THE ASSOCIATION BETWEEN NUTRITION AND DEPRESSION

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Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

The University of Adelaide

September 2020

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List of Abbreviations

5HT	5-hydroxytryptamine (also known as Serotonin)
ABS	Australian Bureau of Statistics
ANOVA	Analysis of variance
AP-1	Activator protein-1
APA	American Psychiatric Association
BDI	Beck Depression Inventory
BDNF	Brain derived neurotrophic factor
BMI	Body mass index
CAT	Catalase
CATI	Computer-assisted telephone interviews
CES-D	Centre for Epidemiological Studies Depression Scale
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DA	Dopamine
DAG	Directed acyclic graph
DALY	Disability Adjusted Life Years
DASS	Depression Anxiety Stress Scales
DepS	Depressive symptoms
DHA	Docosahexaenoic acid
DII	Dietary Inflammatory Index
DNA	Deoxyribonucleic acid
DP	Dietary Pattern

DQES-V3	Dietary questionnaire for epidemiological studies Version 3
DSM	Diagnostic and Statistical Manual of Mental Disorders
E-DII	Energy adjusted dietary inflammatory index
EPA	Eicosapentaenoic acid
FFQ	Food Frequency Questionnaire
GABA	Gamma aminobutyric acid
GBD	Global burden of disease
GDS	Geriatric Depression Scale
GH	Growth hormone
GIT	Gastrointestinal tract
GSH	Glutathione peroxidase
GSR	Glutathione reductase
GWA	Genome-wide association
HDRS	Hamilton Depression Rating Scale
HPA	Hypothalamic pituitary adrenal
ICD	International Classification of Diseases
IDO	Indoleamine 2,3-dioxygenase
IL	Interleukins
INF	Interferons
LZ	Lutein and zeaxanthin
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MUFA	Monounsaturated fatty acid
NADPH	Nicotinamide adenine dinucleotide phosphate
NE	Norepinephrine

NF-κβ	Nuclear factor kappa B
NGF	Nerve growth factors
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NMDA	N-methyl-D-aspartate
NOX	NADPH Oxidase
NPs	Nutrient patterns
NUTTAB	NUTrient TABles for use in Australia
NW15	North West 2015
NWAHS	North West Adelaide Health Study
OR	Odds ratio
PAL	Physical activity level
PCA	Principal Component Analysis
PHQ	Patient Health Questionnaire
PLP	Pyridoxal 5′-phosphate
PLS	Partial least square
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
RRR	Reduced rank regression
SAD	Seasonal Affective Disorder
SCFA	Short chain fatty acids
SEIFA	Socio-economic indexes for areas
SFA	Saturated fatty acid
SOD	Superoxide dismutase
VA	Vitamin A
VB1	Vitamin B1

VB12	Vitamin B12
VB2	Vitamin B2
VB3	Vitamin B3
VB5	Vitamin B5
VB6	Vitamin B6
VC	Vitamin C
VD	Vitamin D
VE	Vitamin E
ω-3 PUFA	Omega 3 Polyunsaturated fatty acid
ω-6 PUFA	Omega 6 Polyunsaturated fatty acid
WHO	World Health Organization
YLD	Years lived with disability

Abstract

Depression is one of the most common mental disorders worldwide, affecting more than 300 million people. In Australia, one in five people aged 16-85, experience mental illness, depression being most common. Emerging evidence indicates that diet may influence the onset of depression.

This study aimed to: 1) determine the association between dietary patterns and depressive symptoms (DepS) in Australian adults by using three dietary pattern analysis methods i.e. principal component analysis (PCA), reduced-rank-regression (RRR), and partial-least squares (PLS) methods; 2) obtain further insights into the physiological mechanisms by establishing the association between nutrient patterns (NPs) and DepS; 3) determine the link between the energy-adjusted dietary inflammatory index™ (E-DII™) score and the risk of DepS.

This thesis utilized data from two stages [Stage 3 and North West 2015 (NW15)] of the North West Adelaide Health Study (NWAHS) cohort. The Centre for Epidemiological Studies-Depression (CES-D) scale and food frequency questionnaire (FFQ) was used to measure DepS and dietary data, respectively.

Our findings showed 16.9% of the participants had DepS and females (20.8%) were more depressed than males (14.2%). The 'prudent' dietary pattern captured by PCA [$OR_{Quartile4vs1}$ = 0.57; 95% CI: 0.35, 0.92 ; p = 0.021, p*trend* = 0.06], RRR [$OR_{Quartile4vs1}$ = 0.66; 95% CI: 0.43, 1.00; p = 0.048; p*trend* = 0.117] and the 'typical Australian' dietary pattern determined by RRR [$OR_{Quartile4vs1}$ = 0.60; 95% CI: 0.40, 0.90; p = 0.014; p*trend* = 0.013] were inversely related with DepS. The 'western' dietary pattern captured by PCA [$OR_{Quartile4vs1}$ = 2.04; 95% CI: 1.13, 3.68; p = 0.017; p*trend* = 0.016] and PLS [$OR_{Quartile4vs1}$ = 1.62; 95% CI: 1.05, 2.50; p = 0.030; p*trend* = 0.054] was positively associated with DepS.

The ‘plant-sourced’ NP was found to be inversely associated with DepS [$OR_{Quartile4vs1}$ = 0.76; 95% CI: 0.48–1.20], whereas an ‘animal-sourced’ [$OR_{Quartile4vs1}$ = 1.00; 95% CI: 0.64–1.56] or ‘mixed-source’ NP [$OR_{Quartile4vs1}$ = 0.84; 95% CI: 0.47–1.48] was not associated with DepS. An inverse association were observed between the ‘plant-sourced’ NP and the ‘(absence of) positive-affect’ factor from the CES-D [$OR_{Quartile4vs1}$ = 0.67; 95% CI: 0.46-1.00; p = 0.048].

A diet with higher E-DII^{TM} score (pro-inflammatory diet) was found to be linked with a 79% increase in odds of reporting DepS [$OR_{Quartile4vs1}$:1.79; 95% CI: 1.14-2.81; p*trend* = 0.026]. Men with a higher DII had a two-fold higher odds ratio of DepS [$OR_{Quartile4vs1}$:2.27; 95% CI: 1.02-5.06; p*trend* = 0.089]. Women with a higher DII had an 81% increase in odds of DepS [$OR_{Quartile4vs1}$:1.81; 95% CI: 1.01-3.26; p*trend* = 0.068]. These associations were also evident in the longitudinal analysis. The meta-analysis (n = 12) showed that a pro-inflammatory diet was associated with a 45% increase in odds of having DepS [$OR_{Quartile4vs1}$:1.45; 95% CI: 1.20,1.74, p-value < 0.01].

Findings from all three studies have contributed to the epidemiological literature by providing empirical support for the relationships between nutrition and depression. In conclusion, ‘prudent’ and ‘typical Australian’ dietary patterns or ‘plant-sourced’ NPs or ‘anti-inflammatory’ diet may be beneficial strategies to alleviate the risk of DepS.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signature: Date: 18/09/2020

Acknowledgements

I would like to express my sincere gratitude to my supervisors; **Dr Tiffany K Gill**, **Professor Amanda J Page** and **Dr Yohannes Adama Melaku** for their motivation, advice, expertise, belief in me, unreserved and continuous support during my PhD study and in related research.

My utmost gratitude to **Professor Amanda** for her kindness, patience, expertise, uninhibited encouragement and support, especially during times when I doubted myself. My sincere thanks to **Dr Tiffany** for her inordinate encouragement, advice, support, critically reviewing my work and spending effort in improving my writing skill. I would like to thank **Dr Yohannes** for his great help in equipping me with skills and insightful thoughts that are essential in my future career.

I am very thankful for my time at **The University of Adelaide** and I will be forever grateful for the people have met and the skills I have learned. I am immensely thankful for the ASI International scholarship supported by University of Adelaide.

I am thankful to **South Australian Health and Medical Research Institute (SAHMRI)** for providing an excellent platform to perform the research and providing their great support and resources.

I would like to extend my gratitude to **Professor Gary Wittert** for his invaluable advice, constructive criticism, and inspiration that encourages me to be critical and insightful.

I want to express my genuine gratitude for the wisdom and guidance received continually from my PhD committee members **Associate Professor Leonie Heilbronn** (Subject expert), **Dr Christina A Bursill** and **Associate Professor Richard Young** **(**Postgraduate co-ordinators).

I am most grateful to the study collaborators **Professor Robert J Adams**, **Dr James R Hébert** and **Dr Nitin Shivappa** for lending me their expertise and intuition to my scientific and technical problems.

I would like to extend my thanks to my wife, **Sumana**, who has stood by me during my hard times and been with me even in my absences. She gave me support and help, discussed ideas and prevented wrong turns. I also want to thank my biggest inspiration, my daughter **Presha**. I want to thank my whole family for supporting me throughout my entire life and for pushing me to be the best I can be.

I am deeply appreciative of many other people who have helped me throughout this process, specially, colleagues from **Vagal Afferent Research Group** and all my friends for their love and care.

Last, but not the least, I am most grateful to the participants from **North West Adelaide Health Study (NWAHS)** along with all the study team members for giving their generous time and efforts.

Prem Raj Shakya

September 2020

Dedication

In memory of my Mom and Dad

Image Source: anncapictures from Pixabay

List of Publications

Publications are listed in order of appearance in this thesis.

1. **Shakya PR**, Melaku YA, Page A, Gill TK. Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares. Clin Nutr. 2020. 39(9):2811-23. https://doi.org/10.1016/j.clnu.2019.12.011
2. **Shakya PR**, Melaku YA, Page AJ, Gill TK. Nutrient patterns and depressive symptoms among Australian adults. Eur J Nutr. 2020. https://doi.org/10.1007/s00394-020-02243-y
3. **Shakya PR,** Melaku YA, Shivappa N, Hébert JR, Adams RJ, Page AJ, Gill TK. Dietary Inflammatory Index (DII®) and the risk of depression symptoms in adults. Clin Nutr. 2020. https://doi.org/10.1016/j.clnu.2020.12.031

Research Presentations

1. **Shakya PR**, Melaku YA, Page AJ, Gill TK. Nutrient patterns and depressive symptoms among Australian adults. **Australasian Epidemiological Association (AEA) Annual Scientific Meeting 2019 Conference, Brisbane, Australia, 23-25 October 2019** (Rapid-fire poster presentation).
2. **Shakya PR**, Melaku YA, Page AJ, Gill TK. The association between Nutrition and Depression. **Lightbulb Sessions, SAHMRI, Australia, 27 July 2020** (Oral presentation).
3. **Shakya PR**, Melaku YA, Page A, Gill TK. Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares. **14th Annual Florey Postgraduate Research Conference, Online, 30 September 2020** (Poster Presentation).

Chapter 1: Introduction

This chapter contains the background (Section 1.1) of the research, and the rationale for this thesis (Section 1.2). Section 1.3 conveys the aims and objectives of this thesis. Finally, Section 1.4 contains the outline of the remaining thesis chapters.

1.1 BACKGROUND

Mental disorders affect around 450 million people worldwide [1]. It is estimated that one in four people in the world are affected due to mental or neurological disorders, placing them among the prominent causes of global burden of disease (GBD) [1]. Globally, this burden is continually growing and has significant impact on health as well as concerns on economic, social and human rights [2]. Mental disorders mainly include depression, anxiety disorder, bipolar disorder, schizophrenia and eating disorders [2]. In Australia, 12% of the total disease burden is comprised of mental illness and substance use disorders [3, 4]. Overall, one in five Australians, aged 16-85 years, experience a mental disorder in any one year and depression is the most common among these [3].

Depression is a common mental disorder that affects over 264 million people of all ages around the world; with more women affected than men [5]. Several risk factors are recognised in depression, such as psychosocial [6], behavioural [7], lifestyle [8], metabolic [9] and genetic [10]. Behavioural risk factors such as poor diet, physical inactivity and smoking are significant contributors for the high prevalence of non-communicable diseases (NCDs), such as coronary heart disease (CHD), type 2 diabetes mellitus (T2DM) and cancer [11]. However, there is now an increasing number of studies [12, 13] suggesting that the same modifiable behavioural risk factors also play a vital role in predicting the

likelihood of common mental disorders, including depression [7, 8, 11], and should, therefore, be targeted as part of the preventive measures [14].

Diet and nutrition have been identified as prominent modifiable determinants that have significant impact on the prevention of mental disorders [13], with emerging evidence supporting the role of diet in depression. For example, a recent meta-analysis of randomised controlled trials (RCT) found that a healthy diet can significantly reduce symptoms of depression [15]. In addition, several studies have examined the association between nutrition and depression, and existing evidence supports important links between diet and depression, although there are inconsistencies in the findings. Various epidemiological studies have shown that people with depressive symptoms (DepS) exhibit higher levels of inflammation and oxidative stress than those without DepS [16-18]. Specific nutrients, such as EPA (Eicosapentaenoic acid), DHA (Docosahexaenoic acid) [19-22], folate [23-26], β-carotene [27], vitamin C (VC) [28], vitamin D (VD) [29-31], potassium [32], selenium [33], iron [34], magnesium [35-37] and zinc [38-40], have anti-inflammatory properties which might explain their inverse association with DepS. These findings have led to more detailed studies on the association between nutrition and depression. However, these studies have several conceptual and methodological limitations.

1.2 RATIONALE FOR THIS THESIS

While the role of diet/nutrition in influencing depression is acknowledged, there are some limitations due to the fact that much of the data comes from cross-sectional associations, use of convenience samples and single analysis methods, such as principle component analysis (PCA), reduced-rank regression (RRR) method or partial-least squares (PLS) method. Furthermore, many studies, on the relationship between diet and depression, have focussed on a single nutrient, thus generating inconsistent results, and

failing to consider the complex interactions between nutrients and food intake. This thesis aims to explore and add to the emerging literature on the association between nutrition and depression by incorporating the currently available methodology with multi-dimentional approaches; which are lacking in previous studies. The thesis used a triangulation method approach [41] which helps to provide a more comprehensive picture on the association between nutrition and depression. Diet and depression are both broad concepts; consequently this thesis specifically investigated the association between diet and depression from a range of perspectives: 1) dietary patterns; 2) nutrient patterns (NPs); and the 3) inflammatory potential of diet [i.e. dietary inflammation index™ (DII®)].

In the first paper (Chapter 4), both cross-sectional and longitudinal analysis was implemented to determine the link between dietary patterns and DepS, using multiple methods (PCA, RRR and PLS). In the second paper (Chapter 5), the association between nutrient pattern and DepS was determined. In this chapter, DepS were explored using three approaches. First, the DepS variable was used as a binary outcome [Centre for Epidemiological Studies Depression Scale (CES-D) score ≥ 16)] and analysed using log-binomial regression. Secondly, DepS were used as a continuous outcome variable, and analysed using negative binomial regression. Third, a factor analysis of CES-D items was performed, to find more specific DepS in terms of factor structure, which were then analysed using ordinal logistic regression. In the third paper (Chapter 6), a mechanistic index, namely the energy adjusted dietary inflammatory index™ (E-DII™), was used to find out the link between the E-DII™ and depression using both primary data analysis and meta-analysis techniques. In addition, the association between E-DII™ and each CES-D item was explored to determine the specific DepS associated with E-DII™. Furthermore, the thesis included extensive socio-demographic, behavioural, metabolic,

and chronic condition data as potential confounders and which may have a link with diet and depression. By using this triangulation of evidence approach to determine the association between nutrition and depression, the results generated are strong and fill some of the gaps in the field of nutritional research. The following subsections will provide a brief background on why these studies were undertaken.

1.2.1 DIETARY PATTERN AND DEPRESSION

People do not eat isolated single nutrients or food groups; they consume meals containing many types of food and nutrients. Hence, the complex combinations of different food and nutrient types may play an important role in understanding the interactive or synergistic role of these foods or nutrients in human physiology and should not be ignored. As a consequence, in the last few years, dietary pattern analysis has been gaining popularity as a complementary approach to investigate the link between diet and disease [42].

Over the past decade, there has been a steady rise in epidemiological studies investigating the relationship between dietary patterns and mental status. The practice of maintaining a healthy diet has been linked to better mental health and vice versa [43-46]. However, the findings are inconsistent probably due to differences in the method used, including the use of different dietary pattern analysis methods [44, 47-49].

In Australian adults, there are only a handful studies that have investigated the link between dietary patterns and the risk of depression [50, 51]. Furthermore, to date, the majority of studies have investigated specific subgroups of the population, for example middle-aged women [50], adolescents [52] or the elderly population [53]. Additionally, some studies have focused on specific foods such as fruit and vegetables [54-56]. Moreover, dietary patterns are likely differ according to gender, socioeconomic status (SES), ethnic

groups and culture [42] and, therefore, replication of these results are necessary in diverse populations.

Most studies have some methodological constraints as they have either only used a hypothesis-driven quality score (a priori) or a data-driven approach (a posteriori) only [42, 57, 58]. For dietary pattern analysis, priori [such as the Mediterranean dietary pattern (MDP) score] and posteriori (factor analysis or PCA) approaches are frequently used. Comparatively new hybrid approaches (e.g. RRR and PLS), combining both priori and posteriori analyses [42, 58, 59], have also been used recently. Earlier studies have used PCA, RRR and PLS to identify dietary patterns associated with T2DM [58], cardiovascular disease (CVD) [60], and musculoskeletal health [59], however, to our knowledge, the association of dietary patterns, derived by all three methods, with depression has not been studied. Therefore, this study aims to fill this research gap by applying all three methods (i.e. PLS, RRR and PLS) to determine the link between dietary patterns and depression.

