices: Table 9.1and Table 9.2**). The coefficients were in a similar direction to the main analyses, and significant or non-significant associations remained the same, when analyses were restricted to those not taking dietary supplements. Among those taking dietary supplements, no associations were found between the respective nutrients and CES-D.

7.5 Discussion

The main aim of this study is to determine if intakes of carotenoids, fatty acids and fruits and vegetables predicts depressive symptoms at follow-up, and whether inflammatory markers mediate this relationship between these nutrients or foods and depression. Inverse associations were observed between fruit and MUFA intakes (both gender groups), n-3 PUFA intake and plasma lutein + zeaxanthin (in males), and depressive symptoms; whereas total fat and SFA intakes were positively associated with depressive symptoms. However, inflammatory markers

only significantly mediated the associations between SFA (both gender groups), total fat, MUFA and fruits with lower carotenoid content (among females), and depressive symptoms. The difference in associations between males and females suggest the presence of a gender difference in the relationship between nutrients, inflammatory markers, and depression.

Our findings align with current evidence that high consumption of fruits as part of a healthy dietary pattern is associated with lower levels of depression (9). Interestingly, we found that intake of fruits with low rather than high carotenoids content was inversely associated with depressive symptoms, which is partly mediated by IL-6. This suggests that other nutrients or chemical compounds may be responsible for this association. For example, quercetin found in high concentrations in apples, berries and grapes, or resveratrol found in the skin of red grapes, may be driving the association observed between 'other fruit' and depressive symptoms (29, 30). We did not find a significant association between vegetables consumption and depressive symptoms, consistent with findings from a prospective study of Australian women (31). In contrast, a Taiwanese study showed that consumption of vegetables, but not fruit, was protective of depression (32). There appears to be a differential effect of fruit and vegetables on depression.

We observed an association between high levels of plasma carotenoids, *β*-carotene, lutein + zeaxanthin and lower depressive symptoms in males, consistent with findings from a study among US adults (33). However, significant associations were not observed with dietary carotenoids. It is possible that plasma concentrations reflect the body's nutritional status more accurately (21), and thus may be a better predictor of depressive symptoms. The literature on dietary carotenoids and depression is scarce. As such, comparison to others' work is limited. One Japanese study showed that higher carotene intake was associated with reduced prevalence of depressive symptoms among men (34) but we did not observe this in our study. The cross-sectional nature of the Japanese study meant that the observed association may reflect the influence of depression on nutritional status rather than a true causal association since reduced appetite and poor eating habits have been reported in individuals with depression (35).

An unhealthy diet has been linked to increased depressive symptoms which could be due to the high SFA and high sugar content. Thus, it is not surprising when we found a positive association between total fat and SFA intakes and depressive symptoms in both gender groups. CRP partially mediated the relationship between SFA and depression which is consistent with current literature where a high SFA diet is associated with biomarkers of inflammations (11) and increased risk of depression (5); but it is only a significant mediator for the association between total fat and depression in females. In contrast, an inverse association between MUFA and depressive symptoms mediated by CRP was observed among females of our study. This was also observed in studies showing that consumption of MUFA-rich foods decreased levels of inflammation (36) and depressive symptoms (37).

A number of nutrients (e.g. total fat and long chain n-3 PUFA in males) and fruits were associated with depressive symptoms but were not mediated by inflammatory markers. Furthermore, the portion of the associations explained by inflammatory markers mediation is small (<10%). It is likely that there are a number of mechanisms mediating the associations between the variables. Animal studies showed that a high fat diet leads to a significant reduction in the brain-derived neurotrophic factor resulting in the development of depression-like behavior (38). Low plasma levels of long chain n-3 PUFA were associated with high levels of corticotrophin-releasing hormone which produce changes in the hippocampus, crucial to emotional regulation (39).

The findings of this study may help in explaining the inconsistencies in literature regarding the diet-depression relationship. For example, in Chapter 6, we found no association between diet quality scores, assessed with the Australian Recommended Food Score (ARFS), and depressive symptoms. Conversely, studies using the Mediterranean diet score or the Alternative Healthy Eating Index showed inverse associations with depressive symptoms (37, 40). It is possible that the ability in detecting a significant diet-depression association is dependent on whether the score places a greater emphasis on higher MUFA and lower SFA intakes.

The relatively large sample size, the prospective study design and the use of the validated measures are amongst the strengths of this study. However, this study is not without limitations. It is not clear if there was a causal-relationship between diet and inflammation since we did not

measure inflammatory markers at follow-up, and reverse causation is possible. Other inflammatory markers may be stronger mediators of the diet-depression relationship, such as TNFα receptor 2, E-selectin and serum amyloid-A which have demonstrated associations with dietary intakes (41). The large loss to follow-up may have introduced selection bias, limiting the generalizability of our study findings to the wider Australian population. Although the validity of the food frequency questionnaire has been evaluated, the use of memory-based assessment method is subject to recall bias, social desirability bias and misreporting (42), thus may result in some degree of misclassification. This misclassification is more likely to be non-differential and would therefore bias the results towards the null. Depression was not defined through clinical diagnosis, but through a self-reported depressive symptom inventory, which may have underestimated the true effect (43), but our focus is on depressive symptoms rather than major depressive disorder. As with any observational study, the potential for residual confounding is also present, although analyses were adjusted for many covariates. The observed association may also be biased by unmeasured factors, for example, stressful life events may promote both depressive symptoms and inflammation (44).

In conclusion, our study is the first to explore the diet-inflammation-depression relationship with the use of appropriate mediation analysis. A number of studies have examined the diet-inflammation, diet-depression, and inflammation-depression relationships independently, but have not examined the relationship between all three factors. Our findings support the hypothesis that inflammation is one of the factors driving the association between fatty acid intake and depression (although it may only be a small contributor), but the hypothesis that antioxidants are associated with depression via inflammation was not confirmed by our study. Further studies measuring dietary intakes, inflammatory markers, and depressive symptoms at multiple time-points are required to clarify the relationship between these variables. Our results also suggest that future studies examining overall diet and depression should incorporate knowledge on underlying diet-depression mechanisms in modelling dietary patterns. Overall, the observed mediation effects by inflammatory markers, if replicated in future studies, may highlight the need for greater emphasis on encouraging consumption of foods that are anti-inflammatory and reduce intake of foods that are pro-inflammatory.

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7.6 Supplementary Tables

Supplementary Table 7.6.1: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and interleukin (IL)-6, stratified by gender, in the Hunter Community Study (n=1439)

Supplementary Table 7.6.2: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and C-reactive protein (CRP), stratified by gender, in the Hunter Community Study (n=1575)

Supplementary Table 7.6.3: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and interleukin (IL)-6, stratified by sex, in the Hunter Community Study, excluding those with IL-6>23pg/L (n=1418)

Supplementary Table 7.6.4: Cross-sectional associations between dietary intakes, nutrient biomarkers, and C-reactive protein (CRP), stratified by sex, in the Hunter Community Study, excluding those with CRP>10mg/L (n=1486)

Supplementary Table 7.6.5: Interleukin (IL)-6 as mediator of the associations between dietary intakes or nutrient biomarkers, and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study, excluding those with IL-6>23pg/L (n=1096)

Supplementary Table 7.6.6: C-reactive protein (CRP) as mediator of the associations between dietary intakes, nutrient biomarkers and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study, excluding those with CRP>10mg/L (n=1145)

Supplementary Table 7.6.1: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and interleukin (IL)-6, stratified by sex, in the Hunter Community Study (n=1439) [a].

	β (95% CI) for IL-6			
	Q2	Q3	Q4	*P*
Females (n=695)				
Dietary Intakes				
Total carotenoids	-0.148 (-0.328, 0.032)	-0.166 (-0.351, 0.019)	**-0.245 (-0.423, -0.066)***	**0.016**
Alpha-carotene	-0.063 (-0.237, 0.111)	-0.134 (-0.306, 0.038)	**-0.158 (-0.328, -0.011)***	**0.047**
Beta-carotene	-0.035 (-0.222, 0.153)	-0.135 (-0.314, 0.043)	-0.113 (-0.288, 0.062)	0.132
Beta-cryptoxanthin	0.004 (-0.171, 0.179)	0.085 (-0.088, 0.258)	-0.071 (-0.240, 0.098)	0.550
Lycopene	-0.123 (-0.302, 0.057)	-0.083 (-0.256, 0.090)	-0.074 (-0.247, 0.100)	0.586
Lutein+zeaxanthin	-0.090 (-0.267, 0.088)	**-0.271 (-0.441, -0.100)**	**-0.286 (-0.464, -0.108)***	**0.001***
Vitamin E	-0.063 (-0.240, 0.114)	0.007 (-0.167, 0.180)	**-0.190 (-0.361, -0.019)***	0.055
Total Fruits	-0.166 (-0.352, 0.019)	-0.092 (-0.270, 0.086)	-0.121 (-0.297, 0.056)	0.390
Carotenoids-rich fruits	0.063 (-0.120, 0.246)	-0.011 (-0.191, 0.169)	-0.084 (-0.260, 0.092)	0.182
Other fruits	0.005 (-0.185, 0.194)	-0.133 (-0.318, 0.052)	**-0.167 (-0.352, -0.007)***	**0.024**
Total Vegetables	-0.030 (-0.215, 0.154)	-0.062 (-0.249, 0.126)	**-0.189 (-0.368, -0.011)***	**0.042**
Carotenoids-rich vegetables	0.017 (-0.174, 0.207)	0.057 (-0.131, 0.245)	-0.160 (-0.343, 0.023)	0.057
Other vegetables	-0.096 (-0.272, 0.079)	-0.105 (-0.279, 0.069)	-0.129 (-0.299, 0.040)	0.159
Total fat	0.070 (-0.081, 0.221)	-0.021 (-0.181, 0.138)	0.055 (-0.134, 0.244)	0.835
Saturated fat	-0.007 (-0.157, 0.145)	-0.040 (-0.203, 0.123)	0.075 (-0.105, 0.255)	0.642
Mono-unsaturated fat	0.124 (-0.027, 0.275)	-0.034 (-0.195, 0.126)	0.092 (-0.095, 0.279)	0.737
Poly-unsaturated fat	0.056 (-0.099, 0.210)	-0.057 (-0.221, 0.107)	-0.015 (-0.189, 0.160)	0.578
Long-chain Omega-3	-0.161 (-0.336, 0.013)	-0.119 (-0.287, 0.048)	-0.148 (-0.319, 0.023)	0.151
Nutrient Biomarkers (n=52)				
Total carotenoids	-0.429 (-1.132, 0.274)	-0.068 (-0.665, 0.529)	-0.500 (-1.107, 0.107)	0.245
Alpha-carotene	0.150 (-0.525, 0.825)	0.085 (-0.492, 0.661)	-0.159 (-0.763, 0.446)	0.620
Beta-carotene	-0.117 (-0.807, 0.572)	-0.287 (-0.934, 0.360)	-0.087 (-0.681, 0.508)	0.678
Beta-cryptoxanthin	-0.292 (-0.959, 0.375)	-0.053 (-0.660, 0.554)	-0.424 (-1.155, 0.327)	0.501
Lycopene	-0.286 (-0.939, 0.367)	-0.060 (-0.647, 0.527)	-0.412 (-1.054, 0.230)	0.371
Lutein+zeaxanthin	-0.047 (-0.742, 0.647)	-0.405 (-1.149, 0.339)	-0.380 (-1.050, 0.291)	0.171
Vitamin E	-0.125 (-0.790, 0.540)	-0.134 (-0.799, 0.531)	0.295 (-0.361, 0.950)	0.262
Males (n=744)				
Dietary Intakes				
Total carotenoids	0.007 (-0.140, 0.154)	0.067 (-0.090, 0.225)	-0.055 (-0.217, 0.107)	0.779
Alpha-carotene	-0.052 (-0.203, 0.098)	0.101 (-0.056, 0.258)	-0.076 (-0.241, 0.088)	0.894
Beta-carotene	-0.065 (-0.211, 0.081)	0.033 (-0.122, 0.188)	-0.105 (-0.272, 0.061)	0.479
Beta-cryptoxanthin	-0.030 (-0.185, 0.125)	-0.073 (-0.232, 0.085)	0.037 (-0.127, 0.201)	0.853
Lycopene	-0.037 (-0.187, 0.113)	0.009 (-0.152, 0.171)	-0.095 (-0.256, 0.066)	0.368
Lutein+zeaxanthin	-0.047 (-0.201, 0.107)	0.056 (-0.098, 0.210)	0.033 (-0.129, 0.194)	0.442
Vitamin E	**-0.165 (-0.316, -0.014)**	**-0.170 (-0.329, -0.011)***	**-0.172 (-0.325, -0.017)***	**0.029**
Total Fruits	-0.076 (-0.226, 0.074)	-0.082 (-0.243, 0.079)	-0.087 (-0.248, 0.074)	0.273
Carotenoids-rich fruits	0.091 (-0.059, 0.241)	0.020 (-0.137, 0.178)	0.075 (-0.092, 0.243)	0.535
Other fruits	0.004 (-0.146, 0.154)	-0.136 (-0.292, 0.020)	-0.119 (-0.278, 0.040)	0.055
Total Vegetables	0.006 (-0.146, 0.158)	-0.026 (-0.180, 0.128)	0.041 (-0.128, 0.210)	0.807
Carotenoids-rich vegetables	-0.091 (-0.246, 0.064)	-0.002 (-0.152, 0.147)	0.011 (-0.158, 0.181)	0.747
Other vegetables	0.038 (-0.114, 0.191)	-0.047 (-0.201, 0.107)	0.078 (-0.084, 0.240)	0.631
Total fat	-0.198 (-0.382, -0.015)	-0.176 (-0.356, 0.004)	-0.188 (-0.361, 0.015)	0.111
Saturated fat	-0.056 (-0.239, 0.127)	-0.102 (-0.278, 0.075)	-0.138 (-0.308, 0.031)	0.088
Mono-unsaturated fat	-0.131 (-0.312, 0.050)	-0.144 (-0.321, 0.033)	-0.163 (-0.335, 0.009)	0.101
Poly-unsaturated fat	-0.070 (-0.241, 0.100)	-0.099 (-0.265, 0.068)	-0.070 (-0.231, 0.091)	0.412
Long-chain Omega-3	0.033 (-0.124, 0.190)	-0.008 (-0.170, 0.153)	0.051 (-0.115, 0.218)	0.694
Nutrient Biomarkers (n=59)				
Total carotenoids	0.124 (-0.326, 0.573)	-0.114 (-0.650, 0.421)	0.005 (-0.485, 0.495)	0.800
Alpha-carotene	0.094 (-0.358, 0.547)	0.021 (-0.531, 0.573)	-0.063 (-0.551, 0.426)	0.697
Beta-carotene	-0.120 (-0.560, 0.321)	-0.077 (-0.582, 0.428)	-0.154 (-0.684, 0.375)	0.594
Beta-cryptoxanthin	-0.062 (-0.539, 0.415)	0.133 (-0.358, 0.623)	-0.226 (-0.684, 0.232)	0.476
Lycopene	-0.043 (-0.533, 0.447)	-0.208 (-0.736, 0.320)	-0.147 (-0.615, 0.320)	0.425
Lutein+zeaxanthin	0.340 (-0.130, 0.809)	0.082 (-0.387, 0.550)	0.232 (-0.261, 0.726)	0.607
Vitamin E	-0.404 (-0.846, 0.039)	-0.161 (-0.613, 0.291)	**-0.482 (-0.932, -0.031)***	0.078