1.2.2 NUTRIENT PATTERNS AND DEPRESSION

In comparison to individual food assessment, dietary patterns based on food groups provide a better link between diet and disease [61], and may also be a better predictor for chronic disease [62]. However, it is difficult to determine the underlying mechanism through analysis of dietary patterns. Studying nutrient patterns (NPs), sometimes referred to as nutrient-based dietary patterns, has distinct advantages over studying food-based dietary patterns [63]. For example, NPs might explain the possible biological mechanisms for the link between diet and depression [64]. Furthermore, nutrients are functionally not exchangeable, and despite substantial differences in dietary patterns, the same nutrients are consumed across the population, which makes it easier to generalise

the findings over a wider population [63]. Dietary behaviour, as well as culture, may affect foods and the way they are processed, however, this may not be the case for nutrients.

Compared to dietary patterns, there is a dearth of literature on NPs. Among the existing studies that have investigated combinations of nutrients, most have focused on cancer patients [65-69], bone mineral density [70-73], obesity [74, 75], sleep [76], metabolic syndrome [77], and the association between inflammation and nutrients [76, 78]. In one recent study, NPs were evaluated for associations with psychological disorders, including anxiety, depression, and psychological distress [79]. A significant inverse association between an omnivore-like NP and depression was observed in men but not for women [79]. However, this study had some methodological limitations, in that the nutrient databank used, which was that of the United States Department of Agriculture, did not reflect the population where the study was undertaken (Iran), therefore, firm conclusions could not be established. In addition, the study did not focus on recognizing the exact components of DepS that could possibly be associated with NPs, to enable full evaluation of the associations.

To our knowledge, no study has been undertaken to assess the association between NPs and depression in Australia. Therefore, in this thesis, we aimed to identify NPs and investigate their associations with DepS in Australian adults, providing insight into the possible relationship between nutrients, and specific DepS.

1.2.3 DII® AND DEPRESSION

Recent literature points towards a role for inflammation in the pathophysiology of depression [8]. Several studies have explored the effect of diet on chronic inflammation [80-82]. Diets consist of various bioactive compounds exhibiting pro- or anti-inflammatory properties [83]. Individuals with DepS have shown elevated plasma levels of pro-

inflammatory biomarkers, including interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C-reactive protein (CRP), compared to healthy controls [84-86]. An elevated level of these inflammatory markers has been shown to play a crucial role in the development of depression [87].

To assess the inflammatory potential of the overall diet, the DII®, a score based dietary assessment tool, has been developed. This index categorises individuals in terms of their diet's inflammatory potential (anti-inflammatory to pro-inflammatory levels) [83, 88]. Lower DII® scores indicate a more anti-inflammatory diet and higher DII® scores indicate a more pro-inflammatory diet [83]. This has led to a desire to explore the link between DII® scores and depression. Studies have shown that individuals following the MDP, which is rich in anti-inflammatory fruits, vegetables, olive oil and legumes, may be protected against depression [89, 90]. On the other hand, higher DII® scores are associated with an increased risk of depression [91]. In this study, we used E-DII™, which was calculated per 1000kcal/d to control for the effect of total energy intake differences among participants.

Some studies have shown that the inflammatory property of diet was associated with an increased risk of DepS [88, 92, 93]. However, there are inconsistent associations between the inflammatory potential of diet and depression or DepS, evident from both cross-sectional [91, 94-101] and longitudinal studies [89, 102-108]. In addition, these studies have not investigated the association between the E-DII™ and specific components of DepS. Therefore, in this thesis, we aimed to explore the association between E-DII™ and DepS in Australian adults, with a focus on identifying specific DepS (from CES-D items) and updating the latest meta-analysis [109] by including the new data from the North West Adelaide Health Study (NWAHS) cohort.

1.3 AIMS AND OBJECTIVES

This thesis aimed to explore the link between diet and depression. The study was conducted in three parts using data from the NWAHS cohort.

The objectives of this thesis are to:

- Investigate the dietary patterns associated with adult depression, using PCA, RRR and PLS methods
- Investigate the NPs associated with depression in adults, providing insight into the possible relationship between specific nutrients and DepS
- Evaluate whether the E-DII™, designed to estimate the inflammatory potential of diet, is associated with depression in adults, focussing on specific DepS and updating the previous meta-analysis.

1.4 FORMAT AND OUTLINE OF THE THESIS

Chapter 1 of this thesis contains an introduction to the diet and DepS, the rationale of the study, as well as aims and objectives. Chapter 2 provides a comprehensive literature review on depression and nutrition focussing on the aims of the thesis, including classification, common variants, assessment, pathophysiological basis, risk factors and treatment. Aspects of nutritional epidemiology, with a particular emphasis on diet and DepS in relation to food groups, nutrients and their inflammatory potential, are also briefly reviewed in this chapter. Chapter 3 provides a description of overall methodology used in the thesis. Chapter 4 describes the link between dietary patterns and DepS using three dietary analysis methods (PCA, RRR and PLS). Chapter 5 describes the link between nutrient patterns and DepS by exploring the factor structure of DepS. Chapter 6 details the association between E-DII™ and DepS. A summary of findings, overall conclusions, study strengths and weaknesses, and the implications of

the study outcomes for future research and clinical practice form the discussion (Chapter 7).

Chapter 2: Literature Review

This chapter begins with a brief background on the current burden of mental disorders (Section 2.1.1) and consisting of a concise review of the literature on depression (Section 2.1.1– Section 2.8). This chapter also explores nutritional epidemiology, with a brief review of various dietary assessment tools (Section 2.9.3). Finally, this chapter explores the link between diet and DepS (Section 2.10), with a specific focus on dietary patterns (Section 2.11), NPs (Section 2.12) and the inflammatory potential of diet (Section 2.13)

2.1 OVERVIEW OF MENTAL HEALTH AND DEPRESSION

2.1.1 CURRENT BURDEN OF MENTAL DISORDERS

Mental disorders cover a broad range of conditions, including both neurological and substance use disorders. Depression and anxiety are leading conditions in terms of prevalence, followed by alcohol and substance abuse, and then the more severe and disabling conditions, such as schizophrenia and bipolar disorder [110]. If untreated, and in extreme conditions, these mental disorders can lead to suicide [110].

According to the World Health Organization (WHO), around 13% of total global burden of disease (GBD) is related to mental disorders, with depressive disorders as the third prominent cause of disease burden, accounting for 4.3% of the GBD [110]. In the calculation of the burden of disease, when only the disability components were considered, mental disorders account for 25.3% and 33.5% of all years lived with a disability (YLD) in low- and middle-income countries, respectively [110].

One of the major risk factors for mental health problems is exposure to a humanitarian emergency that represents a life-threatening risk to the health, safety, security or wellbeing of a population [110]. Armed conflicts, pandemics, famine, natural disasters and other significant tragedies may all involve or lead to a humanitarian disaster [111]. Other factors that increase the risk of developing mental health problems includes poverty, domestic violence and abuse, and the presence of chronic diseases such as cancer, cardiovascular disease (CVD), diabetes and asthma [110]. There are higher mortality rates for people affected with schizophrenia (1.6 times) and major depression (1.4 times) than that of the general population [110]. The social and economic impact of mental disorders are diverse in nature. For examples, studies have revealed that more than 50% of homeless and one third of the prison population have some degree of mental problems [110]. People often lack educational and income-generation opportunities due to mental conditions, thus severely limiting their chance of economic development. These conditions also deprive individuals of social networks and status within a community and eventually hinder economic development at the national level [110].

In 2010, the global economic burden of mental disorders was projected at US$2.5 trillion [112]. In Australia alone, A$9.9 billion, or A$400 per person was spent on mental health-related services in 2016–17, in terms of recurrent expenditure alone [113], which is the continuous and repetitive spending on salaries and wages and non-salary expenditure such as administrative cost, that does not lead to acquisition or enhancement of an asset.

2.1.2 CURRENT BURDEN OF DEPRESSION

Depression was classified as the fourth leading cause of disease burden as assessed by Disability Adjusted Life Years (DALYs) worldwide, for both sexes in 1990 [110]. It is projected to be the leading cause of disease burden by 2030 [110]. A study conducted in 17 nations, revealed that about 1 in 20 people on average experienced depression in the

previous year [114]. Depression can affect all age groups, however, adolescents (aged group 15-24 years) and middle-aged individuals (aged 45-65 years) are more vulnerable compared to others [115]. If untreated, and at its extreme, depression may lead to suicide [110]. The standardised mortality ratio (SMR) for suicide among those with depression is 20.9 in men and 27.0 in women [116].

In Australia, an increased prevalence of depression or feelings of depression has been observed, from 8.9% in 2014-15 to 10.4% in 2017-18, with females at higher prevalence levels compared to males (11.6% compared to 9.1%), although the rise between 2014-15 and 2017-18 was particularly evident among males aged 15-54 years (see *Figure 2.1*).

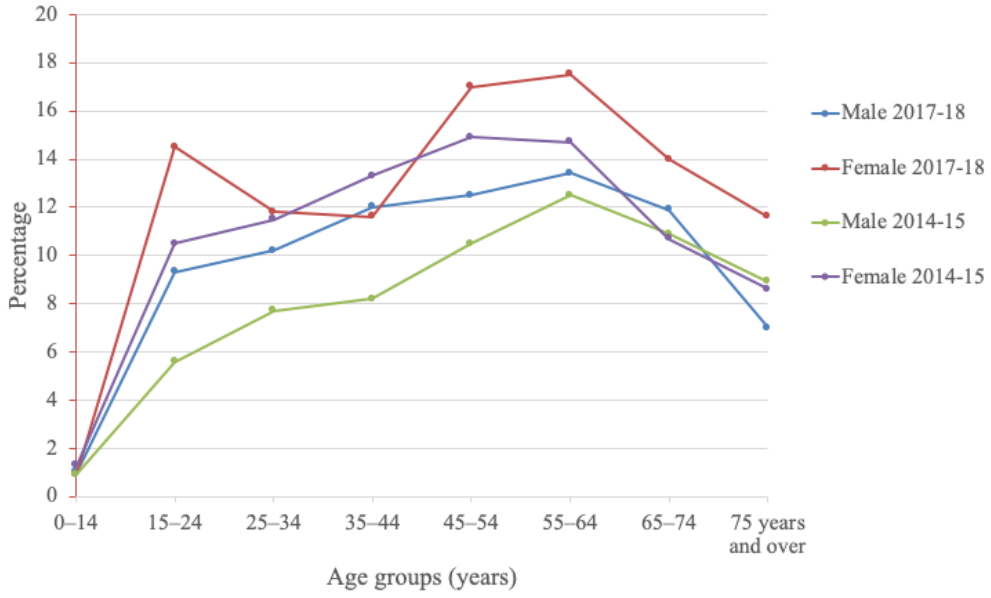

Figure 2.1 Proportions of individuals with depression or feelings of depression in 2014-15 and 2017-18

Adapted from 'National Health Survey: First Results 2017-18' by Australian Bureau of Statistics. ABS catalogue No. 4364.0.55.001. Canberra: Australia. 2018 [115]

The burden of depressive disorders can be categorised into five different headings: classical burden, mortality burden, disability burden, family burden and economic burden.

Classical burden includes residual symptoms following a depressive episode, especially cognitive impairment or social dysfunction, relapse and recurrence, and decreased quality of life [117]. Mortality burden is comprised of suicide, CVD and cerebrovascular disease. Psychosocial and workdays lost encompasses disability burden [117]. The family burden may include disruption of family stability causing separation alongside increased social and economic burden [118]. Evidence shows that depression is related to absenteeism and reduced output in the workplace [119] which creates substantial financial impact on the person or his/her family, employer, and on society as a whole [117]. Once people have a mental disorder, there is often a lack of education and revenue generating opportunities, which may cause a severe reduction in their chance to develop economically as well as socially [110]. In addition, health care costs associated with treating mental disorders, including depression, also plays a significant role in the nation's economic burden. The most common principal diagnosis for hospitalisations with specialised care (14.8%, n = 24,457) was observed due to depressive episodes, followed by schizophrenia (14.1%, n = 23,410) [120]. *Figure 2.2* shows the mental health related hospitalisations according to principal diagnoses along with patients receiving care using various hospital types.

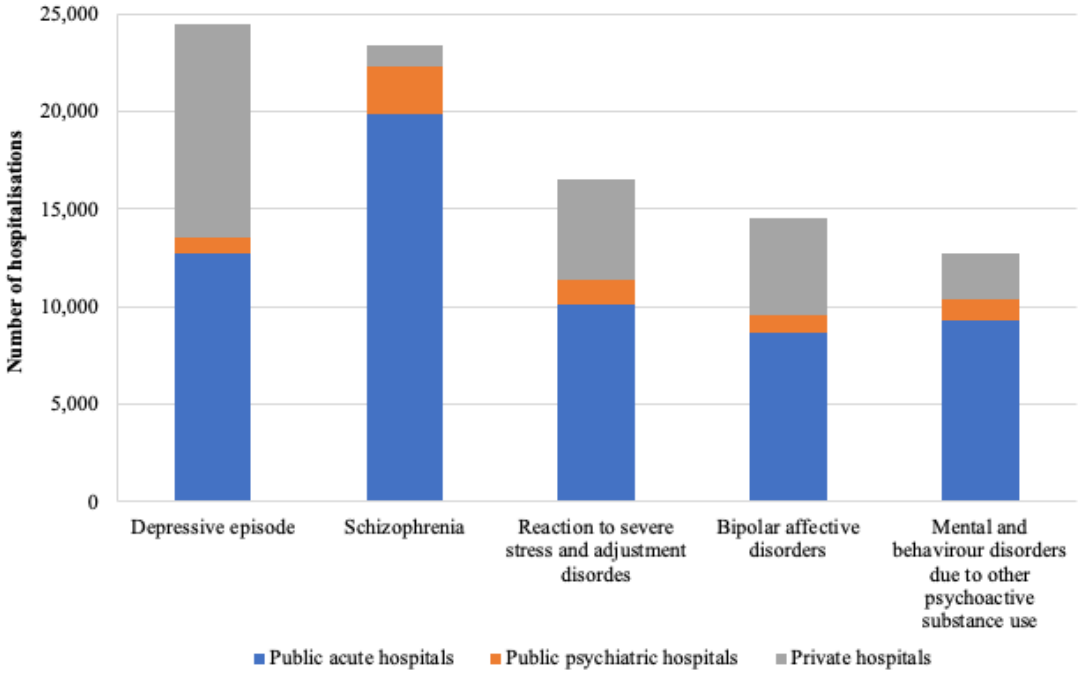

Figure 2.2 Five most common mental health related hospitalization (by hospital type) with specialized psychiatric care in 2017-18

Adapted from: 'Mental health services—in brief 2019' by Australian Institute of Health and Welfare. Cat. no. HSE 228'. Canberra: Australia. 2019 [120]

2.2 BRIEF CHARACTERISATION OF DEPRESSIVE DISORDER

2.2.1 DEFINITION OF DEPRESSION

According to the WHO, depression is a common mental disorder characterized by persistent sadness and decreased interest or pleasure (anhedonia) which people normally enjoy in normal condition with accompanying other symptoms such as low energy, poor concentration, decreased appetite or sleep and low self-worth [114]. Everyone feels upset or unmotivated at some point in their life, however, depression is more severe than just being upset. If these symptoms continue for at least two weeks, it is considered a depressive episode [121].

As psychiatric symptoms or disorders are complicated phenomena they can be diagnosed and measured both categorically (focusing on the specific symptoms) and

dimensionally (focusing on the severity of symptoms) [122]. Thus, depression can be conceptualized from two perspectives. The first perspective is based on category (i.e. based upon clinical diagnosis of a psychiatric disorders such as 'major depressive disorder (MDD)', 'persistent depressive disorder (PDD)' or 'adjustment disorder with depressed mood'). For example, the current MDD diagnosis requires the existence of at least one of two core symptoms, namely: 1) depressed mood and/or 2) anhedonia [123].

From the second perspective, a dimensional approach is used, which is commonly based on a self-report questionnaire, and often defined as depressive symptoms (DepS) or depressed mood. The dimensional approach includes the severity of symptoms, such as 'mild', 'moderate', and 'severe' depression. However, it is still difficult to solely indicate depressed mood or sadness without relating it to other symptoms. For example, according to the Diagnostic and Statistical Manual of Mental Disorders – Fifth Revision (DSM-V), depressed mood refers to 'feels sad, empty, hopeless or appears tearful' [123, 124]. However, the intensity and duration of each symptom may not suffice to fulfil the diagnostic criteria of the DSM-V or the International Classification of Diseases –Tenth Revision (ICD-10) classification systems. These concepts are briefly described in the following sections.

2.2.2 CLASSIFICATION OF DEPRESSION

At present, depression is classified and diagnosed on the basis of the Diagnostic and Statistical Manual of Mental Disorders – Fifth Revision (DSM-V) and developed by the American Psychiatric Association (APA) [123], or the WHO's International Classification of Diseases –Tenth Revision (ICD-10) [125]. These tools are clinician-administered and include a set of semi-structured depression interviews requiring specialised training to administer them. To be diagnosed with depression, the patient needs to fulfil a set of criteria, described in the subsequent sections, proposed by the

DSM-V [123] or ICD-10 [125]. Examples of conditions include MDD, PDD or 'adjustment disorder with depressed mood'.