Data are presented as coefficients and 95% confidence intervals for IL-6 in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] All models adjusted for baseline values of age, smoking status and physical activity.

P<0.05 in bold. **P*<0.01.

Supplementary Table 7.6.2: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and C-reactive protein (CRP), stratified by gender, in the Hunter Community Study (n=1575) [a]

	β (95% CI) for CRP			
	Q2	Q3	Q4	*P*
Females (n=767)				
Dietary Intakes				
Total carotenoids	-0.098 (-0.287, 0.091)	-0.143 (-0.327, 0.040)	-0.167 (-0.349, 0.014)	0.069
Alpha-carotene	-0.070 (-0.250, 0.110)	-0.085 (-0.263, 0.093)	-0.060 (-0.234, 0.114)	0.518
Beta-carotene	-0.164 (-0.358, 0.030)	-0.142 (-0.327, 0.044)	-0.154 (-0.335, 0.027)	0.183
Beta-cryptoxanthin	0.085 (-0.096, 0.265)	0.077 (-0.102, 0.255)	0.044 (-0.132, 0.220)	0.711
Lycopene	-0.094 (-0.278, 0.090)	-0.078 (-0.254, 0.098)	-0.092 (-0.270, 0.086)	0.386
Lutein+zeaxanthin	0.030 (-0.154, 0.215)	-0.059 (-0.243, 0.125)	-0.113 (-0.291, 0.065)	0.107
Vitamin E	-0.009 (-0.192, 0.174)	0.023 (-0.157, 0.204)	-0.153 (-0.330, 0.025)	0.102
Total Fruits	-0.146 (-0.338, 0.046)	-0.165 (-0.348, 0.018)	**-0.189 (-0.370, -0.006)***	0.060
Carotenoids-rich fruits	0.006 (-0.183, 0.194)	-0.005 (-0.189, 0.178)	-0.118 (-0.296, 0.061)	0.162
Other fruits	-0.001 (-0.185, 0.184)	-0.039 (-0.219, 0.142)	-0.037 (-0.216, 0.142)	0.592
Total Vegetables	0.170 (-0.022, 0.361)	0.035 (-0.155, 0.224)	0.013 (-0.170, 0.196)	0.534
Carotenoids-rich vegetables	0.029 (-0.165, 0.222)	-0.066 (-0.258, 0.127)	-0.066 (-0.253, 0.122)	0.285
Other vegetables	-0.090 (-0.273, 0.092)	-0.048 (-0.228, 0.132)	-0.074 (-0.248, 0.101)	0.552
Total fat	0.049 (-0.107, 0.205)	0.074 (-0.091, 0.240)	**0.202 (0.010, 0.395)***	0.050
Saturated fat	-0.068 (-0.223, 0.086)	0.006 (-0.234, 0.102)	**0.280 (0.096, 0.463)***	**0.026**
Mono-unsaturated fat	-0.057 (-0.214, 0.099)	**-0.228 (-0.393, -0.063)**	**-0.234 (-0.424, -0.043)***	**0.002***
Poly-unsaturated fat	0.167 (-0.007, 0.327)	-0.032 (-0.200, 0.135)	0.074 (-0.107, 0.255)	0.653
Long-chain Omega-3	-0.160 (-0.339, 0.020)	-0.120 (-0.293, 0.053)	0.015 (-0.160, 0.191)	0.734
Nutrient Biomarkers(n=64)				
Total carotenoids	-0.290 (-1.003, 0.423)	-0.726 (-1.525, 0.073)	**-1.203 (-1.926, -0.480)***	**0.011**
Alpha-carotene	-0.289 (-1.025, 0.446)	**-0.844 (-1.511, -0.178)**	**-1.065 (-1.717, -0.414)***	**0.002***
Beta-carotene	-0.488 (-1.280, 0.303)	-0.631 (-1.386, 0.124)	**-1.033 (-1.741, -0.326)***	**0.004***
Beta-cryptoxanthin	-0.284 (-0.972, 0.404)	-0.685 (-1.428, 0.059)	**-1.488 (-2.320, -0.656)***	**0.017**
Lycopene	-0.732 (-1.541, 0.077)	-0.696 (-1.430, 0.037)	**-0.840 (-1.629, -0.051)***	0.054
Lutein+zeaxanthin	**-0.919 (-1.728, -0.110)**	**-1.095 (-1.982, -0.208)***	**-1.173 (-1.957, -0.388)***	**0.011**
Vitamin E	-0.222 (-1.045, 0.602)	-0.314 (-1.144, 0.517)	0.169 (-0.647, 0.986)	0.580
Males (n=808)				
Dietary Intakes				
Total carotenoids	-0.042 (-0.205, 0.122)	-0.047 (-0.223, 0.129)	-0.118 (-0.300, 0.064)	0.226
Alpha-carotene	0.071 (-0.099, 0.240)	0.043 (-0.133, 0.218)	0.070 (-0.115, 0.254)	0.529
Beta-carotene	-0.044 (-0.206, 0.119)	-0.034 (-0.208, 0.140)	-0.096 (-0.282, 0.091)	0.361
Beta-cryptoxanthin	0.078 (-0.096, 0.251)	0.061 (-0.117, 0.238)	0.084 (-0.100, 0.269)	0.425
Lycopene	-0.046 (-0.214, 0.121)	-0.021 (-0.202, 0.160)	-0.069 (-0.249, 0.111)	0.530
Lutein+zeaxanthin	-0.072 (-0.242, 0.098)	0.060 (-0.113, 0.232)	-0.031 (-0.213, 0.151)	0.864
Vitamin E	-0.198 (-0.367, -0.030)	-0.169 (-0.341, 0.004)	-0.085 (-0.265, 0.095)	0.307
Total Fruits	-0.038 (-0.207, 0.131)	-0.092 (-0.271, 0.086)	-0.018 (-0.198, 0.162)	0.656
Carotenoids-rich fruits	0.101 (-0.067, 0.269)	0.041 (-0.136, 0.219)	0.116 (-0.069, 0.302)	0.319
Other fruits	0.048 (-0.121, 0.217)	-0.071 (-0.246, 0.105)	-0.092 (-0.270, 0.086)	0.195
Total Vegetables	0.117 (-0.051, 0.285)	0.019 (-0.152, 0.189)	-0.023 (-0.214, 0.168)	0.695
Carotenoids-rich vegetables	-0.038 (-0.210, 0.134)	0.008 (-0.159, 0.175)	0.004 (-0.188, 0.196)	0.869
Other vegetables	0.004 (-0.165, 0.172)	0.019 (-0.154, 0.193)	-0.026 (-0.209, 0.156)	0.865
Total fat	-0.234 (-0.439, 0.003)	-0.082 (-0.283, 0.120)	0.022 (-0.170, 0.214)	0.151
Saturated fat	-0.118 (-0.321, 0.084)	0.053 (-0.141, 0.247)	**0.137 (0.051, 0.325)***	**0.022**
Mono-unsaturated fat	-0.095 (-0.297, 0.107)	-0.092 (-0.292, 0.107)	-0.008 (-0.200, 0.184)	0.802
Poly-unsaturated fat	-0.019 (-0.210, 0.172)	0.013 (-0.174, 0.200)	0.010 (-0.171, 0.191)	0.821
Long-chain Omega-3	0.108 (-0.067, 0.282)	0.040 (-0.139, 0.220)	0.014 (-0.170, 0.198)	0.930
Nutrient Biomarkers(n=64)				
Total carotenoids	0.389 (-0.255, 1.033)	-0.129 (-0.901, 0.643)	-0.081 (-0.763, 0.602)	0.538
Alpha-carotene	0.338 (-0.305, 0.980)	0.263 (-0.554, 1.080)	-0.029 (-0.702, 0.643)	0.802
Beta-carotene	-0.213 (-0.840, 0.414)	0.265 (-0.456, 0.985)	-0.418 (-1.167, 0.331)	0.556
Beta-cryptoxanthin	0.397 (-0.300, 1.093)	0.126 (-0.604, 0.856)	0.081 (-0.616, 0.777)	0.989
Lycopene	0.386 (-0.313, 1.084)	-0.208 (-0.975, 0.558)	-0.185 (-0.836, 0.466)	0.247
Lutein+zeaxanthin	-0.051 (-0.756, 0.653)	0.111 (-0.562, 0.785)	-0.289 (-1.044, 0.465)	0.655
Vitamin E	-0.044 (-0.685, 0.599)	0.113 (-0.575, 0.801)	-0.576 (-1.272, 0.119)	0.199

Data are presented as coefficients and 95% confidence intervals for CRP in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] All models adjusted for baseline values of age, smoking status and physical activity.