2.2.2.1 DSM-V classification of depression

DSM-V criteria for MDD [123] (Table 2.1) is based on the presence of a minimum of five out of nine symptoms, provided below, with at least one of the symptoms being depressed mood or anhedonia during the same 2-week period:

1. Depressed mood
2. Loss of interest or pleasure (anhedonia)
3. Weight imbalance
4. Fatigue
5. Worthlessness feelings
6. Sleep disturbance
7. Slow down (both in thought and physical movement)
8. Poor concentration
9. Suicidal thought

Table 2.1 Diagnostic categories of depression according to DSM-V

Diagnostic category	DSM-5 Criteria	Symptoms duration
Major depressive disorder (MDD)	≥ 5 DepS, with 2 key symptoms (depressed mood or anhedonia), causing significant impairment in social, occupational, or other important areas of functioning	≥ 2 weeks
Persistent depressive Disorder (PDD)	3 or 4 symptoms, with 2 key symptoms (depressed mood or anhedonia) and other DepS	≥ 2 years
Adjustment disorder	2-4 depressive symptoms, with 2 key symptoms (depressed mood or anhedonia), causing significant impairment in social, occupational, or other important areas of functioning	≥ 2 weeks

Adapted from; 'Diagnostic and statistical manual of mental disorders (DSM-5®)' by American Psychiatric Association. American Psychiatric Pub; 2013 [123]

2.2.2.2 ICD-10 classification of depression

A diagnosis based on the ICD-10 classification system requires at least four out of ten symptoms [125], with at least two of core symptoms present most days, while awake and for at least two weeks. In addition to these core symptoms, the severity/degree of

depression further depends upon the presence of other symptoms as shown in Table 2.2. Core symptoms include low mood, diminished interest or pleasure in activities (anhedonia) and fatigue or low energy.

Table 2.2 The ICD-10 diagnostic criteria for the clinical depression

Depression Criteria	Symptoms		State of depression	ICD-10 Code	Number of symptoms
A. Symptoms persisted for at least two weeks B. Symptoms include at least two key symptoms	Core Symptoms	• Persistent sadness or low mood • Anhedonia • Fatigue or low energy	Severe depression	F32.2 and F32.3	≥7, with all three core symptoms
C. Presence of other two symptoms (incl. key symptoms) (altogether four) to be considered 'clinical depression'			Moderate depression	F32.1	5-6
	Other symptoms	• Disturbed sleep • Diminished appetite • Poor concentration • Agitation or slowing of movements • Unworthy feelings • Suicidal tendency	Mild depression	F32.0	4
			Not depressed		<4

2.3 COMMON VARIANTS OF DEPRESSION

Depression is a diverse condition often mistaken for a single clinical mental illness. There are many forms of depression based on severity [126]. Symptoms can range from comparatively minor (but still hindering) to very severe, such as psychotic depression, and, therefore, it is crucial to be informed on the variety of depressive states and the symptoms associated with these states [127]. People having or not having manic episodes are also clearly defined in depression classifications. Both types of depression (presence or absence of manic episodes) can be chronic with relapses when untreated. Depression can be classified into the following groups:

2.3.1 MAJOR DEPRESSIVE DISORDER (MDD)

MDD is also referred to as 'major depressive episode (MDE)' or 'major depression' or 'clinical depression'. MDD is characterised by more persistent bouts of low mood along with associated features, such as anhedonia, low self-esteem and low energy. It is generally categorised into two subtypes, namely unipolar or bipolar; a distinction based on the different courses of the disorders and differing approaches to treatment [128].

2.3.1.1 Unipolar disorder or Unipolar depression

Unipolar depression represents a larger group of disorder where an individual experiences depressive episode only. For simplicity and uniformity throughout the thesis, the term 'Depression' will be used for this type of disorder. This disorder involves low mood and loss of attention and willingness to take part in daily activities, among other symptoms. This lasts for at least two weeks and can affect a person's life including social relationships and career development/work output [128]. Depending on the number and severity of symptoms, it can be further subdivided into mild, moderate, or severe (which is further divided into melancholic or psychotic depression as outlined below).

MELANCHOLIC OR ENDOGENOUS DEPRESSION

Melancholic or endogenous depression refers to a severe form of depression where many of the physical symptoms of depression are present, particularly disturbances in psychomotor function [128]. People with this type of depression experience depressed mood and complete loss of pleasure in almost everything [126].

PSYCHOTIC DEPRESSION

Sometimes people with a depressive disorder will experience psychosis. Such individuals may experience illusions (seeing or hearing things that are not in existence) or misbeliefs, for example, believing they are wrong or wicked, or that they are being scrutinised or followed [121, 126].

2.3.1.2 Bipolar disorder or Bipolar depression

In bipolar disorder (also termed bipolar affective disorder), the person oscillates between episodes of depression and episodes of mania. These oscillations are often separated by periods of 'normal' mood [128].

2.3.2 PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)

Persistent depressive disorder (PDD) also known as Dysthymic disorder or Dysthymia, has similar symptoms but is less severe than MDD. However, although the symptoms are less severe they last longer and, to be diagnosed with dysthymia, a person must have experienced mild depression for more than two years [121, 126]. DSM-V classification has changed its name from dysthymia to PDD while the ICD-10 classification retained the original name (i.e. dysthymia).

2.3.3 ADJUSTMENT DISORDER WITH DEPRESSED MOOD

Adjustment disorder with depressed mood is a less severe form of depression than MDD. To be diagnosed with this type of disorder, people should have two to four symptoms, including depressed mood or anhedonia for the last two weeks. It is also associated with crying.

2.3.4 SEASONAL AFFECTIVE DISORDER (SAD)

SAD, as its name suggested, is a recurring disorder with episodes of major depression, mania, or hypomania linked with seasonal change [123]. The exact cause of the disorder is unclear, but it has been assumed, the variation in light exposure in the different seasons is responsible for this. There is a regular pattern of symptoms, with an onset usually in the autumn/winter and remission in spring/summer [126, 128]. This disorder is rare in Australia, and more likely to be found in countries with shorter days and longer night, for instance, regions in the Northern Hemisphere [121].

2.4 DEPRESSIVE SYMPTOMS (DEPS)

When depression is viewed from a dimensional perspective [122], i.e. symptoms-based approach, the presence of DepS are determined. However, using this approach, the diagnostic criteria of the DSM-V or ICD-10 classification may not be met. Nonetheless, the patient may still need treatment or special care. DepS can be assessed by using the various self-report questionnaires and involve a set of questions related to symptoms of depression. To ensure clarity and consistency throughout the thesis, the term 'DepS' will be used for this sort of depression.

In the next section, brief instruments used to diagnose depression or DepS are discussed.

2.5 ASSESSMENT OF DEPRESSION AND DEPS

Depression can be assessed either clinically at the individual level or at the population level using different tools. Various clinician-rated and self-report questionnaires are available to evaluate the depression and DepS which are described briefly in this section.

2.5.1 CLINICIAN RATING SCALES FOR DEPRESSION

2.5.1.1 Hamilton Depression Rating Scale (HDRS)

The HDRS (also known as Ham-D), a clinician-administered depression assessment scale, is used widely to determine the severity of depression. The original version contains 17 items (HDRS17) relating to DepS experienced over the past week [129]. Four more items were added in a later version, the 21-item version (HDRS21) which is used specifically to assess the subtypes of the depression.

2.5.1.2 Montgomery-Åsberg Depression Rating Scale (MADRS)

MADRS, a 10-item depression scale, is a diagnostic questionnaire used to measure the severity of depression during an episode of exacerbation and is designed specifically for patients receiving anti-depressant treatment. This new scale is a more succinct and precise measure of changes in DepS but equally as reliable as the HDRS. A precise measurement of change in DepS means that significant differences between treatments may be revealed with a smaller number of patients [130].

2.5.2 SELF-REPORTED MEASUREMENT TOOLS FOR DEPS

Many rating scales have been used to assess the severity of DepS on an ordinal scale. Commonly used rating scales are described below:

2.5.2.1 Beck Depression Inventory (BDI)

The BDI, first published in 1961 [131], is one of the screening tools for DepS which can be used to estimate the prevalence of DepS. The BDI scale has gone through multiple revisions. The most recent is BDI-II (1996), a 21 item questionnaire, which includes the assessment of symptoms described in DSM-IV criteria [132]. BDI-II is more reliable and

valid with improved content, construct and criterion validity [132] compared to previous version, BDI-IA (1979) and has been validated against both psychiatric and normal populations [132].

2.5.2.2 Centre for Epidemiological Studies Depression Scale (CES-D)

CES-D, a 20 item self-report questionnaire, is used in epidemiological surveys of the general population. It is aimed at measuring DepS and has been validated against longer scales [133] (Appendix A). This questionnaire comprises four factors, namely depressed affect, positive affect, somatic problems and interpersonal problems. The CES-D also has shorter versions with only 4-16 items, which have been developed for use in different populations [132].

A cut off score ≥16 in the CES-D is usually regarded as clinical depression [133], however, this scale is not generally used for diagnostic purposes. Haringsma *et al.* suggested the optimum cut-off score of 22 for clinically relevant depression (with 84% sensitivity, 60% specificity and 77% positive predictive value) [134]. In terms of reliability, the CES-D has a high internal consistency; Cronbach's α ranges from 0.85 (general population) to 0.90 (psychiatric population) [132].

2.5.2.3 Geriatric Depression Scale (GDS)

This tool has been specifically designed to measure DepS in older adults and can distinguish between DepS and dementia. Two versions of this scale are available, the original or extended version containing 30 items (GDS30) and a short version comprising 15 items (GDS15). GDS30 is more reliable and valid; Cronbach's α was found to be 0.94; as suggested by Stiles and McGarrahan *et al.* [135]. It is recommended not to use GDS with cognitively impaired individuals [135].

2.5.2.4 Hospital Anxiety and Depression Scale (HADS)

This scale is designed to assess anxiety (HADS-A) and DepS (HADS-D) in psychiatric and medical patients. Cronbach's α ranges from 0.78-0.93 for HADS-A and 0.82-0.90 for HADS-D; suggesting HADS is a reliable tool for use in the clinical and research setting [132].

2.5.2.5 Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a widely used questionnaire, for the detection and measurement of depression and its severity in clinical settings. The PHQ-9 consists of 9 questions which are based on DSM-IV criteria for MDD [136]. To be diagnosed with MDD, there should be at least five out of nine DepS, lasting at least two weeks, and with one DepS being depressed mood or anhedonia. Developers of this scale report Cronbach's α to be 0.89 and 0.86 in the validation studies of PHQ-9 [137].

2.5.2.6 Depression Anxiety Stress Scales (DASS)

The DASS, a 42-item self-report instrument, intended to measure depression (D), anxiety (A) and stress (S), with each domain containing 14 items, which is further divided into five subscales of 2-5 items with similar content [4 (S A D A) / 5 (D S A S A) / 5 (D S S D S) / 5 (A D D S A) / 2 (A D)] [138]. The DASS has a high reliability and validity with other measures of anxiety and depression in both the clinical and community settings [139].

2.5.2.7 Depression Anxiety Stress Scales 21 (DASS- 21)

DASS-21[138] is a short-form of the DASS in which each of the three scales contain seven items. It is also well validated and highly reliable compared with other measures

of anxiety and depression [140]. DASS-21 has some advantages over the longer version of the DASS. First, it needs less time to complete and is, therefore, more acceptable by both patient and clinicians. Secondly, the items retained from the full-length versions are generally more robust to those omitted which results in cleaner factor structure.

The details on all of these self-reported measurement tools have been summarised by Smarr *et al.* [132].

2.6 PATHOPHYSIOLOGICAL BASIS OF DEPRESSION

There are different theories and hypotheses that have been recognized as forming the pathophysiological basis of depression. These include the biogenic amine hypothesis, genetic hypothesis, stress hypothesis and the hypothalamic-pituitary-adrenal (HPA) axis hypothesis, inflammatory hypothesis and microbiota hypothesis. Below, these hypotheses and mechanisms are briefly discussed.

2.6.1 THE BIOGENIC AMINE (MONOAMINE) HYPOTHESIS

Many neurotransmitters, found at pre-and post-synaptic membranes of neurons in the brain, have important roles in brain physiology. Evidence indicates that specific neurotransmitters are involved in the development and clinical symptoms of depression [141]. The brain consists of a robust neuronal network of noradrenergic [(norepinephrine (NE)], serotonergic [(5-hydroxytryptamine: 5HT)] and dopaminergic [dopamine (DA)] neurons. NE controls the prefrontal cortex, where the processing of working memory and behaviour regulation, such as the acquisition of emotion and attention, takes place [142]. 5HT is the most predominant neurotransmitter in the brain, with serotonergic neurons innervating all brain areas [143], while dopamine modulates reward and motivation pathways, working memory and attention [143, 144]. The monoamine hypothesis of depression is based upon a reduction in the levels of monoamines (5HT, NE and DA),

decreased function of their transport protein or any abnormalities in receptor function [145]. As a result, depression is associated with a comparative deficit of one or more of the biogenic amines, whereas mania is linked to a comparative excess. Depression can be prevented by adjusting the 5HT levels in the central nervous system (CNS) to their normal range which can be achieved using anti-depressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), or other measures, such as diet (specially tryptophan rich diet), exercise and meditation [141, 146].

2.6.2 GENETIC HYPOTHESIS

As explained earlier in the monoamine hypothesis, there is an important role of monoamines (5HT, NE and DA) in the development of depression, especially in their synthesis, vesicular transport, and their receptor function. As a result, the first genetic studies focussed on finding and analysing the polymorphisms in genes associated with these monoamines [10]. Analysis of a large number of candidate genes has been performed, including examining genes for dopamine receptors (*DRD3, DRD4*), dopamine itself (*SLC6A3*), 5HT transporter *(SLC6A4),* 5HT (*HTR1A, HTR2A, HTR1B, HTR2C*) and NE (*SLC6A2*) [10]. Two types of polymorphism have been identified in these genes, i.e. single nucleotide polymorphism (involvement of variation in single base pair) or short tandem repeat polymorphism (involvement of long stretches of DNA) [10]. Statistically significant associations were observed between polymorphisms, in *SLC6A4* and *SLC6A3* genes, and MDD [147].

Genome-wide association (GWA) studies in the past, have demonstrated an inconsistent association between genetic susceptibility and MDD [148]. However, a recent GWA meta-analysis reported statistically significant associations with 44 independent loci [149], which indicates that genetics and depression could be strongly linked.

2.6.3 STRESS HYPOTHESIS

Evidence suggests that persistent psychological stress causes depression through hyperactivity of the HPA axis, which leads to chronic inflammation [150, 151]. The consistent finding that depressed patients hyper-secrete cortisol during the depressed state; but not after recovery, has led to rigorous exploration of the HPA system [146, 152].

However, not all individuals who have chronic or acute stress become depressed, thus it is still not clear how behavioural stress causes depression [126]. Experimental animal studies on stress suggests that area specific structural and functional alterations may occur in the brain region in response to stress, particularly in the prefrontal cortex (psychological symptoms), amygdala (cognitive symptoms), hippocampus (physical symptoms) and nucleus (emotional symptoms) [153-156].

Persistent stress has been shown to change the gene expression, regulating antioxidant systems, such as superoxide dismutase (SOD), glutathione peroxidase (GSH), glutathione reductase (GSR), catalase (CAT) and NADPH oxidase (NOX) [126]. In addition, studies in mice have shown that glucocorticoid treatment elevated the level of reactive oxygen species (ROS) both in vitro and in vivo (in the brains of mice) [157], presumably through the down-regulation of various antioxidant enzymes, and induced depression-like behaviour [157, 158]. In addition to stress factors, a variety of other endocrine system abnormalities (e.g. secretion abnormalities, including cortisol, growth hormone (GH), or thyroid hormone secretion abnormalities) also affect the HPA axis and its dysregulation [152, 159, 160].

2.6.4 INFLAMMATION HYPOTHESIS

The inflammatory hypothesis is one of the most promising theories linking inflammation to depression. Low grade inflammation may play an essential role in the

development of depression [161-163], supported by reports showing elevated pro-inflammatory cytokines in depressed patients [106, 164]. These cytokines include interferon-gamma (INF-γ), interleukins (IL-1, IL-6), colony-stimulating factors and others (e.g. TNF-α, CRP and serum amyloid proteins) [141]. Cytokine are generally classified into either pro-inflammatory (IL-1, IL-6 and TNF-α) or anti-inflammatory (IL-4, IL-8, IL-10 and IL-13) [141].

Although a complete understanding of the mechanisms leading to depression is not clear, it has been observed that increased pro-inflammatory cytokines may result in diminished neuronal plasticity followed by neurodegeneration [126], which may lead to DepS.

2.6.5 NEUROTROPHIC HYPOTHESIS

The neurotrophic hypothesis was postulated after atrophy of certain prefrontal cortex and hippocampal areas was observed in depressed patients [165]. This is likely to be a consequence of reduced nerve growth factors (NGF), such as brain-derived neurotrophic factor (BDNF) which is an essential controller of neuroplasticity [166, 167]. Some researchers believe that depression may be due to a deficiency or reduction in adult neurogenesis [165]. However, a number of available animal studies do not support this hypothesis [168, 169]. Nonetheless, most investigators agree that neurogenesis is a possible factor in the pathophysiology of depression and requires careful consideration.

2.6.6 GUT MICROBIOTA HYPOTHESIS

The gut microbiota hypothesis is a comparatively new hypothesis postulating that depression may be closely linked to the gut microbes and a dysfunctional microbiota-gut-brain axis [170]. Diet has a strong influence on gut microbiome composition and function [171] through the 'microbiota-gut-brain axis'. Four major information carriers

have been identified that play a role in the 'microbiota-gut-brain-axis' associated with depression. These are: 1) vagal and spinal afferent neurons (neural message); 2) cytokines (immune message); 3) gut hormones (endocrine message); and 4) microbial-derived products, such as short-chain-fatty acids and gamma aminobutyric acid (GABA), cell wall components and neuropeptides [172]. This gut microbiota hypothesis has been supported by a growing number of investigations over the last few decades, exploring the gut-brain axis [170, 173-178].

2.6.7 SUMMARY

A combination of the aforementioned factors (monoamine deficiency, genetics, stress, inflammation and gut microbiota) are likely to contribute to the pathogenesis and development of depression. Among them, the HPA axis provides an important neurobiological link between these factors for the development of depression. All these mechanisms may result in dysfunctional neurogenesis and neurotransmission, ultimately leading to structural and functional change in brain, which manifest as DepS. The multifactorial pathogenesis of depression makes it challenging to understand and there are many investigations providing a comprehensive understanding of the multiple pathophysiological mechanism for depression.

2.7 RISK FACTORS FOR DEPRESSION

Depression is a multifactorial disease with many determinants, including a number of biological, psychological, and social factors [146]. Some of these factors are well recognised and others are yet to be explored as they are newly identified.

Figure 2.3 shows the various risk factors for depression. The factors, including gender, age, socioeconomic status (SES) , race, and culture, may all be related to depression [179]. There is ample evidence to support the fact that, from adolescence to

adulthood, females are at higher risk of depression (around 1.7 times) compared to their male counterparts [180, 181]. Individual with lower SES are also at higher risk of depression, compared to those from middle and upper SES [182]. It is worth noting that these risk factors (i.e. biological, psychological, or social factors) are associated with each other and do not work in isolation.

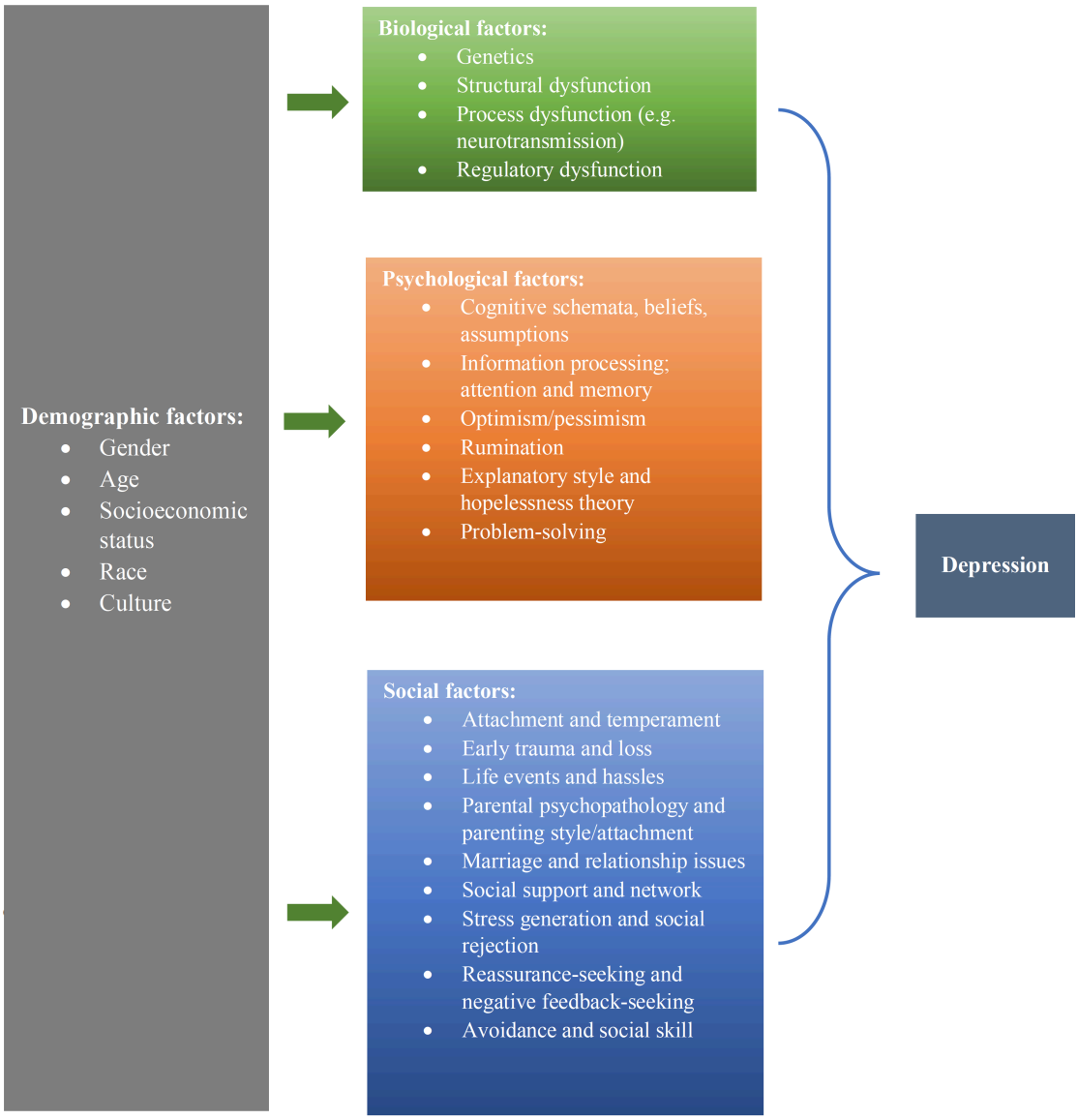

Figure 2.3 Conceptual framework of risk factors of depression

Note: Adapted from Chapter 1 'Assessing risk and resilience factors in models of depression' from the book entitled 'Risk factors in depression' by Dobson KS and Dozois DJA, 1st edition: Amsterdam; Boston: Elsevier/Academic 2008 [179]
(Reproduced with permission)

It is beyond the scope of this thesis to discuss in-depth literature for all the risk factors of depression. However, brief description of the main risk factors are presented.

2.7.1 BIOLOGICAL FACTORS

Biological risk factors for depression include genetic factors, structural dysfunction (related to brain structure), process dysfunction (related to neurotransmission) and regulatory dysfunction (related to neuroendocrine regulatory systems). In response to a stressful experience, depression is accompanied by HPA axis hyperactivity and dysregulation of glucocorticoid release [183]. In addition, this will result in structural and functional changes in the brain, particularly in the prefrontal cortex, amygdala, hippocampus and nucleus; as evidenced from experimental animal studies. Depression is also associated with abnormalities in level of brain neurotransmitters [184], such as acetylcholine (enhances memory) [185], 5HT (regulates sleep, appetite, mood) [186], NE [187], dopamine [188], glutamate (which plays a role in schizophrenia and bipolar disorder) [188-190] and GABA [188, 191, 192].

2.7.2 PSYCHOLOGICAL FACTORS

Environmental stress and adverse life events, such as the death of a family member, marriage breakup, academic failure and social isolation [193], are important triggers for the development of depression [128]. In addition, negative thoughts and self-evaluations are suggestive psychological factors that induce depression. Effective handling the life's problems is also likely to contribute to the onset of the depression [128]. A trauma in early life and childhood maltreatment such as emotional, physical and sexual abuse are also considered as predominant predictors of DepS [194]. There is evidence suggestive of structural and functional differences in brain regions associated with early adversity [195]. Structural difference in the corpus callosum, cerebellum and prefrontal cortex whereas

and functional differences have been identified in the amygdala and anterior cingulate cortex in maltreated children and adolescents compared to non-maltreated peers [195, 196].

2.7.3 SOCIAL FACTORS

Low socioeconomic status (SES), characterised by low-income, low education, unemployment (particularly long term), and also caring for a person with a chronic physical or mental disorder may significantly increase the vulnerability to depression across the lifespan [193, 197, 198]. In addition, marital status (being divorced or widowed) has also been linked with a higher prevalence of depression [199].

Further, the risk of DepS can be independently enhanced by certain lifestyle factors, such as smoking [162]. Physical inactivity is regarded as an independent risk factor for depression, and a physical workout may be protective for good psychological health [200]. Other risk factors for depression may be related to chronic medical problems, such as cancer, diabetes mellitus, obesity, cardiovascular disease or pain [121, 179].

There are few studies on lifestyle factors, such as diet and physical activity and their association with depression. From a public health point of view, prevention strategies for depression have achieved much less attention than treatment strategies [201]. The literature indicates that intensive lifestyle interventions, such as improvements in the diet quality [202], and increased physical activity, should decrease DepS and improve mood [200] respectively. However, there is huge gaps in knowledge due to the complexity and multifaceted causes of this disease.

2.8 TREATMENT OF DEPRESSION

Currently, there are treatment strategies available for depression, both pharmacological and non-pharmacological. Pharmacological therapies include

antidepressants, stimulants, drugs that act upon on N-methyl-D-aspartate (NMDA) receptors or the cholinergic system, drugs having anti-inflammatory or antioxidant properties [203]. Non-pharmacological therapies include physical therapies, psychological therapies, and exercise [204-206].

To date, treatments for depression (both pharmacological and psychotherapy) have shown some positive effects, however, effectiveness is limited to subpopulations of patients and remission is not complete [207]. In psychiatry, compliance plays a key role in the effective treatment with pharmacological drugs [208].

In clinical practice, treatment-resistant depression is commonly seen in up to 60% of MDD patient [209]. It occurs when the patient undergoes with at least one antidepressant trial of adequate dosage and duration but with an inadequate response [146, 209].

Therefore, an innovative approach to treating depression through diet is evolving. Depression can be explored through emerging disciplines, such as 'Nutritional Psychiatry' [13, 210-213], which provides evidence for diet quality as a modifiable risk factor for mental illnesses.

2.9 OVERVIEW OF NUTRITION

Nutrition influences our health, wellbeing, and quality of life [214]. Nutrition can be defined as the science of foods and the nutrients and their ingestion, digestion, absorption, transport, assimilation and excretion [215]. Human nutrition is a very complex field that specifies how nutrients, and other factors that are found in food, provide fundamental nourishment to maintain life. To fully understand nutrition, an integrated approach from the molecular to societal level is required [214].

Nutrients from foods supply the nourishment for every cell in the body, which is required for maintenance of function and for the continual repair, healing, and rebuilding

of cells and organs. Water, carbohydrates, fats, proteins, vitamins, and minerals are the six major classes of nutrients commonly found in foods. Carbohydrates, fats, and proteins provide the energy needed for the body to function whereas vitamins and minerals yield no energy, but they facilitate and regulate the various processes in the body to release energy from the three energy-yielding nutrients [215].

2.9.1 NUTRITION IN HEALTH AND DISEASE

Diet is a modifiable risk factor for chronic diseases. According the WHO, promoting healthy diets and lifestyles are strategic initiatives to mitigate the global burden of NCDs, and require a multi-sectorial approach [216].

As a country develops economically, there are improvements in the food supply, a gradual elimination of dietary deficiencies and, therefore, improvements in the overall nutritional status of the population [216]. At the same time, increased urbanization also brings changes in individual dietary patterns and other lifestyle factors (e.g. shift work), not all of which are beneficial [216].

Variation in diets, work and leisure patterns, known as ‘nutrition transition’ may contribute to the causal factors underlying NCDs, even in the poorest countries [217]. The adverse dietary changes include shifts in the structure of the diet towards a highly energy dense diet, contributing to an increase in sugar and saturated fat (mostly from animal sources) intake and a decrease in intake of complex carbohydrates and dietary fibre, found in fruit and vegetables [217]. Energy-yielding nutrients are utilised in building new compounds for the body and fuelling metabolic processes and physical activities, however, if there is excess, nutrients are rearranged into storage compounds, primarily in the form of body fat. Thus, a higher intake of energy compared to expenditure results in an increase in energy stores and weight gain and vice versa [215]. Along with the dietary

changes, weight gain is further accelerated with lifestyle factors, such as decreased physical activity [218].

In summary, diet interacts with many factors, including income, cost of living, individual preference, cultural beliefs along with geographical, environmental, social and economic factors, and over time these interactions shape dietary consumption patterns. [216]

2.9.2 NUTRITIONAL EPIDEMIOLOGY

Nutritional epidemiology is the sub-discipline of epidemiology which deals with nutritional exposure and their roles for the occurrences of diseases and impaired health conditions [219]. For centuries, epidemiological methods have been used to study the link between diet and disease, and initially, these methods were used to recognise nutritional deficiency, with scurvy is a classic example [220]. In 1747, James Lind performed a small clinical experiment using 12 patients with scurvy. He split these patients into six pairs and gave them either i) a cider, ii) an elixir of vitriol, iii) a paste of garlic, mustard seed, horse-radish, balsam of Peru and gum myrrh, iv) vinegar, v) seawater, or vi) citrus fruits (two oranges and one lemon) [221]. Consumption of citrus fruit was found to be effective in curing scurvy. However, Lind also included cold climate, dampness, lack of fresh air and foggy weather as causative agents for scurvy, obscuring a clear outcome [220]. Sailors were still suffering from scurvy until it became mandatory, in 1854, to provide sailors with citrus fruit [220]. More recently, nutritional epidemiology has dealt with the aetiology of chronic diseases, such as cardiovascular disease and cancer [222].

Over the past few decades, population-based observational studies, applying principles of both nutrition and epidemiology, have provided evidence for an association between nutrition and disease. Similar to many other epidemiological disciplines,

nutritional epidemiology assists with the development of policy and guidelines related to diet and health of the general population. In nutritional epidemiological research, examining the relationship between diet and health should not be focussed on a single nutrient or food group, but rather the overall dietary or nutrient patterns. The nutrient/food intake can be measured directly using a FFQ or indirectly by measuring markers of intake in their biological samples, or by estimating the body size and relative size of body compartments [223].

Generally, there is criticism of the observational nature of epidemiological studies and small trials, stating that "*definitive solutions will not come from another million observational papers or small randomised trials*" [224]. Ioannidis places more emphasis on large scale randomized controlled trials (RCTs) using comprehensive interventions [224]. However, RCTs alone are not the solution in the study of diet and chronic disease as sometimes the results may be misleading. This may be due to the complex nature of dietary intake which has many interactions and synergies across different dietary components. It is challenging to study such interaction with the use of linear drug trial approaches, such as RCTs [225]. In addition, RCTs are relatively short in duration, which creates difficulties in observing the long-term impact of diet on chronic disease. Moreover, ethical challenges are significant issues in the diet-disease relationship within RCTs. For this reason, nutritional epidemiologists still typically rely on the prospective cohort studies, the most robust observational study design in terms of minimising the bias and inferring causality [225]. These studies primarily focussed on the collection of dietary data and the methods used for analysis.

2.9.3 DIETARY DATA COLLECTION

Dietary assessment methods can estimate actual intake or usual intake. The 24-hour recall or food record can be used to estimate actual intake, and a food frequency

questionnaire (FFQ) can be used to estimate the usual intake [226]. When little information about group's dietary intake exists, a combination of both approaches (actual and usual) provides researchers with the most accurate estimate of dietary intake. Diet can also be measured prospectively or retrospectively. Prospective methods include dietary records, while retrospective methods include the FFQ and 24-hour recalls [226, 227].

The food consumption record is a record of all food and beverages consumed in a day and is usually kept by the respondent. Dietary records require trained participants to weigh, measure or estimate, and record all foods consumed. Since dietary records do not rely on memory recall, they are sometimes considered the 'gold' standard for other dietary methods. However, measurement needs to occur over more than one day to capture potential variations due to seasons or days of the week. Dietary records can also be challenging to administer in a large population because of its labour-intensive methodology [226, 227].

In the 24-hour dietary recall, an interviewer obtains accurate and detailed information on all food items consumed by an individual during a recent 24-hour time period [226]. The United States Department of Agriculture has used two days of 24-hour dietary recalls in its national surveys since 1991 [228]. It may be more difficult for subjects to recall two days of diets, but due to the daily variation in food intake of most people, one day is not appropriate for estimating the usual food intakes of an individual [229].

Among the available dietary assessment methods, the FFQ has been widely used, since the 1990s, in an extensive array of epidemiological studies. The FFQ in general ask the participants on their portion of food intake and its frequency in specific period of time [230]. There are three types of FFQs: qualitative, semi-quantitative, and quantitative. Qualitative FFQs ask respondents to answer only a frequency of consumption for each item. Semi-quantitative FFQs ask for frequency responses with a usual serving size listed

with each item. Quantitative FFQs ask for frequency responses and for respondents to select the usual portion size [226]. Table 2.3 summarises the standard dietary assessment methods in nutritional epidemiology, including the methods, collected data, strength and limitations considering a conservative approach.

Table 2.3 Dietary assessment methods in epidemiological studies

Dietary assessment method	Methods	Collected data	Strengths	Limitations
Food consumption record	Objective measurement: interviewer administered questionnaire at household level	Actual intake	Easy application in low literate individuals or those who prepares most meals at home	Recall bias; Unsuitable to individuals who eats frequently outside
Dietary history	Subjective measurement: interview administered questionnaire	Usual intake estimates over a lengthy period	Well assessment of usual dietary intake	Resource demanding; Unsuitable for epidemiological studies
24-Hour dietary recall	Subjective measurement: interview administered questionnaire	Actual intake	Detailed intake data; respondent burden is lesser	Bias prone such as recall bias or interviewer bias, trained interviewer required; resource demanding
Dietary record	Subjective measurement: self-administered questionnaires	Actual intake	Detailed intake data; minimal bias	Significant respondent burden (more knowledge required that other methods), likely under-reporting; resource demanding
FFQ	Subjective measurement: self-, or interviewer-administered questionnaire	Usual intake	Cost-effective and timesaving; appropriate for epidemiological studies	Specific to study groups and research aims; recall bias

Adapted from 'Dietary assessment methods in epidemiologic studies' by Shim JS et al. Epidemiolocal Health.[231]

2.10 DIET AND MENTAL HEALTH

There has been a continual increase in epidemiological and biological studies examining the connections between diet and mental health [12, 232]. Many systematic reviews and meta-analyses on the association between dietary patterns and mental disorders, especially depression or DepS, have been undertaken [43, 233-235]. Broadly, these include healthy (e.g. Mediterranean, Prudent, Japanese) and unhealthy (e.g. western) dietary patterns.