P<0.05 in bold. **P*<0.01

Supplementary Table 7.6.3: Cross-sectional associations between quartiles of dietary intakes or nutrient biomarkers, and interleukin (IL)-6, stratified by sex, in the Hunter Community Study, excluding those with IL-6>23pg/L (n=1418)[a, b]

	β (95% CI) for IL-6			
	Q2	Q3	Q4	*P*
Females (n=684)				
Dietary Intakes				
Total carotenoids	-0.034 (-0.178, 0.110)	-0.044 (-0.192, 0.104)	**-0.103 (-0.246, -0.039)***	**0.014**
Alpha-carotene	-0.076 (-0.215, 0.063)	-0.082 (-0.220, 0.055)	**-0.128 (-0.316, -0.005)***	**0.028**
Beta-carotene	-0.117 (-0.266, 0.033)	-0.100 (-0.242, 0.041)	-0.111 (-249, 0.028)	0.205
Beta-cryptoxanthin	0.062 (-0.077, 0.201)	0.098 (-0.040, 0.236)	0.021 (-0.113, 0.155)	0.741
Lycopene	-0.042 (-0.185, 0.101)	-0.006 (-0.144, 0.132)	0.042 (-0.096, 0.180)	0.405
Lutein+zeaxanthin	-0.042 (-0.185, 0.101)	-0.141 (-0.283, 0.001)	**-0.143 (-0.277, -0.004)***	**0.019**
Vitamin E	-0.005 (-0.146, 0.136)	0.010 (-0.129, 0.148)	-0.087 (-0.224, 0.049)	0.215
Total Fruits	-0.110 (-0.257, 0.037)	-0.068 (-0.209, 0.073)	-0.102 (-0.241, 0.038)	0.290
Carotenoids-rich fruits	0.031 (-0.114, 0.176)	0.010 (-0.132, 0.152)	-0.049 (-0.188, 0.090)	0.369
Other fruits	-0.005 (-0.181, 0.172)	-0.123 (-0.295, 0.050)	**-0.199 (-0.371, -0.026)***	**0.006***
Total Vegetables	0.120 (-0.026, 0.267)	0.061 (-0.088, 0.210)	**-0.023 (-0.164, -0.009)***	**0.037**
Carotenoids-rich vegetables	0.042 (-0.109, 0.194)	0.066 (-0.084, 0.216)	-0.058 (-0.203, 0.087)	0.304
Other vegetables	-0.040 (-0.180, 0.100)	0.017 (-0.122, 0.155)	-0.006 (-0.141, 0.129)	0.842
Total fat	0.057 (-0.063, 0.177)	-0.027 (-0.154, 0.099)	0.082 (-0.067, 0.231)	0.606
Saturated fat	0.001 (-0.119, 0.120)	-0.024 (-0.154, 0.105)	0.053 (-0.091, 0.196)	0.674
Mono-unsaturated fat	0.081 (-0.039, 0.201)	-0.001 (-0.128, 0.126)	0.119 (-0.030, 0.267)	0.297
Poly-unsaturated fat	-0.013 (-0.136, 0.110)	-0.058 (-0.188, 0.072)	0.005 (-0.133, 0.143)	0.796
Long-chain Omega-3	-0.093 (-0.231, 0.046)	-0.120 (-0.253, 0.013)	-0.089 (-0.224, 0.047)	0.187
Males (n=734)				
Dietary Intakes				
Total carotenoids	-0.008 (-0.130, 0.115)	-0.035 (-0.167, 0.097)	-0.099 (-0.234, 0.037)	0.151
Alpha-carotene	-0.067 (-0.192, 0.059)	0.003 (-0.128, 0.135)	-0.099 (-0.236, 0.039)	0.335
Beta-carotene	-0.024 (-0.146, 0.097)	-0.016 (-0.146, 0.114)	-0.145 (-0.285, -0.006)	0.080
Beta-cryptoxanthin	0.052 (-0.077, 0.182)	0.012 (-0.121, 0.144)	0.068 (-0.070, 0.205)	0.478
Lycopene	-0.025 (-0.151, 0.100)	-0.025 (-0.160, 0.110)	-0.083 (-0.218, 0.051)	0.255
Lutein+zeaxanthin	-0.019 (-0.147, 0.109)	0.060 (-0.068, 0.189)	-0.020 (-0.155, 0.116)	0.858
Vitamin E	**-0.146 (-0.274, -0.018)**	**-0.152 (-0.278, -0.027)***	**-0.209 (-0.342, -0.076)***	**0.003***
Total Fruits	-0.084 (-0.209, 0.041)	-0.063 (-0.196, 0.071)	-0.074 (-0.208, 0.060)	0.307
Carotenoids-rich fruits	0.059 (-0.067, 0.184)	0.030 (-0.101, 0.161)	0.073 (-0.066, 0.212)	0.381
Other fruits	-0.075 (-0.201, 0.051)	-0.125 (-0.255, 0.004)	-0.130 (-0.263, 0.002)	**0.031**
Total Vegetables	-0.018 (-0.144, 0.109)	-0.029 (-0.157, 0.099)	0.007 (-0.134, 0.149)	0.965
Carotenoids-rich vegetables	-0.096 (-0.225, 0.033)	0.021 (-0.104, 0.145)	-0.039 (-0.181, 0.102)	0.990
Other vegetables	0.035 (-0.092, 0.162)	-0.086 (-0.214, 0.043)	0.056 (-0.079, 0.191)	0.938
Total fat	-0.149 (-0.303, 0.004)	-0.163 (-0.314, -0.012)	-0.128 (-0.273, 0.016)	0.202
Saturated fat	-0.029 (-0.181, 0.124)	-0.099 (-0.247, 0.048)	-0.077 (-0.219, 0.065)	0.214
Mono-unsaturated fat	-0.052 (-0.204, 0.100)	-0.091 (-0.240, 0.058)	-0.078 (-0.223, 0.067)	0.288
Poly-unsaturated fat	-0.007 (-0.149, 0.135)	-0.032 (-0.172, 0.107)	-0.081 (-0.216, 0.055)	0.167
Long-chain Omega-3	0.007 (-0.124, 0.138)	-0.037 (-0.172, 0.098)	-0.015 (-0.154, 0.124)	0.670

Data are presented as coefficients and 95% confidence intervals for IL-6 in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.
[a] All models adjusted for baseline values of age, marital status, annual household income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.
[b] Participants for nutrient biomarkers are the same as those for initial analyses, hence, sensitivity analyses for this subgroup were not carried out
P<0.05 in bold. **P*<0.01

Supplementary Table 7.6.4: Cross-sectional associations between dietary intakes, nutrient biomarkers, and C-reactive protein (CRP), stratified by sex, in the Hunter Community Study, excluding those with CRP>10mg/L (n=1486)[a, b]

	β (95% CI) for CRP			
	Q2	Q3	Q4	*P*
Females (n=720)				
Dietary Intakes				
Total carotenoids	-0.115 (-0.294, 0.063)	-0.062 (-0.233, 0.110)	-0.117 (-0.287, 0.053)	0.315
Alpha-carotene	-0.077 (-0.246, 0.093)	-0.041 (-0.207, 0.125)	-0.034 (-0.196, 0.128)	0.829
Beta-carotene	-0.062 (-0.244, 0.121)	-0.092 (-0.267, 0.084)	-0.066 (-0.236, 0.105)	0.480
Beta-cryptoxanthin	-0.004 (-0.172, 0.164)	0.062 (-0.103, 0.226)	0.014 (-0.148, 0.177)	0.698
Lycopene	-0.104 (-0.276, 0.069)	-0.036 (-0.200, 0.128)	-0.069 (-0.235, 0.097)	0.637
Lutein+zeaxanthin	0.016 (-0.158, 0.189)	-0.022 (-0.195, 0.150)	-0.042 (-0.208, 0.124)	0.505
Vitamin E	0.023 (-0.149, 0.195)	-0.002 (-0.173, 0.168)	-0.080 (-0.245, 0.086)	0.266
Total Fruits	-0.082 (-0.262, 0.098)	-0.109 (-0.281, 0.063)	-0.132 (-0.303, 0.040)	0.140
Carotenoids-rich fruits	0.039 (-0.137, 0.215)	0.022 (-0.150, 0.194)	-0.054 (-0.220, 0.112)	0.416
Other fruits	-0.035 (-0.180, 0.111)	-0.056 (-0.198, 0.087)	-0.089 (-0.231, 0.052)	0.197
Total Vegetables	0.186 (0.007, 0.365)	0.074 (-0.103, 0.250)	0.074 (-0.096, 0.245)	0.926
Carotenoids-rich vegetables	0.017 (-0.165, 0.200)	0.022 (-0.157, 0.201)	-0.014 (-0.190, 0.162)	0.820
Other vegetables	-0.087 (-0.258, 0.085)	-0.010 (-0.178, 0.158)	-0.001 (-0.163, 0.162)	0.715
Total fat	0.051 (-0.094, 0.197)	0.080 (-0.074, 0.234)	**0.212 (0.033, 0.391)***	**0.026**
Saturated fat	-0.106 (-0.250, 0.039)	-0.052 (-0.207, 0.104)	**0.227 (0.054, 0.400)***	**0.046**
Mono-unsaturated fat	-0.117 (-0.262, 0.027)	**-0.211 (-0.391, -0.032)***	**-0.225 (-0.379, -0.071)***	**0.003**
Poly-unsaturated fat	0.147 (-0.002, 0.296)	0.084 (-0.071, 0.239)	0.054 (-0.115, 0.224)	0.531
Long-chain Omega-3	-0.051 (-0.218, 0.115)	-0.060 (-0.221, 0.102)	0.091 (-0.074, 0.255)	0.305
Nutrient Biomarkers (n=48)				
Total carotenoids	-0.261 (-1.018, 0.496)	0.060 (-0.631, 0.751)	**-0.793 (-1.469, -0.117)***	**0.050**
Alpha-carotene	-0.260 (-0.983, 0.463)	-0.571 (-1.196, 0.055)	**-0.770 (-1.385, -0.156)***	**0.028**
Beta-carotene	-0.262 (-1.009, 0.484)	-0.403 (-1.113, 0.307)	**-0.730 (-1.388, -0.073)***	**0.022**
Beta-cryptoxanthin	-0.292 (-0.897, 0.312)	-0.664 (-1.322, 0.006)	**-1.311 (-2.030, -0.591)***	**0.014**
Lycopene	-0.357 (-1.109, 0.395)	-0.430 (-1.120, 0.261)	-0.637 (-1.382, 0.108)	0.091
Lutein+zeaxanthin	-0.575 (-1.270, 0.121)	**-0.841 (-1.521, -0.160)***	**-1.231 (-2.013, -0.449)***	**0.024**
Vitamin E	-0.355 (-1.076, 0.366)	-0.332 (-1.055, 0.391)	-0.103 (-0.823, 0.618)	0.913
Males (n=766)				
Dietary Intakes				
Total carotenoids	-0.069 (-0.214, 0.076)	-0.005 (-0.159, 0.150)	-0.079 (-0.239, 0.081)	0.496
Alpha-carotene	0.064 (-0.085, 0.213)	0.033 (-0.122, 0.187)	0.057 (-0.105, 0.219)	0.580
Beta-carotene	-0.045 (-0.189, 0.098)	-0.043 (-0.197, 0.111)	-0.050 (-0.213, 0.114)	0.539
Beta-cryptoxanthin	0.053 (-0.100, 0.205)	0.040 (-0.116, 0.195)	0.024 (-0.139, 0.187)	0.802
Lycopene	-0.053 (-0.201, 0.095)	-0.048 (-207, 0.112)	-0.036 (-0.194, 0.121)	0.668
Lutein+zeaxanthin	-0.075 (-0.224, 0.074)	0.029 (-0.123, 0.181)	-0.061 (-0.222, 0.100)	0.789
Vitamin E	-0.112 (-0.261, 0.036)	-0.138 (-0.291, 0.016)	-0.059 (-0.219, 0.100)	0.339
Total Fruits	-0.017 (-0.165, 0.131)	-0.133 (-0.290, 0.025)	0.009 (-0.149, 0.167)	0.661
Carotenoids-rich fruits	0.018 (-0130, 0.166)	0.039 (-0.116, 0.194)	0.099 (-0.063, 0.262)	0.239
Other fruits	0.046 (-0.104, 0.195)	-0.053 (-0.207, 0.101)	-0.049 (-0.205, 0.108)	0.367
Total Vegetables	0.077 (-0.071, 0.226)	0.014 (-0.136, 0.164)	0.003 (-0.164, 0.170)	0.914
Carotenoids-rich vegetables	-0.009 (-0.160, 0.143)	0.062 (-0.085, 0.208)	0.018 (-0.151, 0.187)	0.566
Other vegetables	0.010 (-0.139, 0.158)	0.002 (-0.151, 0.154)	-0.045 (-0.206, 0.115)	0.615
Total fat	-0.280 (-0.459, -0.102)	-0.132 (-0.308, 0.043)	-0.037 (-0.205, 0.131)	0.313
Saturated fat	-0.001 (-0.164, 0.163)	-0.010 (-0.178, 0.157)	**-0.215 (-0.391, -0.039)***	**0.026**
Mono-unsaturated fat	-0.146 (-0.322, 0.031)	-0.158 (-0.332, 0.016)	-0.057 (-0.225, 0.110)	0.835
Poly-unsaturated fat	-0.092 (-0.260, 0.076)	-0.011 (-0.175, 0.153)	-0.027 (-0.185, 0.132)	0.943
Long-chain Omega-3	0.029 (-0.125, 0.182)	0.018 (-0.139, 0.175)	-0.049 (-0.211, 0.112)	0.555
Nutrient Biomarkers (n=59)				
Total carotenoids	0.393 (-0.218, 1.004)	-0.273 (-0.991, 0.446)	0.044 (-0.598, 0.685)	0.662
Alpha-carotene	0.540 (-0.060, 1.140)	0.327 (-0.438, 1.091)	0.262 (-0.368, 0.891)	0.626
Beta-carotene	0.105 (-0.502, 0.712)	0.463 (-0.231, 1.156)	-0.140 (-0.885, 0.606)	0.930
Beta-cryptoxanthin	0.516 (-0.157, 1.190)	0.312 (-0.363, 0.986)	0.109 (-0.568, 0.785)	0.900
Lycopene	0.030 (-0.655, 0.715)	-0.233 (-0.944, 0.479)	-0.262 (-0.874, 0.350)	0.282
Lutein+zeaxanthin	-0.067 (-0.741, 0.607)	-0.042 (-0.693, 0.609)	-0.193 (-0.910, 0.524)	0.214
Vitamin E	-0.188 (-0.812, 0.437)	0.013 (-0.648, 0.675)	-0.513 (-1.155, 0.129)	0.189