The Mediterranean diet, is named after the staple diets, consumed in Mediterranean countries and includes the high consumption of fruits, vegetables, cereals, legumes, nuts, fish, and the use of olive oil as a cooking fat as the main basis of this diet [236, 237]. The 'prudent diet' has been used to describe the fat and cholesterol-controlled diet that focusses on fruits, vegetables, low-fat dairy, whole grains and juices [32]. The 'Japanese diet' is a whole-foods-based diet containing fish, seafood, added sugars, and fat [238]. The 'traditional' diet is characterised by a high intake of vegetables, fruit, fish and unprocessed meat [61]. The Mediterranean diet [237, 239, 240], Japanese diet [241] and traditional diet [61, 242] have been shown to have an inverse association with DepS [243].

In the last few decades, there has been an increased trend for the consumption of a 'western diet'. As the name suggests this diet is typically consumed in westernized societies but has spread from high-income countries to low-income countries due to the ready availability and affordability of this diet. These diets, including processed foods, fast food, convenience products, snacks, and sugary soft drinks, are generally lacking fibre, vitamins and minerals [244]. Unhealthy diets such as the 'western diet' [61, 241, 245, 246] and diets high in processed foods (such as sweets, fried food, processed meats, refined grains, and high fat diary) [202], meat and processed meats [239], and biscuits and snacks [247] have all previously been found to be associated with increased odds for depression [243].

In the Australian context, there have only been a few studies which have analysed the association between diet and DepS. In 2010, a cross-sectional study on adolescents in the Australian Healthy Neighbourhood Study, found that an association between diet quality and depression existed over and above the influence of socio-economic, family, and other confounding factors [52]. The quality of the diet was determined using a healthy diet score based on the Australian dietary guidelines for children and adolescents.

2.10.1 INDIVIDUAL NUTRIENTS AND FOOD GROUPS ASSOCIATED WITH DEPRESSION

Many nutrients are suggested to be effective against depression, including ω-3 polyunsaturated fatty acids (ω-3 PUFAs), magnesium, zinc, folate, VD, calcium and iodine [232, 248]. In addition, some of the food groups such as 'fruit and vegetables' and fish, have been found to be strongly effective for DepS. The common nutrients and food groups that have been found to be linked with mental disorders/ DepS are described briefly in the following sections.

2.10.1.1 Macronutrients: Carbohydrates

Carbohydrates, in either a simple or refined form, are often associated with rapid mood changes and depression [249]. Carbohydrate rich meals trigger the release of insulin in the bloodstream, which facilitates the uptake of most amino acids into peripheral tissues, such as muscle [250]. However, tryptophan, an essential amino acid, which contributes to the production of 5HT, is unaffected by insulin and so the proportion of tryptophan levels in the blood is increased relative to the other amino acids [249]. Tryptophan produces niacin, essential in 5HT production which can subsequently lead to an increased feeling of well-being, relief from depression and anxiety and promotion of better sleep [249, 251, 252]. This action may explain the cravings for carbohydrates by individuals who suffer from DepS, with ingestion of simple carbohydrates a type of self-medication. [249, 252].

2.10.1.2 Macronutrients: Protein

Proteins are comprised of molecules known as amino acids. There are 22 known amino acids and generally categorised into essential, conditionally essential, and non-

essential [253]. Many neurotransmitters in the brain, for example dopamine and 5HT, which are known to affect mood, are made up of the essential amino acids (tyrosine and tryptophan) [251, 254]. Tryptophan is contained in many protein foods such as turkey, milk, cottage cheese, chicken, eggs, red meat, soybeans, tofu, and nuts, especially almonds [253].

2.10.1.3 Macronutrients: Fats

Both animal and vegetable sources of fat deliver a vital source of energy and are regarded as building blocks for cell membranes in terms of the phospholipid bilayer as well as a number of hormones and hormone-like substances [253]. Saturated fatty acids (SFA) are highly stable and found mostly in animal fats and tropical oils [253]. Monounsaturated fatty acids (MUFAs) have a bend in the structure at the position of the double bond and are not packed together as tightly as SFAs and considered relatively stable compared to polyunsaturated fatty acids (PUFAs) [253]. MUFAs, including oleic acid, are present in olive oil, almonds, peanuts, and avocados. PUFAs, include linoleic acid [or omega-6 (ω-6)], which has two double bonds, and linolenic acid [or omega-3 (ω-3)], with three double bonds [253].

FATS: CHOLESTEROL

Total cholesterol levels have been linked to depression, and suicidal tendencies [255]. People who had attempted suicide had significantly lower serum cholesterol than those who non-suicidal patients [256]. According to research by Golomb *et al.* (as cited in Lalovic *et al*, 2007), low levels of serum cholesterol have been linked to suicidality and violence [257]. This could be explained by an alteration in mood or behaviour due to reduced expression of 5HT receptors in the brain cell membrane. It has been hypothesized that lower cholesterol content in brain cells may be due to lower serum cholesterol which

subsequently affects the serotonergic system by lowering lipid micro-viscosity of brain cell membranes or synaptic plasticity [257, 258].

Conversely, there are some studies which indicate that cholesterol-lowering does not negatively affect patient mood, such as depression and anxiety [259, 260]. Studies have found that decreased serum cholesterol might influence mental health in susceptible individuals with pre-existing psychiatric illness or chronic alcoholism [260].

FATS: ESSENTIAL FATTY ACID

ω-3 PUFA

ω-3 PUFA consist of α-linolenic acid (ALA), EPA and DHA and can be mainly found in cold-water fatty fish, such as salmon, mackerel, tuna, herring, and sardines, as well as some nuts and seeds [261]. A deficiency of dietary ω-3 PUFAs can induce modifications in neurotransmitter systems that may be linked to the aetiology of depression [262-264]. ω-3 PUFAs also has anti-inflammatory properties and in depressed patients' inflammatory markers have been found to be elevated [265-267]. Moreover, ω-3 PUFAs can reduce oxidative stress which is increased in people who are depressed [268, 269].

Several prospective studies have investigated the association between fish (as fish is a very rich source of ω-3 PUFA) and risk of DepS, however, the results were inconsistent [270-272, 273] . Some studies found gender-specific results, such as a protective effect of ω-3 PUFA only for women [274, 275] or men [276]. However, most of the meta-analyses have shown an inverse association between fish or ω-3 PUFA intake and risk of DepS [20, 277, 278].

ω-6 PUFA

ω-6 PUFAs consist of linoleic acid, arachidonic acid and adrenic acid which are found in plant, vegetable seeds and oils. Margarine (a spread used for flavouring, baking, and cooking) and many processed foods are rich sources of ω-6 PUFAs [279]. Low levels of ω-3 PUFAs and high levels of ω-6 PUFAs have also been associated with neuropsychiatric disorders such as depression and anxiety [280].

2.10.1.4 Vitamin B12 and Folate

Low vitamin B12 [VB12 (or cyanocobalamin)] levels are associated with cognitive impairment, dementia, depression, peripheral neuropathy, and degeneration of the spinal cord, whereas, folate deficiency has been consistently associated with evidence of depression [281]. It has been shown in clinical trials that VB12 delays the onset of signs of dementia if administered correctly prior to the onset of the first symptom, in a precise clinical window of time [251]. VB12 supplementation has been shown to enhance cerebral and cognitive functions in older people [282].

On the other hand, impaired folate metabolism impacts both methylation (epigenetic) as well as the DNA synthesis process, both of which have been implicated in the development of diseases, including depression [283]. Moreover, depressed individuals with lower folate levels have been found to be less responsive to antidepressant treatment, a higher likelihood of relapse [284] and reduced cognitive performance [285]. Contrary to this, adequate intake of folates is protective against the development of DepS [286].

2.10.1.5 Vitamin B6

Theoretically, a low level of vitamin B6 (VB6) may be one probable reason behind depression as the active form of VB6 cofactor, or also known as pyridoxal 5′-phosphate (PLP), is involved in tryptophan metabolism [287]. Tryptophan is a precursor for 5-HT which plays a role in mood alleviation [288]. An inverse association has been observed between low levels of plasma PLP and DepS in a few studies of low sample size [(i.e. (Hvas *et al.; n* = 140) [289] and (Baldewicz *et al*; *n* = 134)[287]], however, in the SUN cohort study, a study undertaken with 9,670 participants, no significant association was observed between VB6 and depression [24]. Therefore, further research is warranted to confirm whether there is an association between VB6 and depression.

2.10.1.6 Minerals

Calcium

Depression is associated with cognitive impairment due to disturbed calcium homeostasis. Performance in neuropsychological tests was significantly reduced in the MDD group and serum calcium levels were lower compared to healthy controls [290]. In addition, there was an age-dependent association was observed between serum calcium and neuropsychological performance. In the healthy control group, there was a positive correlation between serum calcium levels and neuropsychological performance in the younger age groups but a negative correlations for the older age groups [290]. However, only an inverse association was observed in individuals with MDD across all age groups [290]. This highlights the central role of calcium pathways in normal and pathological cognitive ageing [290].

Iodine

Iodine is an essential trace element needed for thyroid hormone [thyroxine (T4) and triiodothyronine (T3)] synthesis. Thyroid hormone is critical for energy, metabolism, body temperature, growth, immune function and brain performance [291]. Increased perinatal mortality and mental retardation are regarded as the most severe outcomes of iodine deficiency [292]. Notably, children and pregnant women are vulnerable groups for iodine deficiency. Generally, iodine is consumed via iodised salt (salt fortified with iodine), or in any seafood, such as seaweed, shrimp, or cod. Iodine helps to maintain adequate T4 and T3 levels in the brain, which is required to assist with activation of key neurotransmitters, such as dopamine, NE, 5HT, GABA, and acetylcholine [291].

Zinc and Iron

Zinc and iron are both present in similar dietary sources such as liver, red meat, fish, and poultry [293]. Therefore, deficiencies in zinc and iron often co-occur [293, 294]. Some studies have found a link between zinc and neurotransmitters involved in the monoamine hypothesis [295, 296]. Some biological mechanisms indicate an inverse relationship between zinc and depression, such as: 1) A decrease in the synaptic zinc level, resulting from deficiency of dietary zinc, may increase the glutamatergic levels which can subsequently activate N-methyl-D-aspartate (NMDA) receptors [297], activation of which is associated with depression. 2) decreased zinc can downregulate BDNF activity which decreases the neurogenesis signalling pathways and neuroplasticity, processes which can accompany depression [298]. 3) The antioxidant properties of zinc may play an important role in pathophysiology of depression [299].

The most common form of anaemia (lacking sufficient healthy red blood cells) is caused by iron deficiency. There is similarity in the symptoms between iron deficiency and depression such as fatigue, sleepiness and irritability [300]. The studies on dietary iron

intake and risk of depression are scarce. A meta-analysis by Li *et al* showed that dietary zinc (n = 9 studies) and iron (n = 3 studies) intake were significantly associated with a decreased risk of depression [34]. However, interpretation of the results is limited due to the low number of studies.

Selenium

Low intake of selenium has also been found to be associated with lowered mood status [301]. There is also evidence from intervention studies, that increasing selenium intake improved mood and diminished anxiety [302, 303].

Lithium

For half a century, lithium has been used for the treatment of individuals with bipolar disorder and has anti-manic, anti-depressant, and anti-suicidal properties [304]. This element has also been used for therapeutic purposes, as an augmenting agent, in various psychological disorders, such as depression, schizoaffective disorders, aggression, impulse control disorder, and eating disorders [251]. However, careful observation is needed when treating with lithium due to its toxic side effects.

Magnesium (Mg^{2+})

Mg^{2+} is an essential micronutrient that acts as a co-enzyme/activator for several enzymatic reactions that are necessary for proper brain function. Mg^{2+} is typically found on nuts, seeds, green leafy vegetables and whole grains [33]. Pharmacologically, Mg^{2+}, an endogenous NMDA receptor antagonist, has recently gained popularity because of its possible role in the pathophysiology of, and treatment response, in depression [305]. A meta-analysis of this nutrient by You *et al* revealed that serum Mg^{2+} levels were lower in patients with depression than in controls. However, it should be cautiously interpreted as Mg^{2+} levels from other sources, such as plasma and cerebrospinal fluid (CSF), were

not significantly different between depressed patients and controls [305]. Further, there is an inconsistent association between Mg^{2+} intake and DepS, with an inverse relationship between DepS and Mg^{2+} intake reported in a number of cross-sectional studies [36, 37, 306], whereas, no association was found in prospective cohort studies [307, 308].

2.10.2 FRUIT AND VEGETABLES CONSUMPTION

Fruit and vegetables intake could be used as a simple indicator/marker of diet quality since many studies have demonstrated that fruit and vegetables intake is a primary component of a healthy diet [61, 241, 309, 310] although there are inconsistent findings [311-314]. Some studies have demonstrated significant associations between the consumption of fruit intake and depression, but not vegetable intake [55, 237]. A recent meta-analysis showed that fruit and vegetables intake might be inversely associated with the risk of depression [315], which was further evidenced by Saghafian *et al.* [56].

2.10.3 PROCESSED FOOD AND SUGARY DRINKS

Increased consumption of processed and sugar foods and beverages is one of the most likely reasons behind the growth of obesity, a metabolic disorder due to excessive fat accumulation, and other NCDs such as T2DM and CHD [316]. An association between metabolic disturbance and risk of depression has been observed in several prospective studies [81, 105, 317-322]. In obesity, elevated cortisol secretion and higher HPA axis reactivity to psychological and physiological stress is observed [323].

Additionally, there may be a bidirectional link between obesity and depression [324], as risk factors for obesity are also linked with depression. There are some cross-sectional studies which found a positive association between consumption of fast foods, snacks, sweets and DepS [325, 326]. Moreover, a prospective study observed a positive association between soft and fruit drink consumption and the risk of depression [327]. Another meta-

analysis also showed that high-consumption of soft-drinks may increase the risk of depression [328]. However, in the SUN cohort study, Sanchez-Villegas *et al*. did not observe a significant association between the consumption of sugar-sweetened beverages and risk of depression. Nonetheless, they observed that higher exposure to added sugars and poor-quality carbohydrates was associated with a higher risk of depression [329].

2.10.4 COFFEE/TEA INTAKE AND DEPRESSION

Coffee and tea are the most consumed drinks worldwide after water. There is a wide variation in drinking patterns with the variation in intake and type of beverages consumed; variation dependent on cultural and geographical factors. Polyphenols (e.g. chlorogenic acid and catechins) found in coffee and tea, have antioxidant and anti-inflammatory properties [330], while caffeine has been suggested to modulate dopaminergic transmission and facilitate the release of 5HT [330]. However, the inconsistent association between these beverages and depressive disorders persists. In a study undertaken in a Japanese population coffee consumption was inversely associated with depression, but not tea or green tea [331]. However, a meta-analysis demonstrated an inverse association between tea consumption and depression [332].

2.10.5 MEAT CONSUMPTION AND DEPRESSION

Worldwide, meat is regarded as a significant source of protein, fat and energy for humans, and accounts for a large part of the diet [333]. Meat contains a variety of essential micronutrients, such as niacin, iron, zinc, vitamin B_1 and B_{12} [334]. However, meat consumption is directly associated with obesity [335], which is a risk factor for depression [336]. In this way, it is speculated that meat consumption and depression are linked and a meta-analysis has also supported this by showing that meat consumption is associated

with increased odds of depression, however, further research is required to confirm the findings [337].

2.11 DIETARY PATTERNS AND DEPRESSION

Traditionally, researchers examined diet-disease relationship using a single or a few nutrients or food groups. Although, this research is invaluable, it has some conceptual and methodological limitations. First, people do not eat isolated nutrients, rather they eat meals containing various food groups with complex combinations of nutrients that are likely to be interactive or synergistic [42]. Second, the effect of a single nutrient may be too small to be detectable but cumulative effects of multiple nutrients may be sufficiently large to be detected [42]. Third, substitution effects may also play a substantial role in change of dietary habits, for example high consumption of some foods is associated with lower intake of other foods. Therefore, studying single nutrients or food groups is not enough. Consequently, a new concept of studying diet as a pattern analysis has been developed, which takes into account the inter-relationship of food choices and also reflects the mutual exposure to various dietary components [338].

In this context, two methods have been commonly used. The first, known as the priori method, uses a priori defined dietary indices, and is mainly designed to evaluate overall diet quality. These indices are constructed primarily based on i) dietary recommendation; and ii) adherence to particular food groups. Examples of dietary recommendation based indices, include the Healthy Eating Index (HEI) [339] or Alternative HEI [340], which are both based on the US Dietary Guidelines or the Dietary Approaches to Stop Hypertension (DASH) [341] promoted by the National Heart, Lung, and Blood Institute. An example of an index which is based upon a particular food/cuisine is the Mediterranean dietary index [342] which was developed to assess adherence to the Mediterranean diet and has been frequently used in dietary pattern research. The second

approach is the posteriori method which is driven by the data collected and specific types of analyses (predominantly cluster analysis). PCA and factor analysis lies in this group. Other methods have been developed, such as RRR and PLS, which encompasses both the priori and posteriori approaches. The details of these methods (PCA, RRR and PLS) are described in the subsequent methodology chapter of this thesis (Chapter 3).

Studies related to the examination of the association between dietary patterns and depression, using a whole dietary approach, are summarized in Table 2.4.

The studies can be broadly classified as examining 'healthy' and 'unhealthy' dietary patterns. Healthy dietary patterns comprise a range of food groups depending on the country of origin, but all include fruit and vegetables. Dietary patterns, which have a higher consumption of processed foods, such as sweetened desserts, chocolates, fried foods, processed meats, refined grains and high-fat dairy products, are defined as an 'unhealthy' dietary pattern.

The majority of studies point towards the fact that healthy dietary patterns have an inverse association with DepS [90, 237, 239, 241-243, 343, 344] while unhealthy dietary patterns have a positive association [89, 245, 313, 345], although there are some inconsistent findings [49, 246].