Data are presented as coefficients and 95% confidence intervals for CRP in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] All models adjusted for baseline values of age, marital status, annual household income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.

P<0.05 in bold. **P*<0.01.

Supplementary Table 7.6.5: Interleukin (IL)-6 as mediator of the associations between dietary intakes or nutrient biomarkers, and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study, excluding those with IL-6>23pg/L (n=1096)[a, b]

	Females (n=524)			Males (n=575)		
	β (95% CI)	*P*	Mediating Effect	*β* (95% CI)	*P*	Mediating Effect
Total Fruits	-0.053 (-0.113, -0.001)	0.050	Direct: -0.0528 (-0.1097, -0.0059)	-0.030 (-0.086, -0.006)	0.029	Direct: -0.0298 (-0.0834, -0.0056)
Q4 vs Q1	-0.193 (-0.405, 0.020)	0.046	Indirect: -0.0020 (-0.0090, 0.0042)	-0.145 (-0.336, -0.005)	0.035	Indirect: -0.0013 (-0.0056, 0.0017)
Q3 vs Q1	-0.187 (-0.395, 0.018)	0.077		-0.054 (-0.232, 0.125)	0.556	
Q2 vs Q1	-0.133 (-0.348, 0.082)	0.225		-0.037 (-0.229, 0.156)	0.710	
Other fruits	-0.050 (-0.108, -0.001)	0.049	Direct: -0.0491 (-0.1054, -0.0009)	-0.028 (-0.084, -0.008)	0.021	Direct: -0.0276 (-0.0812, -0.0077)
Q4 vs Q1	-0.225 (-0.435, -0.015)	0.036	Indirect: -0.0032 (-0.0103, -0.0003)	-0.146 (-0.334, -0.004)	0.027	Indirect: -0.0019 (-0.0068, 0.0014)
Q3 vs Q1	-0.175 (-0.382, 0.031)	0.096	**% total effect mediated: 6.4%**	-0.137 (-0.320, 0.046)	0.144	
Q2 vs Q1	-0.135 (-0.347, 0.077)	0.211		-0.053 (-0.245, 0.139)	0.590	
Total fat	0.069 (0.008, 0.131)	0.027	Direct: 0.0698 (0.0111, 0.1304)	0.099 (0.041, 0.157)	0.001	Direct: 0.0993 (0.0435, 0.1569)
Q4 vs Q1	0.206 (0.021, 0.392)	0.029	Indirect: 0.0031 (-0.0023, 0.0110)	0.319 (0.111, 0.526)	0.003	Indirect: 0.0020 (-0.0020, 0.0073)
Q3 vs Q1	0.153 (-0.071, 0.377)	0.180		0.125 (-0.093, 0.343)	0.261	
Q2 vs Q1	0.072 (-0.104, 0.247)	0.424		0.157 (-0.061, 0.375)	0.157	
Saturated fat	0.068 (0.008, 0.128)	0.027	Direct: 0.0682 (0.0108, 0.1273)	0.105 (0.047, 0.163)	0.001	Direct: 0.1043 (0.0499, 0.1624)
Q4 vs Q1	0.190 (0.003, 0.376)	0.047	Indirect: 0.0026 (-0.0028, 0.0103)	0.332 (0.128, 0.535)	0.001	Indirect: 0.0011 (-0.0017, 0.0052)
Q3 vs Q1	0.143 (-0.070, 0.356)	0.189		0.267 (0.059, 0.474)	0.012	
Q2 vs Q1	0.054 (-0.120, 0.228)	0.546		0.174 (-0.040, 0.389)	0.111	
Mono-unsaturated fat	-0.084 (-0.145, -0.022)	0.008	Direct: -0.0840 (-0.1444, -0.0255)	-0.113 (-0.171, -0.055)	0.001	Direct: -0.1131 (-0.1705, -0.0575)
Q4 vs Q1	-0.210 (-0.393, -0.018)	0.032	Indirect: -0.0046 (-0.0131, 0.0006)	-0.325 (-0.530, -0.121)	0.002	Indirect: -0.0022 (-0.0081, 0.0028)
Q3 vs Q1	-0.206 (-0.429, -0.009)	0.041		-0.037 (-0.249, 0.176)	0.737	
Q2 vs Q1	-0.034 (-0.209, 0.141)	0.073		-0.012 (-0.225, 0.199)	0.908	
Long-chain Omega-3[c]				-0.102 (-0.160, -0.045)	0.001	Direct: -0.1029 (-0.1601, -0.0475)
Q4 vs Q1				-0.338 (-0.538, -0.138)	0.001	Indirect: -0.0001 (-0.0036, 0.0031)
Q3 vs Q1				-0.176 (-0.364, 0.011)	0.065	
Q2 vs Q1				-0.141 (-0.335, 0.052)	0.153	

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intakes or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] Mediation analyses were carried out where there are significant associations between dietary intakes or nutrient biomarkers and depressive symptoms. Total effects were partitioned into Direct effects (dietary intake on depressive symptoms independent of inflammation) and Indirect effects (mediation via inflammatory markers).

[b] All models adjusted for age, marital status, annual household income, education, smoking status, physical activity, BMI use of antidepressants and self-reported depression/anxiety disorder, diabetes, stroke and heart attack

[c] n=56 for males

P<0.01 in bold.

Supplementary Table 7.6.6: C-reactive protein (CRP) as mediator of the associations between dietary intakes, nutrient biomarkers and Centre for Epidemiologic Studies-Depression scale, stratified by sex, in the Hunter Community Study, excluding those with CRP>10mg/L (n=1145)[a, b]

	Females (n=546)			Males (n=599)		
	β (95% CI)	*P*	Mediating Effect	*β* (95% CI)	*P*	Mediating Effect
Total Fruits	-0.052 (-0.111, -0.007)	0.038	Direct: -0.0516 (-0.1078, -0.0034)	-0.026 (-0.081, -0.003)	0.036	Direct: -0.0252 (-0.0782, -0.0025)
Q4 vs Q1	-0.222 (-0.429, -0.014)	0.037	Indirect: -0.0027 (-0.0091, 0.0018)	-0.166 (-0.355, -0.002)	0.038	Indirect: -0.0005 (-0.0025, 0.0047)
Q3 vs Q1	-0.172 (-0.377, 0.032)	0.098		-0.052 (-0.229, 0.125)	0.563	
Q2 vs Q1	-0.161 (-0.374, 0.053)	0.140		-0.002 (-0.193, 0.188)	0.980	
Other fruits	-0.056 (-0.115, -0.003)	0.021	Direct: -0.558 (-0.1122, -0.0023)	-0.029 (-0.084, -0.027)	0.039	Direct: -0.0283 (-0.0813, -0.0030)
Q4 vs Q1	-0.229 (-0.434, -0.024)	0.029	Indirect: -0.0039 (-0.0125, 0.0036)	-0.193 (-0.373, -0.013)	0.036	Indirect: -0.0008 (-0.0049, 0.0025)
Q3 vs Q1	-0.185 (-0.390, 0.021)	0.078		-0.142 (-0.329, 0.045)	0.138	
Q2 vs Q1	-0.139 (-0.349, 0.070)	0.192		-0.068 (-0.258, 0.121)	0.480	
Total fat	0.096 (0.036, 0.156)	0.002	Direct: 0.0961 (0.0388, 0.1552)	0.120 (0.063, 0.178)	0.001	Direct: 0.1209 (0.0662, 0.1773)
Q4 vs Q1	0.265 (0.048, 0.482)	0.017	Indirect: 0.0030 (0.0002, 0.0114)	0.390 (0.187, 0.592)	0.001	Indirect: 0.0013 (-0.0016, 0.0065)
Q3 vs Q1	0.176 (-0.007, 0.359)	0.059	**% total mediated effect: 3.1%**	0.230 (0.016, 0.444)	0.035	
Q2 vs Q1	0.028 (-0.146, 0.203)	0.751		0.183 (-0.029, 0.394)	0.090	
Saturated fat	0.088 (0.028, 0.147)	0.004	Direct: 0.0880 (0.0311, 0.1467)	0.125 (0.068, 0.182)	0.001	Direct: 0.1254 (0.0709, 0.1816)
Q4 vs Q1	0.230 (0.017, 0.443)	0.034	Indirect: 0.0028 (0.0005, 0.0108)	0.373 (0.175, 0.571)	0.001	Indirect: 0.0025 (0.0004, 0.0090)
Q3 vs Q1	0.154 (-0.030, 0.339)	0.101	**% total mediated effect: 3.2%**	0.302 (0.104, 0.501)	0.003	**% total mediated effect: 2%**
Q2 vs Q1	-0.074 (-0.248, 0.100)	0.405		0.186 (-0.023, 0.395)	0.082	
Mono-unsaturated fat	-0.112 (-0.173, -0.052)	0.001	Direct: -0.1126 (-0.1722, -0.0549)	-0.123 (-0.179, -0.067)	0.001	Direct: -0.1234 (-0.1791, -0.0694)
Q4 vs Q1	-0.301 (-0.515, -0.087)	0.006	Indirect: -0.0033 (-0.0046, 0.0135)	-0.367 (-0.566, -0.168)	0.001	Indirect: -0.0010 (-0.0054, 0.0026)
Q3 vs Q1	-0.223 (-0.412, -0.034)	0.021	**% total mediated effect: 2.9%**	-0.083 (-0.291, 0.125)	0.435	
Q2 vs Q1	-0.037 (-0.209, 0.135)	0.671		-0.012 (-0.222, 0.198)	0.911	
Long-chain Omega-3				-0.112 (-0.169, -0.056)	0.001	Direct: -0.1125 (-0.1683, -0.0584)
Q4 vs Q1				-0.368 (-0.562, -0.173)	0.001	Indirect: -0.0003 (-0.0043, 0.0035)
Q3 vs Q1				-0.179 (-0.362, 0.004)	0.055	
Q2 vs Q1				-0.148 (-0.335, 0.039)	0.122	
Plasma lutein + zeaxanthin[c]				-0.173 (-0.391, -0.044)	0.015	Direct: -0.1719 (-0.3753,- 0.0039)
Q4 vs Q1				-0.856 (-1.608, -0.104	0.026	Indirect: -0.0186 (-0.0939, 0.0434)
Q3 vs Q1				-0.732 (-1.108, -0.056)	0.034	
Q2 vs Q1				-0.536 (-1.139, 0.066)	0.081	

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intakes or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] Mediation analyses were carried out where there are significant associations between dietary intakes or nutrient biomarkers and depressive symptoms. Total effects were partitioned into Direct effects (dietary intake on depressive symptoms independent of inflammation) and Indirect effects (mediation via inflammatory markers).

[b] All models adjusted for age, marital status, annual household income, education, smoking status, physical activity, BMI use of antidepressants and self-reported depression/anxiety disorder, diabetes, stroke and heart attack

[c] n=57 for males

P<0.01 t in bold.

PART 4: DISCUSSION AND CONCLUSIONS

CHAPTER 8: General Discussion

This chapter summarises the key findings from the body of research conducted for this thesis, discuss the strengths and limitations of the research, and provides recommendations for future research.

8.1 Study findings, strengths and limitations

This thesis included a series of studies investigating the association between overall diet and depression. The main aim was to fill some of the gaps in literature examining the diet-depression relationship via various study designs and analysis methods to provide new insights into the relationship between diet and depression. Overall, the evidence presented in this thesis supports a weak association between the consumption of a healthier diet and a reduced likelihood of developing depression or depressive symptoms. However, study findings need to be interpreted cautiously. The key findings and strengths and limitations, grouped according to study, are summarised below:

8.1.1 A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults.

This systematic review found that the FFQ was most commonly used to measure dietary intake while depression was assessed with symptom inventories, particularly the Centre for Epidemiologic Studies – Depression scale (CES-D). Most studies used diet quality scores or indices to define overall diet, where higher scores usually indicate greater adherence to current dietary guidelines hence a healthier diet. Two key dietary patterns, namely the Healthy diet and Western diet, were identified; although the characteristics varied according to country as did the diet quality score or statistical method used to define overall diet. The Healthy diet is characterised by high intakes of fruit, vegetables, fish and wholegrains, whereas the Western diet is comprised of high intakes of refined grains, processed meat, food or snacks, and high-sugar high-fat products. The synthesis of study findings concluded that there is an association between consumption of the Healthy diet and a reduced likelihood of developing depression, but showed no significant associated between the Western diet and odds of depression. The

association between the Healthy diet and odds of depression is consistent with that observed between the Healthy diet and cardiovascular disease (CVD), type-2 diabetes and cancer (1, 2). Interestingly, the Western diet was not associated with depression, unlike the strong positive association observed with other chronic diseases (3), although this may be due to the small number of included studies.

Strengths and limitations

This review is the first to statistically (4)pool study estimates examining the relationship between overall diet and depression, although a number of systematic reviews were published concurrently (5, 6). The strength of conducting a meta-analysis is the ability to more accurately quantify the association between overall diet and depression (4), instead of a qualitative comparison of studies which can be relatively subjective. Furthermore, the meta-analysis revealed the level of heterogeneity of the included studies, and provided a better understanding of the differences in design, conduct and analysis (7), which can be taken into consideration in the design of future primary research. The high level of heterogeneity, however, remains a concern of this study as the pooled study estimate can be compromised. While the sources of heterogeneity were explored in meta-regression and subgroup analyses, the true cause of heterogeneity was not identified. The inclusion of a number of studies with large sample size can have a disproportionately large influence on the results. Stratifying the analysis by sample size may help verify the stability of the results (7) but this was not conducted. Furthermore, a number of factors influencing the heterogeneity were not explored due to a lack of detail in reporting the studies. The absence of randomised controlled trials which are considered to be the most reliable form of scientific evidence for establishing cause and effect means that the meta-analysis findings may have a higher risk of bias. Only methodologically rigorous observational studies were included to minimise the bias introduced, but the inconsistent adjustment for confounders among studies suggests that confounding bias is likely to exist. Despite the rigour of the inclusion and exclusion process, the majority of the evidence included was cross-sectional in nature, which makes determining the causal direction of the diet-depression relationship difficult.

8.1.2 Biochemical validation of the Older Australian's food frequency questionnaire using carotenoids and vitamin E

The purpose of the validation study was to comply with the criteria for high quality research, which is a prerequisite for inclusion in the meta-analysis. In the meta-analysis, a total of nine 'Neutral' studies, which could have been included, were eliminated because they did not use a validated tool to measure dietary intake. As discussed in Section 3.1, the DQES v2 used to measure dietary intakes among ALSWH participants was demonstrated to be reliable and valid via multiple testing. The Older Australian's FFQ used in the HCS had only been validated once against weighed food records, thus a second validation study was conducted comparing reported intakes of carotenoids and vitamin E to those measured in plasma, to determine the ability of the FFQ in measuring these nutrients among the HCS participants. The study found that the Older Australian's FFQ demonstrated reasonable validity for the assessment of carotenoids (except lutein + zeaxanthin), Vitamin E, fruit and vegetable intakes, as shown by significant correlations and/or high quartile agreements (≥70% within the same/adjacent quartile) between the methods for α-carotene, β-carotene, β-cryptoxanthin, lycopene and Vitamin E. The study estimates also compare well with similar studies in Australia and in other countries. The study also showed that the FFQ is a good measure of fruit and vegetable intake. The ability of the Older Australian's FFQ to accurately capture intakes of these nutrients and foods is important as the meta-analysis implicates fruits and vegetables as potentially protective, which contain a number of components that may lower the risk of depression including carotenoids and vitamin E. This finding is useful in proceeding to studies of diet and depression using HCS data such as the one conducted in Chapter 7. However, the FFQ may not be equally valid in measuring lutein + zeaxanthin intake due to the weaker correlation and lower quartile agreement between the methods.

Strengths and limitations

The study methods complied with that of the EURopean micronutrient RECommendations Aligned Network of Excellence (EURRECA) scoring system of a "good" quality validation study. The EURRECA was also used in the quality rating of dietary assessment tool used in studies included in the meta-analysis. The subset of HCS participants included in the study is

representative of all study participants in terms of age, gender and total energy intake, thus results can be generalised to the entire study cohort, that is, the FFQ can reasonably rank all HCS participants according to their intakes of carotenoids, Vitamin E, and fruits and vegetables. The analysis did not adjust for confounding as the study estimates generated from subgroup analyses based on the identified potential confounders (e.g. smoking, BMI, and alcohol) did not differ substantially from the combined study estimates. However, the study may have been under-powered for subgroup analyses. Adjustment for these potential confounders could still be carried out to verify the consistency of the results. The lack of comprehensive Australian-based data for carotenoids resulted in having to modify the existing nutrient database to include carotenoid estimates from the U.S Department of Agriculture (USDA) database. In using different nutrient database sources from other countries, there is an increased chance of a measurement error. However, Chapter 7 ranks individuals into quartiles of dietary intake in relation to depression, thus the effect of this potential measurement error is likely to be reduced. Beyond this thesis this biochemical validation is important to the ongoing use of the HCS dietary data for exploring any number of other diet-disease relationships.

8.1.3 Prospective study on the association between diet quality and depression in mid-aged women over 9 years

This primary research investigated the association between diet quality and incident depression using a longitudinal study design, allowing the temporal relationship between diet and depression to be established. This study complements that of the meta-analysis, in that the study design and conduct was based on the most commonly used methods identified by the meta-analysis. This study used a validated FFQ to measure dietary intake and a diet quality score to define overall diet, and the CES-D to measure depressive symptoms, and also met the quality rating for a ‘Positive’ study.

The causal direction of diet quality on incident depression was examined in two ways. First, analysis was carried out where diet quality at one survey predicted odds of depression at the following survey. In this analysis, diet quality scores were categorised into tertiles and coded as a lagged time-varying variable to account for the effects of time on dietary intakes. A test for linear trend across increasing diet quality tertiles was also conducted. Results showed no

significant dose-response relationship between diet quality tertiles and depression after adjustment for confounders, but the highest tertile of diet quality was associated (borderline significance) with a 6% reduced odds of depression compared to the lowest tertile. Second, changes in diet quality over a period of six years in relation to incident depression were examined. Results showed that women who maintained a moderate-high score had 6-14% lower odds of depression compared to women who maintained a low score. Among women who improved or worsened their score over the six years, there appeared to be no significant impact on their odds of depression, although point estimates showed similar effects, both in magnitude and direction. Both analyses showed that a good quality diet is associated with lower odds of depression, providing a strong argument for improving diet quality in the prevention of incident depression. Interestingly, this study showed that extreme adherence to high diet quality (i.e. highest tertile or long term maintenance of moderate-high score) is essential for a beneficial effect.

Strength and limitations

The use of multiple assessments of dietary intakes at three time-points provided the advantage of examining changes in diet quality over time. As such, in depth exploration of different levels of compliance to diet quality for a period of six years could be explored, which provided insight into the duration of time needed for dietary interventions to have an effect on depression outcome. Diet quality was treated as a time-varying variable considering participants changed their diet quality throughout the study, as evident by almost half of study participants increasing or decreasing their score at six-year follow-up. Some confounders included in the adjusted analyses were also coded as time-varying covariates, such as smoking and physical activity, which are likely to change over time. All studies to date failed to account for the time-varying status of dietary intake and confounders, which may bias the study findings (8), as attested in Chapter 6 where accounting for time-varying or not had an impact on detecting an association. Findings from this study have also provided stronger support towards a causal relationship between diet and depression, using a longitudinal design with repeated measures of both dietary intakes and depression over a long period of time. In excluding participants with depression prior to Surveys 2 and 3, this chapter showed that reverse causality is unlikely.