While systematic reviews on dietary patterns and depression, have shown potential benefits for specific dietary patterns, performing a meta-analysis on this topic is difficult due to the substantial heterogeneity [43]. Despite this, a number of systematic reviews and meta-analysis on dietary pattern and depression have been published [15, 44-47, 234, 235, 346] and Table 2.5 tabulates the currently available systematic reviews and meta-analysis for the association between dietary pattern and depression.

Table 2.4 Summary of studies on dietary patterns and depression

(table continues)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Depressive disorder outcome	Identified dietary patterns (DPs)	Adjusted variables	Association with the depression
Jacka *et al*., 2011, Norway [242]	HHS cohort, community-dwelling adults	cross-sectional	FFQ, 169 items; PCA	HADS, seven items	Western Traditional Healthy	Sex, age group, income, education, PA, smoking, alcohol, and EI	**Healthy diet:** decreased odds of depression in men **Western diet:** increased odds of depression in both men and women. **Traditional diet:** reduced depression in women.
Rienks, D. *et al.*; 2013; Australia [239]	ALWSH cohort; 3 y follow up	cross-sectional and longitudinal, (n = 6060; women)	FFQ; Factor analysis, Multiple logistic regression	CES-D, ten items, (baseline and three-year follow-up)	Cooked vegetables Dairy High fat and sugar Meat and processed meat Mediterranean	Age, residential area, education, income, occupation, marital status, smoking, PA, BMI, TEI, NIDDM, heart disease, stroke, mean stress score, HTN	**Mediterranean DP:** decreased odds of DepS. No association with **other DPs**.
Jacka *et al*., 2010, Australia [61]	Geelong Osteoporosis Study	cross-sectional; women (n = 1046; age: 20–94 y)	FFQ, 74 items; Factor analysis	DSM-IV-TR Research Version GHQ-12	Western Modern Traditional	Age, PA, SES, smoking, alcohol consumption, EI, BMI	**Western diet:** higher GHQ-12 scores **Traditional dietary pattern**: lower odds for major depression **Healthy diet:** No association in men (inverse association with women)

Table 2.4 (table *continued)*
Summary of studies on dietary patterns and depression

(table continues)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Depressive disorder outcome	Identified dietary patterns (DPs)	Adjusted variables	Association with the depression
Tsai *et al.*, 2012, Taiwan [344]	Taiwan cohort, follow up for four years.	P\prospective; (n = 1609; age: ≥60 y; sex: 57.6% men)	FFQ	CES-D, ten items, (baseline and four-year follow-up)	Meat and poultry	Age, sex, economic status, formal education, living setting, alcohol drinking, smoking status, betel nut chewing, PA, functional status, T2DM, HTN, heart disease, cancer, chronic kidney disease, stroke, gout, hip fracture, lower-back pain, cognitive status joint pain/arthritis, gallbladder/liver disease	Increased adherence to vegetables associated with decreased odds of DepS in older age
Nanri *et al*., 2010, Japan [241]	Municipality employees	cross-sectional; (n= 521)	Diet history; 67 items	CES-D ≥16; 20 items;	Healthy Japanese Animal food Westernized breakfast	Age, education, income, marital status	Increased adherence to healthy Japanese DP associated with decreased odds of DepS
Samieri *et al*., 2008, France [247]	Three-city study cohort subsample,	cross-sectional; (n= 1724; age: 65 year; sex: n = 647 males, n=1077 females)	FFQ containing 40 items; Cluster analysis	CES-D, 20 items	Biscuits and snacking Healthy Pasta eaters (men) and Pizza, sandwich eaters (women)	Age, education, income, marital status	'Healthy cluster' had lower errors in the MMSE, and the women in the 'healthy cluster' had borderline lower DepS
Sugawara *et al*.; 2012, Japan [49]	Japanese resident (Iwaki district)	cross-sectional; (n=791; age: 22–86 year; sex: n=488 females; cases: n= 97)	Diet history, 65 items, PCA	CES-D ≥16; 20 items;	Healthy Western Bread and confectionery Alcohol and accompanying	Age, sex, BMI, exercise habits, education, current smoking, marital status, T2DM and HTN.	No association

Table 2.4 (table *continued)*
Summary of studies on dietary patterns and depression

(table continues)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Depressive disorder outcome	Identified dietary patterns (DPs)	Adjusted variables	Association with the depression
Chocano-Bedoya *et al*.; 2013, USA [246]	The NHS cohort; follow up 12 year	cohort, female US registered nurses (n = 50,605; women age: 50-77 year)	FFQ, a total of 131 items, measured at (baseline and every four years); PCA	Strict and broad definition	Prudent Western	Age, BMI, TEI, smoking status, menopause status, PA, HRT, marital status, retired, multivitamin use, cancer, caffeine intake, T2DM, hypercholesterolemia, HTN, heart disease, psychological stress, or well-being at baseline	No association
Akbaraly *et al.*; 2009, UK [202]	The Whitehall II Study cohort; follow up five year	Cohort; civil servants working in offices of London (n=3486; age: 35–55 year; 73.8% men; cases: n=416	FFQ, a total of 127 items, Factor analysis	CES-D, 20 items questionnaire	Whole food Processed food	Age, sex, employment grade, energy intake, educational level, marital status, PA, smoking, HTN, T2DM, CVD, stroke, antidepressant use, cognitive functioning	Processed food DP: increased odds of DepS
Liu *et al.*, China, 2007 [347]		Cross-sectional study; n=906;	FFQ containing 85 food items, PCA	CES-D ≥16	Processed food pattern Whole plant food pattern Animal food pattern	Age, menopausal years, education, marital status, living space and income, BMI, coffee, alcohol drink, supplements usage, TEI, and HTN, obesity and T2DM	Processed foods: Increased odds of depression and stress whole plant foods: reduced risk of depression and stress.
Kim, T. H. *et al.*, Korea, 2015 [313]	Tertiary university hospital	Case-control study, n=116, adolescent girls (aged 12-18 years)	FFQ; Multivariate adjusted regression analysis	Korean version of the BDI > 16	Fast foods Processed foods Green vegetable and fruits	Menstrual regularity and energy intake	Fast foods increased risk of depression.
Nguyen, B. *et al.*, Australia, 2017 [54]	2.7 years of follow-up,	Cross-sectional and prospective; n=60,404 adults aged ≥ 45 years (53.6% women)	logistic regression models	KPDS (K10)	Fruit and vegetable	Age, sex, highest education level, marital status, annual household income, smoking status, alcohol intake, PA and chronic disease history	Increase in fruit and vegetable intake may help to reduce psychological distress in middle-aged and older adults.

Table 2.4 (table *continued)*

Summary of studies on dietary patterns and depression

(table continues)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Depressive disorder outcome	Identified dietary patterns (DPs)	Adjusted variables	Association with the depression
Gregório, M. J. *et al*.; 2017; Portugal [348]	EpiDOC cohort	Cohort; n=7,591; men and women	FFQ, Posteriori DP approach, logistic regression models	HADS	Meat Fruit and vegetables	Age, Sex, education, employment status, NUTS II, smoking habits, PA and alcohol habits	Meat DP: increased odds of depression
Oddy, W. H. *et al*.; 2018; Australia [245]	Western Australian Pregnancy Cohort (Raine) Study	Cohort; n=843, adolescents	FFQ developed by CSIRO, Australia Structural equation modelling	BDI	Healthy Western	Sex, maternal ethnicity, maternal education, dietary misreporting, PAL, smoking, alcohol consumed and family income category	Western DP: associated with increased odds of DepS
Oddy, W.H *et al.*; 2009; Australia [345]	Western Australian Pregnancy Cohort (Raine) Study, 14-year follow up	Cross-sectional; n=1598, adolescents	FFQ developed by CSIRO, 212 items, factor analysis	Child Behaviour Checklist for Ages 4–18 (CBCL/4–18)	Healthy Western	TEI, BMI category, PA, screen use, family structure, family income, family functioning and gender at age 14 and maternal education at pregnancy	Western DP: increased odds of DepS
Weng *et al.*; 2012; China [349]	The aerobic exercise intervention study	Cross-sectional; n=5003, 2606 boys and 2397 girls; adolescents; 11-16 years	FFQ, 38 items, PCA, Bivariate logistic regression	The Chinese version of the DSRS for Children	Animal Snack Traditional	Age, gender, maternal education, paternal education, family income, BMI and PA	Snack and animal food patterns: Increased risk of depression and anxiety traditional diet pattern: decreased risk of depression

Table 2.4 (table *continued)*
Summary of studies on dietary patterns and depression

(table continues)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Depressive disorder outcome	Identified dietary patterns (DPs)	Adjusted variables	Association with the depression
Hodge *et al.*; 2013, Australia [53]	MCCS cohort; 12-year follow up	Prospective study; 8660	FFQ; 121-item; Logistic regression	KPDS (K10); K10 score ≥ 20	Modified Mediterranean Australian	Age, Sex, dietary energy intake, PA, education, smoking status, history of asthma, HTN, arthritis, gallstones, Kidney stone, SEIFA, number of relatives visited at least once a month, number of friends could visit without invitation, number of people in the household and social activity.	Traditional Australian DP: decreased odds of depression.
Lucas, M. *et al.*; 2014, US [89]	NHS participants 12-year follow-up (1996–2008)	Prospective analysis; 2594 incident cases of depression using the stricter definition and 6446 using the broader definition; middle-aged and older women	FFQ, RRR	MHI-5 score, a subscale of the SF-36 Health Status Survey	Inflammatory DP	Age, BMI, TEI, smoking, physical activity, menopause status and HRT, marital status, retirement, education, husband education, ethnicity, multivitamin use, reported a diagnosis of cancer, high BP, hypercholesterolemia, heart diseases, diabetes, alcohol intake, caffeine intake	Inflammatory DP: increased odds of DepS
Le port *et al.*; 2012, France [350]	GAZEL cohort; Employees of national Gas and electricity company (EDF-GDF); 10 years follow up	Prospective; 12,404; 9,272 men and 3,132 women	FFQ, 35 items, Generalized Estimating Equations (GEE) logistic regression	CES-D ≥17 for men and CES-D ≥23 for women,	**For men;** Low fat, Healthy diet, Western diet, Fat-sweet, high Snacking. **For women;** low-fat, healthy diet, traditional diet, animal protein pattern, high dessert and high snacking.	Age, employment position, professional activity, BMI, marital status, PA, tobacco smoking status and alcohol intake at baseline.	A traditional pattern in women and healthy pattern in both sexes were found to be associated with decreased DepS

Table 2.4 (table *continued)*
Summary of studies on dietary patterns and depression

Author; year; country	**Study and years of follow-up**	**Study design; sample size; sex of participants**	**Dietary data collection and analysis method**	**Depressive disorder outcome**	**Identified dietary patterns (DPs)**	**Adjusted variables**	**Association with the depression**
Miki *et al*.; 2018; Japan [351]	Furukawa Nutrition and Health Study; 3 year follow up	Prospective study; N=903; 804 men and 99 women ages 19–68 y	The Japanese version of FFQ-BDHQ, 46 items, RRR	CES-D ≥16	**Dietary pattern 1** with higher loading on vegetables, mushrooms, seaweeds, soybean products, green tea	Age, sex, works, marital status, job grade, night or rotating shift work, overtime, job strain, PA, leisure-time smoking, sleep duration, BMI and TEI	DP1: lower risk of depression among Japanese employees

Abbreviation; ALWSH: Australian longitudinal study on Women's Health; ARFS: Australian Recommended Food Score; BDHQ: Brief Self-Administered Diet History Questionnaire; BDI: Beck depression inventory; BMI: body mass index; CSIRO: Commonwealth Scientific and Industrial Research Organisation; DP: Dietary Pattern; DQES: Dietary Questionnaire for Epidemiological Studies; EPA: eicosapentaenoic acid; EpiDOC: EpiReumaPt; FFQ: Food frequency questionnaire; GAZEL: GAZ and ELectricité; GHQ: General Health Questionnaire; HRT: hormone replacement therapy; HTN: Hypertension; KPDS: Kessler Psychological Distress Scale; NIDDM: Non-insulin dependent diabetes mellitus; RRR: reduced-rank regression; SUN: Seguimiento Universidad de Navarra; MCCS: Melbourne collaborative cohort study; MUFA: monounsaturated fatty acid; NHS: Nurses' Health Study; NUTS II: Nomenclature of Territorial Unit for Statistics; PA: physical activity; SEIFA: Socio-Economic Indexes for Areas; DSRS: Depression Self-rating Scale; SES: socioeconomic status;, SFA: saturated fatty acid; TEI: total energy intake

Table 2.5 Systematic reviews and meta-analysis of dietary pattern and depression

(table continues)

Author; year	Study duration	Study methods; the number of studies	Conclusion
Quirk, S.E et al.; 2013 [43]	January 1965 to October 2011	Systematic reviews and meta-analyses (PRISMA guidelines); 25 studies (5 cohort, 1 case-control, 19 cross-sectional); 9 countries	First systemic review article and no firm conclusion has been drawn as there is inconsistency in the results. Further research is warranted.
Sanhueza, C. et al.; 2013 [352]	Up to May 2010, follow up ranges from 2-13 years	Only longitudinal study included;11 studies	Folate, ω-3 PUFA and MUFA; olive oil and fish; and a diet rich in fruits, vegetables, nuts and legumes: decreased odds of depression Further research is needed with robust prospective cohort studies.
O'Neil, A. et al.; 2014 [44]	Up to August 30, 2012	Child and adolescent group only; 12 studies (3 cohorts and nine cross-sectional)	Consistent cross-sectional association between unhealthy DP and worsened mental health Inconsistent results with healthy DP and better mental health
Lai, J. S. et al.; 2014 [234]	Up to August 2013	A systematic review and meta-analysis; community-dwelling adults; a total of 21 studies [20 observational studies; but only 13 observations were included in the meta-analysis (4 cohorts and nine cross-sectional) and 1 RCT)]	Healthy diet pattern: decreased odds of depression Western diet: No statistically significant association
Li. Y. et al.; 2017 [46]	Up to September 2016	Meta-analysis, 21 studies (11 cohort, 6 cross-sectional, 4 case-control); 10 countries	Healthy pattern: decrease the risk of depression Western pattern: increased risk of DepS

Table 2.5 *(continued)*
Systematic reviews and meta-analysis of dietary pattern and depression

Author; year	Study duration	Study methods; the number of studies; included age groups	Conclusion
Rahe, C. et al.; 2014 [235]	Up to May 2013	A systematic review (PRISMA guidelines); Only descriptive analysis due to a high level of heterogeneity, 16 studies (9 Prospective and 7 cross-sectional)	Dietary patterns might influence the onset of depression, but no firm conclusion has been drawn.
Opie, R. S. et al.; 2014 [346]	April 1971 to May 2014	A systematic review (PRISMA guidelines); 17 RCT studies with a whole-of-diet approach	Dietary intervention studies have the potential to achieve improved depression scores
Khalid, S. et al.; 2017 [47]	1970 up to April 2016	Systematic review; 20 studies (17 cross-sectional and 3 prospective); 1,09,533 unique individual participants (51,834 males and 49,588 females)	Unhealthy dietary pattern and worsening of mental health have positive association but inconsistent.
Mannan, M. et al.; 2016 [324]	1961 to January 2015	Systematic review and meta-analysis (PRISMA guidelines); 14 studies (7 obesity to depression and seven depression to obesity	Reciprocal and bidirectional association between depression and obesity in adolescents. The strength of the association was found to be stronger in the direction of depression leading to obesity than for obesity leading to depression.
Molendijka, M. et al.; 2018 [45]	Up to March 6th, 2017	Systematic review and meta-analysis (PRISMA guidelines); 29 studies	High-quality diet, regardless of type (i.e. healthy/prudent or Mediterranean): lower risk of DepS over time. Intake of fish and vegetables but not fruit was associated with a lower risk of DepS No association between low-quality diets and higher depression incidence.
Firth, J. et al.; 2019 [15]	Up to March 2018	Meta-analysis (PRISMA guidelines); 16 RCT studies; 45,826 individuals	Diet can play a role in the treatment and also self-management of DepS across the population

Abbreviation; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomised Controlled Trial

2.12 NUTRIENT PATTERN (NP) AND DEPRESSION

Traditionally, nutritional analysis was performed by looking at only one particular food group or nutrient, which may miss capturing the fundamental intricacy of the diet, the complex interaction with different components and variation in food and NPs existing within and between populations [42, 62]. Limited work has been undertaken using NPs analyse when compared with dietary patterns analyses. Most of the studies using NPs have been undertaken with cancer patients [65-67, 353-363], however some studies have explored associations between NPs and bone mineral density [70-73], obesity [74, 75], metabolic syndrome [77], brain and cognitive health [78, 364] and inflammation [76].

While dietary patterns provide an overall knowledge of the link between diet and disease [61] and possibly better disease prediction compared with individual foods [62], the interpretability of the core mechanisms is difficult to measure using this method because the food groups contain multiple nutrients and therefore it is difficult to identify the specific nutrient or possible interactions between the nutrients that may explain the food group effect. Additionally, nutrients are functionally not exchangeable, with the same nutrients consumed across all populations [63]. Therefore, the NP approach may better reflect the role of nutrients in complicated biological mechanisms and its association with the disease than the use of food based dietary pattern [67, 356, 358].

2.12.1 SPECIFIC NUTRIENT PATTERNS RELATED TO DEPRESSION

Only one relevant study has been identified the association between NPs and depression, which is provided in Table 2.6.

Table 2.6 Summary of the study on nutrient patterns (NPs) and depression

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Outcome measures	Identified (NPs – food components	Adjusted variables	Association with the depression
Salehi-Abargouei *et al*.; 2018; Iran; [79]	SEPAHAN project	Cross-sectional study; n=3846; 1712 males and 2134 females; 18-55 years	FFQ; 106-item, PCA, binary logistic regression	HADS ≥ 11	Omnivore Grains and dairy Fruits and vegetables	Age and energy intake, marital status, education status, antidepressant use, family size, smoking status, PAL, breakfast skipping, chronic disease and BMI	An 'omnivore' like diet: decreased odds of psychological disorders

Abbreviations: SEPAHAN: Study on the Epidemiology of Psychological Alimentary Health and Nutrition; HADS: Hospital-Anxiety- and Depression Scale

2.13 DIET, DEPRESSION AND INFLAMMATION

Diets can be pro-inflammatory or anti-inflammatory depending on the hormonal responses they generate [365]. There are various inflammatory markers in the body, with the earliest marker of cellular inflammation being the high sensitivity CRP (*hs*CRP). Inflammatory cytokines expressed by the activation of NF-kB, such as TNF-α, IL-1β, and IL-6, are also potential markers of cellular inflammation. However, they are present at low levels in the blood and have a short half-life [365].

Dietary changes may influence chronic disease risk when they persist over time. To calculate the overall inflammatory potential of a diet, a novel tool named the DII® was created which can categorize an individual's dietary consumption from anti- to pro-inflammatory. This index is associated with serum inflammatory markers, including CRP, IL-6 and TNF-α [366-368]. A higher DII® score reflects a more pro-inflammatory diet (foods such as SFA, ω-6 PUFA, and refined carbohydrates), whereas, a lower DII® score reflects a more anti-inflammatory diet (foods such as wild-caught salmon, nuts, dark green leafy vegetables, berries, sweet potatoes and spices) [100, 164].

Numerous studies have linked depression with increased inflammatory markers [83, 106, 107, 369]. Innate immune cells get activated, in response to infection and produce pro-inflammatory cytokines. Prolonged activation of these cells, as occurs in chronic or systemic infection, produces constant signalling to the brain that leads to the development of DepS [370]. Furthermore, MDD are more prevalent in patients with conditions that lead to chronic inflammation [371].

Studies have shown that following the MDP, rich in fruits, vegetables, olive oil and legumes, may be protective against depression [89]. On the other hand, a recent meta-analysis on DII® and depression revealed that a pro-inflammatory diet (higher DII® score) is independently linked with an increased risk of depression, particularly in women [164]. However, more well-designed prospective longitudinal studies with improved methodology are warranted to confirm these findings.

To date, nine cross-sectional [91, 94-101] and six longitudinal studies [102-107] have been undertaken to examine the association between the inflammatory potential of the diet and depression/DepS using DII® as a tool (See Table 2.7). In addition, some authors have used the RRR method (See Table 2.8) to determine the inflammatory potential of the diet by using inflammatory biomarkers, such as CRP, IL-6 and TNF-α as a response variable [89, 108].

Table 2.7 Summary of the studies on DII® and depression

(table continues)

Study; year; Country	Case definition	Outcome measures (DepS)	Assessment of Inflammatory diet	Food parameters derived	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Identified DII score	Association with the depression
Açik M et al.; 2019; Turkey [94]	DepS	Zung Self-Rating Depression Scale ≥ 50	DII®	29	NA	Cross-sectional; 134 female students aged 19–24 years who stay in Cebeci Girls 'Dormitory	3-days food intake records with 24-hour diet recall method; Binary logistic regression analysis	-0.92 to +2.15	Higher DII® : an increased risk of depression incidence.
Adjibade et al.; 2017; France [102]	DepS	CES- D (French) score ≥17 for men and ≥23 for women	DII®	36	SU.VI.MAX cohort; 12.6 years	Prospective cohort; 3,523	24-h dietary record every two months	-4.99 to +5.82	No association
Adjibade et al.; 2019; France [103]	Incident DepS	CES-D (French) ≥17 for men and ≥23 for women	ADII	34	NutriNet-Santé study, follow up 5.4 y.	Prospective cohort; 26,730 participants (aged 18–86 y)	ADII, multivariable Cox proportional hazards	-48.0 to +15.12	Proinflammatory diet Increased risk of DepS (women, middle-age adults, and participants with overweight or obesity)
Akbaraly, 2016; UK [104]	Recurrent DepS	CES-D ≥ 16 or treated by anti-depressants	DII®	27	Whitehall II; five years	Prospective cohort; 4246 participants (3178 Men; 1068 women), aged 60.9±5.9 years	FFQ, Logistic regression model	−3.35 to +4.23	High score of DII® : increased odds of recurrent DepS at least in women
Bergmans et. al.; 2017; USA [91]	Depression	PHQ-9 ≥ 10	DII®	28	NHANES 2007–2012	Cross-sectional; 11,592; age >20 years	Multivariate logistic regression	−5.29 to +4.71	Higher DII score over a twofold higher odd of depression.

Table 2.7 *(*table *continued)*
Summary of the studies on DII and depression

(table continues)

Study; year; country	Case definition	Outcome measures (DepS)	Assessment of Inflammatory diet	Food parameters derived	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Identified DII score	Association with the depression
Haghighatdoost et al., 2018, Iran [95]	Highest tertiles of mental health disorders profile	HADS ≥ 8	DII®	27 nutrients, onions, tea and caffeine	SEPAHAN project	Cross-sectional; 3363, Female 59%,	106-item dish-based FFQ; Binary logistic regression analysis for and Multivariate logistic regression	-5.55 to +4.61	Pro-inflammatory diet: increased risk of higher mental health disorders profile scores.
Jorgensen et al., 2018; US [96]	Current depression	PHQ-9	DII®	28	NHANES 2007–2012	Cross-sectional, 11,624; age ≥ 18 years without CVD diagnosis	Multivariable logistic regression,	-2.99 to +8.75	Pro-inflammatory diet: increased risk for DepS even in those with high Framingham risk score
Phillips et al.; 2017; Ireland [97]	DepS	CES-D ≥ 16	E-DII™	26	Cork and Kerry Diabetes and Heart disease Study (Phase II);	Cross-sectional; 3,043; Males 2,047;	Self-completed FFQ; Logistic regression analyses	-5.10 to +3.68	Pro-inflammatory diet adverse mental health
Salari-Moghaddam et al.; 2018; Iran [98]	Depression	HADS ≥ 8	DII®	29	SEPAHAN project	Cross-sectional; 3,363;	106-item DS-FFQ	-4.49 to +5.39	Pro-inflammatory diet: positively associated with psychological disorders.
Salari-Moghaddam et. al.; 2019; Iran [99]	Depression	HADS ≥ 8	FDII	28	SEPAHAN project	Cross-sectional, 3363 participants	106-item DS-FFQ, FDII	−14.67 to +8.29	Greater FDII score was positively associated with psychological disorders. (in women but not in men)
Sánchez Villegas et al.; 2015; Spain [105]	Depression	Use of antidepressants and/or Physician diagnosis	DII®	28	SUN Project; 8.5 years	Prospective cohort; 15,093; female 8847;	28-item FFQ;	−3·16 to +0·66	A higher DII®: an increased risk of developing depression

Table 2.7 (tabl*e continued*)
Summary of the studies on DII and depression

Study; year; country	Case definition	Outcome measures (DepS)	Assessment of Inflammatory diet	Food parameters derived	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Identified DII score	Association with the depression
Shivappa et al.; 2018; Iran [100]	At least mild level of DepS	DASS-21(Persian) score > 9	DII®	31	NA	Cross-sectional, 300 adolescent girl aged 15-18 years	168-item FFQ,	Not mentioned	Proinflammatory diet: greater odds of having at least moderate DepS
Shivappa et al.; 2016; Australia [107]	DepS	CES-D ≥ 16	DII®	24	ALSWH; 12 years	Prospective cohort; 6,438 (All women)	101-item FFQ, DQES-V2;	-1.60 to +3.23	Lower DII® scores: with a lower risk of developing depression in women
Shivappa et al.; 2018; US [106]	DepS	CES-D-10 score ≥ 10	DII®	26	Osteoarthritis Initiative (OAI); Eight years	Prospective cohort; 3608 participants (1577 males, 2071 females; mean age: 60.6 years)	FFQ, Cox's regression analysis	−5.54 to +3.57	Pro-inflammatory diet: higher incidence of depressive symptoms
Wirth et al.; 2017; US [101]	DepS	PHQ-9 score ≥ 10	DII®	27	NHANES	Cross-sectional; 18,875; (Male 49%)	24-hour dietary recalls	−5.62 to +4.82	Women with DepS have more pro-inflammatory diets relative to those without DepS

Abbreviations: ALWSH: Australian longitudinal study on Women's Health; CES-D: Centre for Epidemiological Studies Depression Scale; DASS-21: Depression Anxiety Stress Scales 21; DQES: Dietary questionnaire for epidemiological studies; HADS: Hospital-Anxiety- and Depression Scale; SEPAHAN: Study on the Epidemiology of Psychological Alimentary Health and Nutrition; SUN: Seguimiento Universidad de Navarra; FFQ: Food frequency questionnaire; NHANES: National Health and Nutrition Examination Survey; PHQ: Patient health questionnaire;

Table 2.8 Summary of the studies on the inflammatory dietary pattern (IDP) score/OR empirical DII and depression (by measuring CRP, IL6 and TNF-α)

Author; year; country	Study and years of follow-up	Study design; sample size; sex of participants	Dietary data collection and analysis method	Outcome measures (Depression or DepS	Association with the depression
Lucas et al., 2014; US [89]	NHS, 12 years	Prospective cohort; 43,685 baseline participants; Incident cases of depression; stricter definition (n= 2,594) and broader definition (n=6,446) in all women	FFQ, RRR	**Strict definition** of depression (self-reported physician-diagnosed depression and regular antidepressant use) and **broader definition** (clinical diagnosis or regular antidepressant use)	Inflammatory dietary pattern: a higher depression risk
Vermeulen et al., 2017; Italy [108]	InCHIANTI study	Prospective cohort; 827 baseline participants, 356 participants at follow-up, aged ≥ 65 years	FFQ, RRR	CES-D score ≥ 20	No association

Abbreviations; DepS: Depressive symptoms; EPIC: European Prospective Investigation into Caner and Nutrition; NHS: Nurses' Health Study; MHI-5: mental health inventory; InCHIANTI (Invecchiare in Chianti, ageing in the Chianti area); IADL: Lawton Instrumental Activities of Daily Living

It is evident from the aforementioned studies that a higher DII® or pro-inflammatory diet contributes to a greater risk for depression or DepS, albeit there are some inconsistent findings. Similarly, anti-inflammatory diets may also help to lessen the depression or DepS. The exact mechanisms behind the link between DII® and DepS are not fully clarified, however, many studies have pointed towards circulating inflammatory markers and an increased inflammatory response which may enhance the risk of developing depression [372-374].

2.13.1 SUMMARY

It is evident from the literatures that depression is a common mental health disorder and global public health problem. However, there remain gaps in knowledge due to the complexity and multidimensional causes of this disease. Among the many possible risk factors, diet is one of the more promising means for the prevention and treatment of depression. Early research has advanced from cross-sectional epidemiological studies reporting associations between individual nutrient intake (i.e. macronutrients and micronutrients) to food groups (i.e. fruits, vegetables and fish intake), and still further to use longitudinal and novel mechanistic studies.

Complementary approaches such as dietary and nutrient patterns have been found to be effective in studying diet-disease relationship compared to single food groups or nutrients. However, inconsistent associations between diet and depression have persisted, mainly due to the array of different methods used for dietary assessment and depression measurements. Many studies, including systematic reviews and meta-analyses, have suggested that a healthy diet may help to alleviate the risk of DepS. In contrast, unhealthy dietary patterns are associated with increased risk of DepS. Some foods (e.g. fish, fruits and vegetables) and nutrients (e.g. ω-3 PUFA, folate, Mg^{2+} and

zinc) have been found to decrease the odds of DepS while SFA or processed foods were found to increase the risk of DepS. More recently, the literature suggests a role of inflammation in the pathophysiology of depression, which could be accessed using a mechanistic tool such as the DII®. However, there remain gaps in the current understanding of the association between diet and depression.

Based on the literature presented above, this study aimed to explore the link between diet and depression using a large community-based cohort and novel analysis techniques in order to further clarify the association between diet and depression. More specifically the objectives are to:

- Investigate the dietary patterns associated with adult depression, using PCA, RRR and PLS methods
- Investigate the NPs associated with depression in adults, providing insight into the possible relationship between specific nutrients and DepS
- Evaluate whether the E-DII™, designed to estimate the inflammatory potential of diet, is associated with depression in adults, focussing on specific DepS and updating the previous meta-analysis.

The data, methods and analyses used to fulfil these objectives are outlined in the following chapters.

Chapter 3: Methods

3.1 OVERVIEW OF THE DATA USED

The data used in this thesis were from the North West Adelaide Health Study (NWAHS). For each of the aims of the study, detailed methods are provided in Chapters 4 to 6. However, a brief description of the data and analysis methods used is provided below.

3.2 NORTH WEST ADELAIDE HEALTH STUDY (NWAHS)

The NWAHS was established in 1999, in Adelaide, South Australia (SA), as a joint effort between SA Health, the Queen Elizabeth Hospital, the Lyell McEwin Hospital, the University of Adelaide, the University of South Australia and the Institute of Medical and Veterinary Science. The fundamental aim of the NWAHS project was to provide longitudinal self-reported and measured data to contribute to prevention strategies and the management of chronic disease conditions and their risk factors.

The methodology of the NWAHS is described in detail elsewhere [375]. However, in brief, the original sample region represents nearly fifty percent of the metropolitan area of Adelaide, the capital of South Australia (SA) and thirty three percent of the overall population of SA. The data collection was undertaken in three main stages between 1999 and 2010. A self-completed questionnaire, Computer-Assisted Telephone Interview (CATI) and clinical assessments were used to collect the data. Participants were initially randomly selected using their landline telephone listing in the Electronic White pages. Stage one (1999-2003) included 4056 participants, aged 18 years and over. In Stage 2 (2004-2006), 3564 participants completed questionnaires (telephone and/or self-complete) and 3205 had clinical assessments. In the third stage (2008-2010), 2871 participants were assessed, of which 2487 had their clinical assessments. In addition to

these three major stages, there was a self-reported survey undertaken in 2015 [North West (NW15)], using both postal and online methods. Dietary data were collected as part of Stage 3 (2008-10, *n* = 2,500) only. However, Center for epidemiological studies-depression (CES-D) data were collected in both Stage 3 and NW15. In this thesis, a total 1743 participants and 859 participants were involved in the cross-sectional study (analysis of Stage 3 data only) and longitudinal analysis (analysis of data from both Stage 3 and NW15) respectively of dietary patterns (Chapter 4) and the energy-adjusted dietary inflammatory index (E-DII™) (Chapter 6) analyses with depressive symptoms (DepS). In Chapter 5, to select variables, two approaches were used: i) dietary data, covariates and DepS (prevalent DepS) were used from Stage 3; ii) DepS (incident DepS) were used from NW15. DepS were examined at two different time points, in 2010 (Stage 3, *n* = 1743) and 2015 (NW15, *n* = 1,024). *Figure 3.1* depicts the study timeline, stages, and sample size for NWAHS and subsamples used for this thesis (Chapters 4 to 6).

3.3 STUDY POPULATION

Our study population in Stage 3, when dietary data were collected, included the participants aged 24 years and over. After excluding all implausible energy intake values (n = 41) and missing data (n = 136), the final sample size aged between 24-94 years was 1,743 participants for the cross-sectional study (Stage 3) and 859 participants for the longitudinal study (Stage 3 and NW15). Variables that were collected at each stage are presented in Appendix B.