However, like all observational studies, residual confounding is likely to exist even with adequate adjustment in analyses. The diet quality score used in this study has not been widely applied in studies to predict chronic diseases, thus the ability to predict depression is unclear, which may be the reason why the associations were modest in magnitude. Similar analyses using other diet quality indices to explore the association between diet quality and depressive symptoms using prospective cohort data could be carried out to further complement results from this study. As discussed in Chapter 5, the different formats of the DQES v2 used at each survey, and the use of self-reported depression status could bias the association towards the null. Repeated assessments of exposure and outcome using the same instruments will also result in a similar effect, as participants may remember and repeat the same answers each time (9). If, in fact, a true causal association exists between diet quality and depression but is masked by these methodological shortcomings, this is of great clinical and public health significance. Caution should be applied when generalising study findings to the national female population. Although the retention rate was high (>80% of the initial sample), those who remained at Survey 6, were more likely to be married, to be employed and have higher education compared to the 2011 census (10).

8.1.4 Longitudinal diet quality is not associated with depressive symptoms in a cohort of mid-aged Australian women

This study is an extension to Chapter 5, but aimed to provide a different perspective on the diet-depression relationship. The study methods for Chapter 6 are similar to Chapter 5 with respect to study population, measures for dietary intake, diet quality, depressive symptoms and confounders. However, Chapter 6 has a different aim to Chapter 5. Instead of examining whether high diet quality prevents new cases of depression, this chapter examined whether good diet quality relieves depressive symptoms in individuals with existing depressive disorder or subthreshold depression. As such, participants with depression prior to Survey 3 were not excluded from analysis, and depressive symptoms were treated as a continuous outcome variable to reflect changes in symptoms rather than depression cases. Contrary to findings from Chapter 5, no significant association between diet quality and depressive symptoms were found. However, as explained in Chapter 6, the heavier focus on a clinical diagnosis of depression in Chapter 5 can translate into differences for the association between diet quality and depression,

with larger association observed between diet quality and having a depressive disorder than sub-clinical depressive symptoms. Most studies identified by the meta-analysis that demonstrated an association between diet quality and depression also looked at new cases of depression rather than changes in depressive symptoms.

Secular trends in overall diet quality were also examined to provide insights into study-wide compliance with diet quality over time. Results showed minimal changes in diet quality among study participants over a period of 12 years, although almost half of participants increased or decreased their diet quality at the six-year follow-up in Chapter 5. Note, however, that the secular trends observed here reflect the average yearly change in diet quality score for the entire study cohort, rather than changes at the individual level after a period of six-years, thus the difference in findings between Chapters 5 and 6. Of major concern is the suboptimal diet quality of the overall study sample. Even among the highest quintile, the average score is 44 out of 74, indicating that participants lacked diversity in the foods they consumed. This pattern of dietary intake is consistent with worldwide assessment of diet quality where the average healthy diet score was far from the maximum score even among higher income countries (11). Given that suboptimal nutrition is associated with poor individual and population health and higher chronic disease rates (12), it is possible that a suboptimal adherence to national dietary recommendations may partially be responsible for increased depression risk, countering the beneficial effect of a higher diet quality, resulting in non-linear associations.

Diet quality was re-assessed with the MDP, and the association with depressive symptoms was re-analysed to determine the robustness of study findings. The ARFS appears to be a better predictor of depressive symptoms than the MDP. The most interesting finding is that the coding of exposure and confounding variables into time-varying or not has a large impact on the significance and strength of the association between diet quality and depressive symptoms. This suggests that previous significant findings in other studies may have been biased by not accounting for time-varying status of exposure and confounding variables.

Strengths and limitations

The strengths of this study are like those described in Section 8.1.3 – longitudinal design, the availability of data at multiple time points, and the inclusion of time-varying variables.

Furthermore, this study highlighted the importance of accounting for time-varying confounding. While the ARFS may be a better predictor of depressive symptoms than MDP, a number of limitations to this diet quality index should be considered. First, the ARFS is a measure of food diversity more so than the absolute amount consumed. It may likely be the frequency and quantity of specific foods that are important in the diet-depression relationship instead of a variety of nutrient dense foods but estimates of actual amounts of nutrients and foods consumed were not available at Surveys 5 and 6 due to the use of a shortened version of DQES v2. Second, the ARFS lacks specificity on fat quality. As shown in Chapter 7 different types of fats differ in their associations with depressive symptoms. Third, the broad inclusion of many fruits in the ARFS scoring method may be problematic. As indicated in Chapter 7, intake of specific fruits (e.g. fruits with high flavonoids) may be associated with lower depressive symptoms rather than total fruit intake. The lack of differences in diet quality over time may be a result of repeated assessments of diet using the same instruments, as participants may remember and repeat the same answers each time (9). Similar to the limitations addressed in Chapter 6, residual confounding is likely to exist and misclassification bias due to measurement errors is possible.

8.1.5 Inflammation mediates the association between fatty acid intake and depression in older men and women

As identified in the meta-analysis, the Healthy diet is characterised by high intakes of fruits and vegetables, fish and whole grains. It was proposed that the high content of antioxidants and omega-3 fatty acids of these foods are what constitute the anti-depressive properties of this dietary pattern (13-15). Conversely, the Western diet appears to be associated with increased odds of depression, although the association was not significant, which is mainly due to the high glycaemic index (16) and high fat content (17). At the same time, these dietary components have been shown to affect inflammatory cytokine production (18, 19), and inflammation appears to predict depression risk (20). Hence, inflammatory processes are thought to be one of the fundamental mechanisms underlying the association between diet and depression.

This study showed suggestive evidence that inflammation is one of the factors mediating the diet-depression relationship. Results showed that carotenoids and vitamin E initially thought to

be on the diet-inflammation-depression pathway were not associated with depressive symptoms, but suggest that other dietary components (e.g. phytochemicals) or a combination of food constituents may be responsible for this mechanism, further supporting the importance of examining food groups and dietary patterns instead of isolated nutrients. While plasma carotenoids were inversely associated with depressive symptoms in males, there was no evidence of mediation by inflammatory markers. As expected, saturated fat intake was positively associated with depressive symptoms, while high mono-unsaturated fat intake was associated with lower depressive symptoms (in females only), and this is partially mediated by CRP. A number of significant associations between diet, inflammatory markers and depressive symptoms were observed in females only, suggesting a gender difference in the relationship pathway. This study further highlighted the fact that the pathophysiology of depression is complex, and the way in which diet affects depression often involves several biological pathways, as evident by a small mediation effect by inflammatory markers.

Identification of underlying biological pathways and markers allows us to focus on important aspects of diet that need strengthening in order to improve depression outcome. As discussed in Chapter 7, findings of this study provided a better understanding of why some studies showed a significant inverse association between a healthy dietary pattern or high quality diet and depression, while some did not, indicating that studies with non-significant results may not have focused on dietary components most relevant to depression.

Strengths and limitations

This study is among the first to employ mediation analyses to examine the underlying biological pathway linking the association between diet and depression. Mediation analyses were carried out with the most commonly used Baron and Kenny causal steps approach (21), which is simple and widely understood. Most readers will be able to understand the results with little difficulty and the analyses can be easily replicated by other researchers. However, this method has been criticised for having low power in detecting mediating effects (22). It is very likely that IL-6 and CRP are important mediators for the associations observed in a number of nutrients/foods with depression but the mediating effects may have been masked by the shortcoming of this method.

As discussed in Chapter 7, the use of a prospective cohort design helped in understanding the temporal relationship between these three factors, but it is also limited by only having baseline data for dietary intakes and inflammatory markers. Multiple measurements at various time points to compare change in trajectories for all three factors would have provided a stronger evidence of the mediation effect. The ideal way of conducting this study is to first measure dietary intake, followed by the inflammatory markers, then depressive symptoms. On the other hand, dietary intake was measured using a twice-validated food frequency questionnaire. In particular, this FFQ can accurately rank participants into quartiles of carotenoids, vitamin E, and fruits and vegetables intakes. The previous validation study by Smith et al. also demonstrated that the FFQ is a valid tool in measuring the different types of fatty acids intake (23). However, the ability of the FFQ in capturing lutein + zeaxanthin intake is unclear, which may bias the association observed between this nutrient and inflammation or depressive symptoms in this study.

The use of only two inflammatory markers may not be a comprehensive representation of the inflammatory processes, which could be the reason why the mediation effects of these inflammatory markers were small. Other inflammatory markers such as TNF-α receptor 2, E-selectin and serum amyloid-A have demonstrated associations with dietary intakes (24) and depression (25) respectively, and could be important mediators of the diet-depression relationship. However, their mediating effects could not be tested as data for these markers were not available at the time of study. This study examined the mediation effect for each inflammatory marker separately, but it is possible that the combined effects of inflammatory markers could potentially explain a larger proportion of the association between diet and depression. In addition, the intake of fish was not examined, although it was highly correlated with omega-3 fatty acid. The inclusion of fish intake in the analyses would help to elucidate whether the beneficial effect observed between fish and depression is attributable to its omega-3 fatty acid content.

8.1.6 Concluding remarks

Taken together, the findings of this thesis provide some evidence towards a causal association between overall diet and depression. However, the evidence presented supports diet as a

universal prevention strategy to new cases of depression but is less clear regarding diet as a therapeutic strategy for depressive symptoms. Where there is a significant association between diet and depression, it is often modest in magnitude, which is common with epidemiological studies. Furthermore, inflammation only partially explains the relationship between diet and depression, which is consistent with current literature regarding the diverse aetiology of depression.

The studies undertaken as part of this thesis complemented each other and demonstrated a range of appropriate methods. The meta-analysis summarised the published literature and identified current gaps in research which served as the rationale for the design of subsequent studies in this thesis. The ability of the Older Australian's FFQ to accurately capture carotenoids, vitamin E, and fruits and vegetables intakes was essential to ensure high methodological quality of Chapter 7. Chapters 5 and 6 provided varied perspectives on the temporal relationship between overall diet and depression which comprehensively summarised the role of diet in depression. Finally, this thesis goes beyond the association between overall diet and depression, and examined inflammatory markers as mediators of the observed diet-depression relationship to help clarify potentially causal biological mechanisms.

However, like all observational studies, residual confounding is likely to exist. The use of diet quality scores instead of statistical derivation of dietary patterns may be problematic, as compliance to diet quality is often suboptimal in the general population, which could be the reason why significant health benefits were not observed. This thesis comprised mainly of secondary analyses of existing data which posts a number of limitations. Without any control over data collection, some data important to the research questions of this thesis was not available. For example, Surveys 5 and 6 of ALSWH lack data on absolute amounts of nutrients and foods, thus Chapters 5 and 6 had to rely on ARFS as a measure of diet quality despite the uncertainty regarding the ability of this tool in predicting chronic diseases. Likewise, for Chapter 7, IL-6 and CRP were the only two inflammatory markers available at the time of study which may not be most comprehensive. In addition, Chapter 7 lacks data across multiple time-points, thus the contribution of this chapter's findings to the overall evidence presented in this thesis in elucidating the causal directionality of diet and depression is limited. As such, the findings and

conclusions reached need to be interpreted with caution, and further evidence are needed to support the arguments presented here.

8.2 Recommendations for Future Research

Since the publication of our meta-analysis, more studies examining the association of dietary pattern or diet quality and depression have been published. This provides an opportunity to conduct an updated meta-analysis which may help address the limitations in the first one. Following the publication of more cohort studies and RCTs, the updated meta-analysis can include these studies to elucidate the temporal sequence of the diet-depression relationship, and eliminate the possibility of reverse causation. While we try to match the study characteristics as closely as possible, the pooled study estimate in our meta-analysis revealed a high level of heterogeneity. This problem can be solved as more studies using similar measurements and analysis methods are published and results can be pooled. For example, studies using the *a priori* method can be pooled based on the dietary indices/scores used. However, studies using pattern analysis may still be difficult to pool due to the subjective analytical approaches, and the fact that different dietary patterns will emerge from different study populations. One way to reduce heterogeneity may be to pool studies of the same country where dietary habits and intakes are similar, and studies that used similar approaches at each step of pattern analysis.

Randomised controlled trials (RCTs) are needed to eliminate residual confounding and to confirm the existent of a causal relationship between overall diet and depression. Despite the weaker associations observed between diet quality and depression in Chapters 5 and 6, findings from other studies (presented in Chapters 1 and 2) demonstrated stronger inverse associations between diet quality and depression, constituting enough support to replicate these findings in RCTs. Most RCTs to date comprise participants who have greater susceptibility to depression such as those with type-2 diabetes and/or at high risk of cardiovascular disease to ensure accrual of an adequate number of cases (26). If dietary modification is to be considered as a population prevention strategy to depression, findings from these RCTs may not be useful as they lack generalisability. However, conducting RCTs in non-selected groups may be impractical due to the relatively high cost. A much larger number of participants would be

necessary for detection of small differences, and a substantially longer follow-up period would be needed before an effect can be measured (27). Low compliance by the intervention group to dietary modifications and adoption of a healthier diet by the control group due to absence of blinding are common in RCTs (28), and may result in insufficient differences between the groups, affecting the power of the study to find an effect (26). Similarly, for ethical reasons, the control group is assigned to a relatively healthy diet (although the food/nutrient of interest is lower in content) again reducing the between-groups variation (28). Considering these limitations, it is proposed that well-designed RCTs and population-based observational studies serve as complementary forms of research to ensure that the results of clinical trials are translatable to practical strategies for the general population (29).

Much of the evidence presented in this thesis explored overall diet as preventative to depression or depressive symptoms. For example, Chapter 2 did not include studies with a primary focus on depressed patients, and Chapter 5 excluded participants with depression at baseline. Although Chapter 6 attempted to examine diet quality as potentially beneficial for relieving depressive symptoms regardless of depression status, there was no specific focus on those with existing depression. Thus, the evidence for dietary intervention as therapeutic to major depression is weaker in comparison. Given the limitations in pharmacological and psychological treatments, research into dietary improvement as a depression management strategy is an area that warrants greater attention.

Chapters 5 and 6 relied on diet quality scores to define overall diet. While the use of dietary indices has several advantages (e.g. provide summary measures of compliance to dietary guidelines which can be translated to practical advice), statistically derived dietary patterns remains useful. Specifically, most dietary indices were developed to assess compliance to a dietary intake that is healthy as they are based on national dietary recommendations. Often, the Western diet had to be statistically derived. It is important to examine the Western diet in relation to depression especially when it was found to affect depression independent of the Healthy diet. Studies that explored both the Healthy and Western diet found no evidence that both patterns jointly influence depression, that is, poor compliance to the Healthy diet is associated with poorer depression outcome, regardless of intake of Western diet, and vice-versa (30-32). Furthermore, concurrent research into both types of diet provides useful

information regarding which unhealthy foods to avoid in addition to what healthy foods should be consumed for a lower likelihood of developing depression.

As discussed in Chapter 2, the substantial heterogeneity in the meta-analysis could be a result of large variations in the definition of diet quality and patterns. Therefore, standardising measures of diet quality or dietary patterns in future studies are required to ensure findings are comparable. However, it is recognised that the difficulties in standardising the definitions of overall diet is a reflection of the challenges often confronted in nutrition research as great variation exists in dietary habits across cultures and countries. In spite of this, future studies should aim to replicate the design and conduct of existing studies especially in terms of constructing a standard definition of diet quality or employing a standard statistical analysis to identify dietary patterns. More specifically, factor analysis and/or principal component analysis involve several subjective decisions at almost every steps, thus studies using this method should clearly outline the strategy for their analyses, and include justification for their decisions.

Another *a-posteriori* method, reduced rank regression (RRR), has been recently introduced to nutrition epidemiology to derive dietary patterns (33). RRR combines two information sources – prior disease-specific information and dietary data from the study, thus it is more objective than factor or cluster analysis. This method involves choosing disease-specific response variable (e.g. nutrients, biomarkers, etc.) and deriving from the data combinations of food intake that explain as much response variation as possible (33). As such the derived dietary pattern may be better at predicting the disease of interest. To date, the statistical methods used in dietary pattern derivation are purely exploratory and do not incorporate existing knowledge on nutrients or foods that are important in the development of depression, which explains the inconsistencies in findings among studies using these methods. Future studies can consider using the RRR in deriving dietary patterns. However, the RRR method is dependent on the availability of the response variable, thus when there is no clear information regarding disease aetiology, no response variables can be justified (34). Furthermore, for many chronic diseases a complex interplay of metabolic pathways may link dietary intake to disease, thus it is often difficult to determine whether to consider only one biological pathway or all potential pathways, and how to select the best set of responses (34). Therefore, pattern analysis may still be useful when exploring diseases whose causative relationship to dietary exposures is not clear.

In addition, it is recommended that studies use several dietary indices to assess overall diet quality to compare how well these measures relate to depression. Many indices have been developed to measure overall diet quality but they vary greatly in the way they were constructed and what they measure. The components of diet that were measured could range from nutrients only, to recommended amount for food groups, to diversity within specific food groups (35). Furthermore, some indices were derived based on epidemiological associations with a specific disease outcome such as cardiovascular disease and cancer, and the ability of these indices to predict other disease outcome is unknown. Although all indices reflect a healthy diet, they may be poor choices for evaluating diet quality in relation to depression. If a true association exist between diet quality and depression but is masked by the poor performance of the chosen diet quality score/index, this would have greatly affected the interpretation of study findings. The use of several indices can help eliminate this concern.

There appears to be some differences between categorical and dimensional approaches to depression (36). The majority of studies examining the diet-depression relationship categorised participants into those with or without depression. Studies examining the association of diet with different levels of depression from a dimensional approach (e.g. comparing no depression to subthreshold depression, and to minor and major depression) are lacking. Future investigation into the diet-depression relationship can consider defining depression within a spectrum of increasing severity of symptoms or different subtypes of depression, as a more comprehensive approach to elicit the role of diet in depression. It is possible that the association between diet and depression differs according to depression severity or depression subtypes. Furthermore, comparing varying degrees of depression severity is likely to reduce residual confounding as there may be greater unmeasured differences between individuals with or without depression, but fewer differences between those with severe and less severe depression.

There is evidence showing that the association between diet and depression differs across age groups (30), and depression appears to manifest differently at different ages (37), thus exploring the diet-depression relationship across the lifespan is necessary. The first onset of depression is often mid-to-late adolescence and early adulthood, and given that most lifestyle habits are formed earlier in life, preventive activities targeting adolescents and young adults are needed. Conversely, having depression at an older age is equally if not more disabling than having

depression at a younger age (37), thus promotion of healthier dietary habits should also target the middle-to-older age groups.

Adequate adjustment for confounders is important in determining whether a true association exists between overall diet and depression. However, there was great variation across studies in the selection of covariates to adjust for in statistical analyses. It is recommended that the selection of confounders is based on background knowledge of the causal structure connecting exposure to outcome, and based on statistical associations of the covariate with the exposure and outcome (38). A graphical analysis of the structural basis for evaluating confounding such as directed acyclic graphs (DAGs) is the most robust approach to selecting variables for adjustment when there is sufficient knowledge of the causal pathways, as it formalises the theoretical justification for covariate selection and provides a better understanding of bias due to under- and over-adjustment (38). Alternatively, a subset of these covariates identified based on background knowledge can be selected on the basis of statistical associations. Having said that, regardless of which one or a combination of both approaches is used, future studies should clearly describe how variables are measured and provide a rationale for *a priori* selection of potential confounders. If variables were selected based on statistical associations, the models should be presented and the criteria used for inclusion or exclusion clearly described. In the same way, as discussed in Section 8.1.3, adjustment for time-varying confounding needs to be considered in future studies using data at multiple time points.

This thesis has focused on the public health aspects of diet in relation to depression, but of equal importance are research that focus at the level of treating the individual. As summarised in Section 1.1.4, antidepressants and psychological treatments are generally effective in treating depression. Despite this, continued research aiming at evaluating current medical and psychological treatments, as well as developing strategies to improve general coping skills, are needed. Many people attempt to cope with symptoms of depression without professional help and turning to alternative therapies including naturopathy, exercise, relaxation and meditation. However, little is known about their effectiveness. Future studies should thus focus on providing evidence regarding the diverse range of self-help treatments including those related to diet such as vitamin and mineral supplements, traditional medicine and herbal remedies.

Knowledge of the pathophysiology of depression has evolved substantially in the past decade (20). However, to further reduce the burden of depression, it is crucial to look beyond currently proposed mechanisms and biological basis of diet and depression in order to develop new strategies for the prevention or treatment of depression. Studies can combine the examination of diet quality and its nutrient content and food constituents for a more complete characterisation of the aspects of diet most relevant to depression. An emerging field suggests that the microbiome–gut–brain axis is of substantial relevance to mood and behaviour (39). Hence, new dietary interventions could potentially focus on improving gut health which may in turn improve depression outcome. Future studies should also investigate potential biomarkers as mediators in the diet-depression relationship to elucidate causal biological factors such as oxidative stress, neurotrophic and epigenetic mechanisms.

8.3 Final Conclusions

The World Health Organization Mental Health Action Plan 2013-2020 highlighted the need to use information on risk and protective factors for mental health to put in place actions to prevent mental disorders, and to promote mental well-being (40). There was great emphasis on strategies to influence social and economic determinants but lifestyle strategies were not specifically addressed. However, it is about time to use this emerging understanding of the impact of lifestyle behaviours to develop cost-effective population-level initiatives for reducing the burden of depression. This thesis presented some epidemiological evidence that a causal relationship between overall diet and depression is plausible. Consequently, dietary modifications can be an effective population prevention strategy, and can also be a novel therapeutic strategy for those with depression. Policies aiming at prevention, as well as public health messages and educational programs can consider integrating these new findings regarding diet with previously understood social and economic risk factors in the efforts to combat depression. From a clinical perspective, recommendations for dietary improvement can be routinely provided to all patients with depression and possibly incorporated into treatment guidelines.

It should be acknowledged that research on diet as a true causal risk factor for depression is still developing, and the evidence to date is not particularly strong. The associations observed

between diet and depression, if any, are modest in magnitude. But given the size of the burden of depression, the benefits of even a minimal impact of diet on the prevalence of depression will be substantial. Moreover, universal prevention approaches are more cost-effective than clinical interventions, thus promotion of healthy eating habits may constitute as an inexpensive, sustainable and effective option to preventing depression or relieving depressive symptoms, further contributing to reducing the global burden of this mental disorder. Given that diet is a modifiable risk factor for other chronic diseases (e.g. cardiovascular disease, type 2 diabetes, and certain cancers), population wide healthy eating promotion would also contribute to greater reduction in all-cause mortality and morbidity.

A number of community-based healthy eating programs in Australia were carried out to promote healthy eating habits across all age groups. For example, the currently running “Shape up Australia” campaign by the National Preventive Health Agency aims to encourage a healthier lifestyle including healthy eating among the adult population, and the “Go for 2&5 Campaign” launched in 2005 by the Department of Health and Ageing aimed specifically at increasing fruits and vegetables intakes among children and adolescents. However, the promoted public health messages of these campaigns have a heavier focus on the prevention of cardiovascular disease, type-2 diabetes and some cancers. With the emerging understanding that diet could be a modifiable risk factor to depression, current or future campaigns should incorporate this knowledge, and further reinforce current rationales for adopting healthy eating behaviours to include prevention of mental disorders and for improving mental health and wellbeing.

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Appendices

Table 9.1: Longitudinal associations between quartiles of baseline dietary intake or nutrient biomarkers, and Centre for Epidemiologic Studies-Depression scale (CES-D) for dietary supplement users, stratified by sex, in the Hunter Community Study (n=251) [a].

	β (95% CI) for CES-D			
	Q2	Q3	Q4	*P*
Females (n=124)				
Dietary Intakes				
Total carotenoids (n=87)	-0.029 (-0.681, 0.607)	0.101 (-0.529, 0.699)	-0.084 (-0.703, 0.514)	0.506
Alpha-carotene	-0.095 (-0.790, 0.598)	-0.053 (-0.649, 0.535)	-0.119 (-0.670, 0.557)	0.194
Beta-carotene	0.085 (-0.469, 0.561)	0.021 (-0.473, 0.341)	-0.039 (-0.599, 0.521)	0.413
Beta-cryptoxanthin	0.079 (-0.563, 0.713)	-0.037 (-0.624, 0.574)	-0.041 (-0.612, 0.575)	0.548
Lycopene	0.100 (-0.463, 0.686)	0.019 (-0.542, 0.607)	0.124 (-0.568, 0.859)	0.384
Lutein+zeaxanthin	-0.117 (-0.697, 0.427)	-0.049 (-0.672, 0.574)	-0.053 (-0.596, 0.445)	0.486
Vitamin E (n=84)	0.009 (-0.576, 0.578)	-0.044 (-0.624, 0.557)	-0.029 (-0.624, 0.543)	0.802
Long-chain Omega-3 (n=98)	0.101 (-0.401, 0.591)	-0.040 (-0.621, 0.492)	-0.048 (-0.624, 0.476)	0.140
Nutrient Biomarkers (n=7)				
Total carotenoids	0.405 (-0.764, 1.316)	0.524 (-0.687, 1.295)	-0.397 (-1.551, 0.540)	0.801
α-carotene	0.101 (-0.784, 1.043)	0.031 (-0.800, 0.819)	-0.395 (-1.142, 0.616)	0.675
β-carotene	0.411 (-0.690, 1.238)	-0.270 (-1.065, 0.789)	-0.171 (-0.932, 0.853)	0.817
β-cryptoxanthin	-0.608 (-1.571, 0.419)	-0.127 (-0.803, 0.846)	-0.644 (-1.752, 0.622)	0.875
Lycopene	-0.204 (-1.179, 0.826)	0.695 (-0.288, 1.412)	-0.204 (-1.077, 0.733)	0.670
Lutein+zeaxanthin	-0.272 (-1.057, 0.777)	0.256 (-0.890, 1.137)	-0.897 (-1.767, 0.237)	0.107
Vitamin E	1.475 (-0.232, 1.998)	0.675 (-0.110, 1.376)	0.687 (-0.136, 1.542)	0.537
Males (n=127)				
Dietary Intakes				
Total carotenoids (n=89)	0.030 (-0.565, 0.605)	-0.029 (-0.610, 0.482)	-0.031 (-0.591, 0.503)	0.206
α-carotene	-0.092 (-0.683, 0.574)	-0.021 (-0.544, 0.480)	0.027 (-0.496, 0.591)	0.684
β-carotene	-0.097 (-0.637, 0.451)	0.021 (-0.473, 0.513)	-0.025 (-0.548, 0.618)	0.461
β-cryptoxanthin	-0.033 (-0.589, 0.612)	-0.028 (-0.677, 0.506)	-0.048 (-0.691, 0.591)	0.483
Lycopene	-0.140 (-0.743, 0.445)	-0.148 (-0.757, 0.453)	-0.137 (-0.697, 0.475)	0.104
Lutein+zeaxanthin	0.032 (-0.553, 0.475)	0.061 (-0.561, 0.437)	0.019 (-0.576, 0.498)	0.780
Vitamin E (n=87)	-0.112 (-0.645, 0.410)	0.114 (-0.485, 0.788)	0.078 (-0.563, 0.781)	0.814
Long-chain Omega-3 (n=99)	-0.118 (-0.762, 0.418)	-0.117 (-0.708, 0.457)	-0.237 (-0.764, 0.196)	0.093
Nutrient Biomarkers (n=8)				
Total carotenoids	-0.695 (-1.230, 0.160)	0.286 (-0.654, 0.980)	-0.501 (-1.380, 0.057)	0.106
α-carotene	0.225 (-0.634, 0.835)	-0.242 (-0.962, 0.726)	-0.283 (-0.930, 0.615)	0.662
β-carotene	-0.470 (-1.052, 0.360)	0.193 (-0.634, 0.803)	-0.805 (-1.806, 0.025)	0.208
β-cryptoxanthin	-0.218 (-0.854, 0.541)	-0.201 (-0.930, 0.641)	-0.314 (-1.064, 0.492)	0.499
Lycopene	-0.325 (-1.125, 0.522)	-0.759 (-1.498, 0.199)	-0.640 (-1.262, 0.041)	0.525
Lutein+zeaxanthin	-0.514 (-1.084, 0.552)	-0.698 (-1.433, 0.012)	-0.749 (-1.614, 0.039)	0.144
Vitamin E	-0.568 (-1.007, 0.320)	-0.539 (-1.267, 0.436)	-0.265 (-0.913, 0.563)	0.601

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles.

[a] All models adjusted for baseline values of age, marital status, annual household income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.

Table 9.2: Longitudinal associations between quartiles of baseline dietary intake or nutrient biomarkers, and Centre for Epidemiologic Studies-Depression scale (CES-D) for non-dietary supplement users, stratified by sex, in the Hunter Community Study (n=1215) [a].

	β (95% CI) for CES-D			
	Q2	Q3	Q4	*P*
Females (n=605)				
Dietary Intakes				
Total carotenoids (n=602)*	-0.010 (-0.189, 0.170)	0.095 (-0.090, 0.273)	-0.059 (-0.233, 0.105)	0.360
Alpha-carotene	-0.095 (-0.270, 0.085)	-0.045 (-0.212, 0.136)	-0.110 (-0.286, 0.058)	0.315
Beta-carotene	0.100 (-0.085, 0.283)	0.038 (-0.143, 0.219)	-0.055 (-0.229, 0.125)	0.313
Beta-cryptoxanthin	0.090 (-0.085, 0.261)	-0.015 (-0.192, 0.158)	-0.053 (-0.224, 0.127)	0.320
Lycopene	0.087 (-0.090, 0.274)	0.010 (-0.160, 0.184)	0.115 (-0.059, 0.289)	0.341
Lutein+zeaxanthin	-0.089 (-0.265, 0.095)	-0.039 (-0.223, 0.144)	-0.051 (-0.215, 0.130)	0.753
Vitamin E (n=605)	0.008 (-0.170, 0.187)	-0.028 (-0.205, 0.148)	-0.010 (-0.187, 0.168)	0.642
Long-chain Omega-3 (n=599)	0.093 (-0.099, 0.268)	-0.017 (-0.203, 0.149)	-0.039 (-0.213, 0.135)	0.420
Nutrient Biomarkers (n=68)				
Total carotenoids	0.361 (-0.450, 1.159)	0.247 (-0.412, 0.905)	-0.409 (-1.137, 0.318)	0.382
α-carotene	0.080 (-0.645, 0.811)	0.008 (-0.667, 0.685)	-0.263 (-0.910, 0.384)	0.366
β-carotene	0.271 (-0.489, 1.001)	-0.138 (-0.833, 0.557)	-0.042 (-0.698, 0.591)	0.544
β-cryptoxanthin	-0.576 (-1.339, 0.187)	-0.090 (-0.819, 0.606)	-0.513 (-1.402, 0.401)	0.813
Lycopene	-0.178 (-0.946, 0.601)	0.566 (-0.060, 1.182)	-0.172 (-0.845, 0.501)	0.802
Lutein+zeaxanthin	-0.140 (-0.834, 0.554)	0.124 (-0.658, 0.905)	-0.765 (-1.535, 0.005)	0.084
Vitamin E	1.242 (-0.100, 1.784)	0.533 (-0.078, 1.144)	0.653 (-0.004, 1.310)	0.304
Males (n=610)				
Dietary Intakes				
Total carotenoids (n=608)	0.014 (-0.173, 0.135)	-0.020 (-0.192, 0.138)	-0.033 (-0.202, 0.153)	0.554
α-carotene	-0.077 (-0.245, 0.161)	-0.017 (-0.144, 0.199)	0.032 (-0.009, 0.010)	0.543
β-carotene	-0.082 (-0.252, 0.064)	0.014 (-0.119, 0.182)	-0.008 (-0.184, 0.168)	0.609
β-cryptoxanthin	-0.005 (-0.172, 0.156)	-0.006 (-0.170, 0.154)	-0.011 (-0.178, 0.149)	0.483
Lycopene	-0.120 (-0.285, 0.042)	-0.144 (-0.317, 0.029)	-0.118 (-0.276, 0.045)	0.215
Lutein+zeaxanthin	0.025 (-0.143, 0.179)	0.051 (-0.120, 0.216)	0.010 (-0.159, 0.182)	0.746
Vitamin E (n=610)	-0.083 (-0.244, 0.073)	0.110 (-0.060, 0.274)	0.088 (-0.088, 0.251)	0.131
Long-chain Omega-3 (n=598)	-0.107 (-0.275, 0.048)	-0.109 (-0.279, 0.061)	**-0.258 (-0.442, -0.099)***	**0.008***
Nutrient Biomarkers (n=67)				
Total carotenoids	-0.568 (-1.106, 0.041)	0.162 (-0.528, 0.853)	**-0.691 (-1.249, -0.132)**	0.090
α-carotene	0.100 (-0.506, 0.708)	-0.118 (-0.838, 0.602)	-0.162 (-0.813, 0.495)	0.545
β-carotene	-0.347 (-0.926, 0.240)	0.071 (-0.514, 0.681)	**-0.925 (-1.715, -0.152)**	0.178
β-cryptoxanthin	-0.094 (-0.730, 0.541)	-0.165 (-0.836, 0.507)	-0.290 (-0.941, 0.360)	0.365
Lycopene	-0.299 (-1.000, 0.399)	-0.645 (-1.379, 0.103)	-0.607 (-1.227, 0.020)	0.313
Lutein+zeaxanthin	-0.521 (-1.091, 0.559)	**-0.659 (-1.304, -0.011)**	**-0.801 (-1.592, -0.118)***	**0.031**
Vitamin E	-0.344 (-0.883, 0.196)	-0.415 (-1.143, 0.312)	-0.170 (-0.789, 0.449)	0.478

Data are presented as coefficients and 95% confidence intervals for CES-D in three upper quartiles of dietary intake or nutrient biomarkers compared with lowest quartile. P-values are from tests of linear trends across quartiles; *P*<0.05 in bold. **P*<0.01.

[a] All models adjusted for baseline values of age, marital status, annual household income, education, smoking status, physical activity, use of antidepressants and self-reported depression/anxiety disorder.