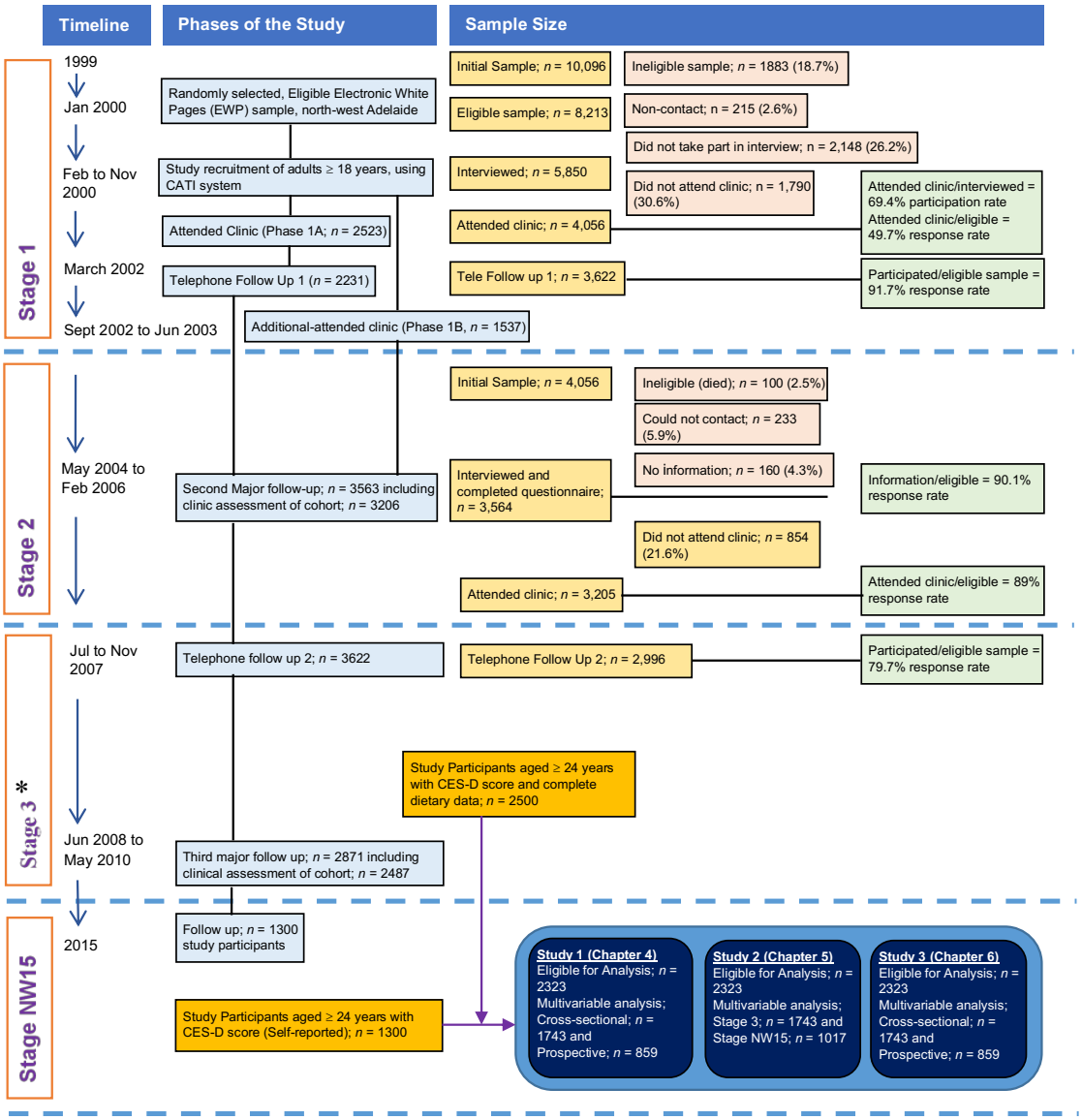

Figure 3.1. Study timeline, stages and sample size of the NWAHS cohort profile and subsamples used for studies (Chapters 4 to 6) in this thesis

*dietary data were collected in Stage 3 only

Adapted from 'Cohort Profile: The North West Adelaide Health Study (NWAHS)' by Grant JF et al. Int J Epidemiol. 2008; 38:1479-86. [375]

3.4 DIETARY ASSESSMENT AND FOOD GROUPS

Dietary intake was assessed by the dietary questionnaire for epidemiological studies version 3 (DQES-V3), a self-completed validated food frequency questionnaire (FFQ) developed by Cancer Council Victoria was used [376]. This FFQ was designed to assess the food intake over the preceding 12 months. A food composition database, the Australian NUTTAB95 (NUTrient TABles for use in Australia; published by Australian

Government Publishing Service, Canberra, 1995), was used to determine total daily intakes of food items and nutrients [377]. For the dietary pattern analysis, food items were categorized into thirty-nine food groups, whereas nutrients from each food items were compiled into thirty-one nutrient groups for the nutrient pattern analysis. Details of the measurement of covariates used in the three studies (Chapters 4 to 6) are described in their corresponding chapters.

3.5 DIETARY DATA ANALYSIS METHODS IN NWAHS

3.5.1 PRINCIPAL COMPONENT ANALYSIS (PCA)

PCA is a statistical tool that transforms a large number of interrelated variables into a reduced set of 'factors' , composed of a weighted set of the original variables, that can be used to explain specific patterns of behaviour [378]. PCA has been used widely in nutritional epidemiology and can capture the various patterns of diet from multiple food and nutrients [378]. The weights (also known as factor loadings or coefficients) are chosen to condense each factor independent of the others and to sequentially explain the largest amount of the possible total variance. Higher factor loadings indicate a greater weighted correlation within a specific pattern. The orthogonal (varimax) rotation was used to rotate the factors for easy interpretation and minimise the correlation between the factors. Usually, there is a similar number of factors, as there are variables. This is why the optimal number of factors should be pre-selected to be included in the final iteration as it is not possible to include all factors. This can be achieved by three common approaches:

1. Use of an eigenvalue which is a measure of how much of the variance of observed variables a factor explains. If an eigenvalue of a factor is greater than one, then the factor explains more variance than a single observed value
2. using a scree plot

3. factor (component) interpretability

Figure 3.2 shows the visual representation of PCA approach.

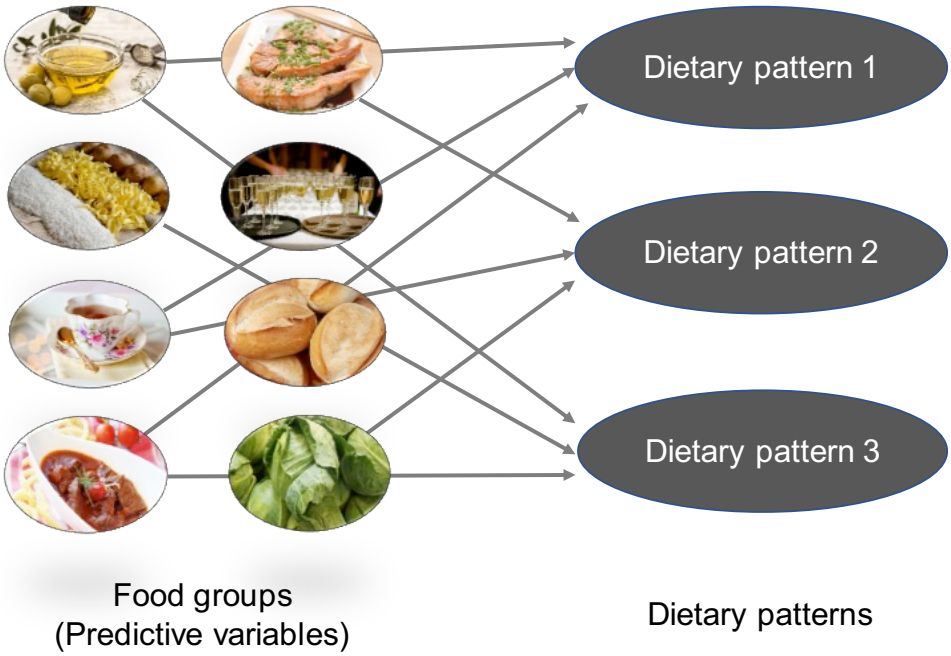

Figure 3.2. Visual Representation of PCA

Adapted from ' 'Next generation' approaches in diet pattern analysis: Assessing the impact of different statistical methods and physiological intermediate variables' by Glicksman R. ProQuest Central; ProQuest Dissertations and Theses Global: University of Toronto; 2016. [379]

3.5.2 HYBRID METHODS COMBINING PRIORI AND A POSTERIORI APPROACHES

Recently, statistical techniques that combine priori and posteriori approaches, such as RRR and PLS, have been proposed as an alternative technique to derive dietary patterns.

3.5.2.1 Reduced Rank Regression (RRR)

The RRR method is primarily used to derive dietary patterns by merging multivariate approaches with prior information of diet-disease interactions [58]. In RRR, factors (predictor variables) that maximise the explained variable in the response variable, are determined from food intake data, also known as predictor variables. The commonly used response variables to derive dietary patterns are disease-related

nutrients, biomarkers of intake, or biomarkers of the disease process [58, 59, 379, 380]. In contrast to PCA, RRR identifies factors that explain as much response variable as possible. Disease prediction can be significantly achieved with RRR since this method integrates a priori knowledge into a posteriori dietary patterns derivation. RRR has been applied to a variety of different health outcomes, including cardiovascular disease, diabetes, bone mineral densities and metabolic syndrome, however, the lack of generalizability across study populations and health outcomes remains a known weakness in RRR [59, 60, 379]. *Figure* 3.3 shows a visual representation of RRR.

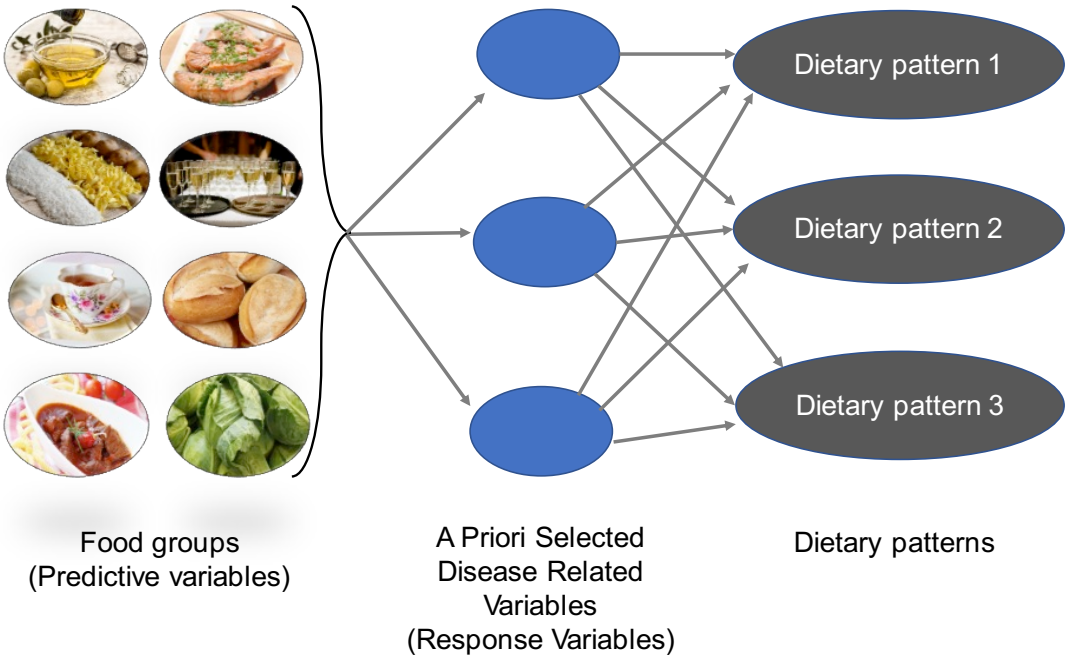

Figure 3.3. Visual representation of RRR

Adapted from "Next generation approaches in diet pattern analysis: Assessing the impact of different statistical methods and physiological intermediate variables" by Glicksman R. ProQuest Central; ProQuest Dissertations & Theses Global: University of Toronto; 2016. [379]

3.5.2.2 Partial Least Square (PLS) Analysis

The PLS method is a bridge between PCA and RRR. PLS uses a similar response variable to that of RRR and balances the two goals of explaining predictor variation and explaining response variation [60, 381]. Consequently, the PLS method is thought to have more pathophysiological relevance to disease outcomes than the other two methods (i.e.

PCA and RRR), however, this may not always be true [58, 59, 379] since choosing the right response variables plays an important role pattern development. *Figure* 3.4 shows a visual representation of PLS.

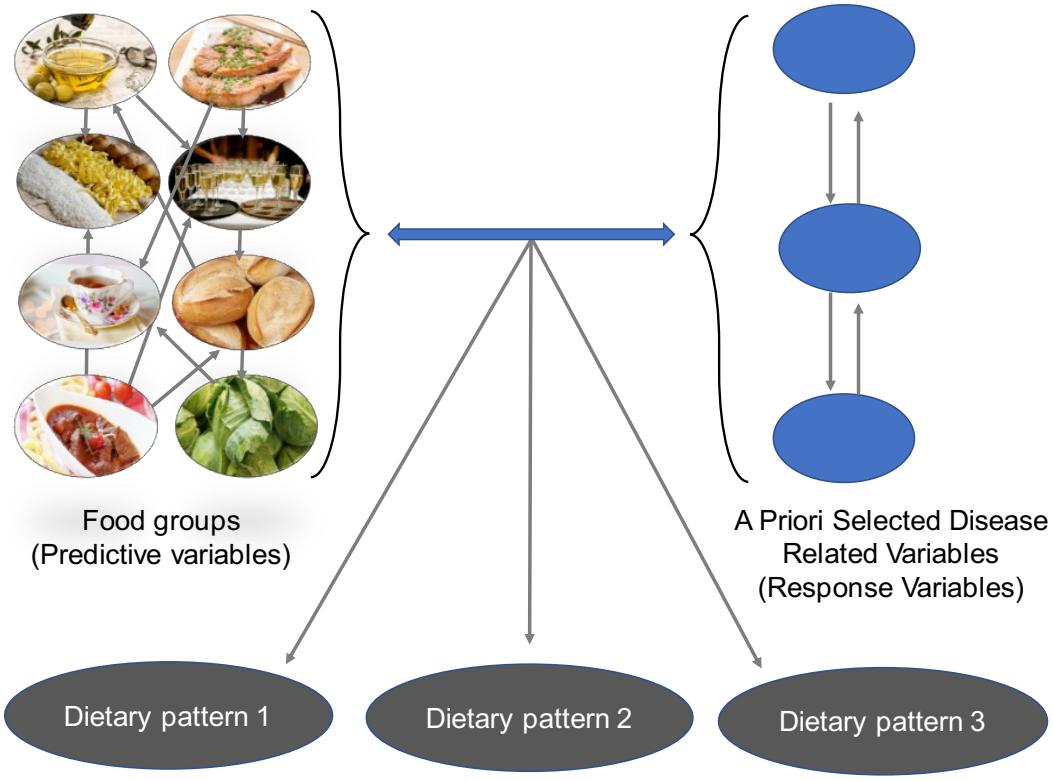

Figure 3.4. Visual representation of PLS

Adapted from ' 'Next generation' approaches in diet pattern analysis: Assessing the impact of different statistical methods and physiological intermediate variables' by Glicksman R. ProQuest Central; ProQuest Dissertations and Theses Global: University of Toronto; 2016. [379]

3.5.3 ENERGY ADJUSTED DIETARY INFLAMMATORY INDEX (EDII™) CALCULATION

Revised versions of DII® calculations have been utilized in this thesis which has been developed by Shivappa *et al.* [83]. The steps on how the revised version of DII® has been calculated are illustrated in Appendix C. The E-DII™ is a specific modification of the DII®, with its development described in detail in Chapter 6. Briefly, E-DII™ has been used, which is a logical extension of the original DII®, but is calculated per 1000 calories of food consumed, and requires the use of the energy-standardized version of

the world database to control for the effect of total energy intake. The E-DII™ for this study was computed using data on 29 out of the 45 variables, including pro-inflammatory (carbohydrate, protein, fat, SFA, iron, cholesterol, trans-fat, VB12) and anti-inflammatory components (alcohol, fibre, MUFA, ω-3 PUFA, ω-6 PUFA, niacin, thiamine, riboflavin, magnesium, zinc, vitamin A (VA), VC, VE, VD, VB6, folic acid, β-carotene, tea, garlic and onions).

3.6 STATISTICAL ANALYSIS

Descriptive statistical analysis was used for computing the baseline characteristics in all three studies and the details have been given in their respective chapters. Briefly, mean and standard deviations were calculated for continuous and normally distributed variables. Chi-square and analysis of variance (ANOVA) test were applied for categorical variables and continuous variables respectively. Kruskal Wallis tests was used for continuous but non-normal distributed variables.

Depending upon the nature of data, generalized linear models have been applied. For example, log-binomial regression models (family-binomial; link-log) were used when the outcome variable was in dichotomous form (CES-D cut-off score $\geq$ 16) as in Chapter 4. Negative binomial regression model (family-nbinomial; link-nbinomial) were used, when the outcome variable was the DepS score (count variable with over-dispersed distribution) and the predictor variables were NPs (factor scores from 31 nutrients) as in Chapter 5. Ordinal logistic regression analysis (family-binomial; link-logit) was used to determine the association between quartiles of both NPs and factor structure from the CES-D score as in Chapter 5. In Chapter 6, similar logistic regression analysis was used to determine the association between quartiles of both DII and individual CES-D score.

Table 3.1 summarises the process of statistical models building and the statistical approaches used in this study. Log- and negative binomial regression along with ordinal logistic regression were used for statistical analysis depending on the type of data.

In addition to these statistical tests, various subgroup analyses were also performed in all three studies to determine whether one group had different results compared to the overall results. Furthermore, various sensitivity analysis was also performed in all the three studies to determine the robustness of the results by examining the extent to which they were affected by variations in methods, models, values of unmeasured variables, or assumptions [382]. Briefly, for subgroup analyses, Poisson regression (family-Poisson; link-log) was performed to assess the association of dietary patterns/NPs/ DII® within various subgroups such as sex, educational status, work status, income status, physical activity level (PAL), smoking status, hypertension and CVD. For sensitivity analyses, the final model was further adjusted with antidepressant use and missing covariates in Chapter 4 whereas in Chapter 5, sensitivity analysis was performed using familial status in the final model. The details described in more detail in each of the respective study chapters.

Table 3.1 Summary of predictors, outcome and confounding variables and statistical approaches

Abbreviations: bin: binomial; E-DII™: Energy adjusted dietary inflammatory index; CES-D: Centre for epidemiologic studies depression scale; DepS: Depressive symptoms, fam: family; HTN: Hypertension, SEIFA: Socio-Economic Indexes for Areas; PAL: Physical activity level; BMI: Body Mass Index; T2DM: Type 2 Diabetes Mellitus; CVD: Cardiovascular disease

Study	Predictor and outcome variables and type of data	Model	Covariates (adjusted for)	Statistical approaches (family and link)	Additional analysis
Chapter 4	Predictor: Dietary patterns (quartiles of factor scores) Outcome: DepS (CES-D score ≥ 16) Type of data: Binary	Model 1	sex, age and total energy intake	Log-binomial regression [family=binomial (link='log')]	Sensitivity analysis Subgroup analysis Mediation analysis
		Model 2	Model 1 + marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality		
		Model 3	Model 2 + BMI, bodily pain, HTN, T2DM and CVD		
Chapter 5	Predictor: Nutrient patterns (quartiles of factor scores) Outcome: DepS (CES-D score) Type of data: Both binary and continuous	Model 1	sex, age and total energy intake	Log-binomial regression [family=binomial (link='log')] Negative binomial regression [family=nbinomial (link=nbinomial')] Ordinal logistic regression [family=binomial (link='logit')]	Sensitivity analysis Subgroup analysis
		Model 2	Model 1 + marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality, BMI, bodily pain, HTN, T2DM and CVD		
Chapter 6	Predictor: E-DII™ (quartiles of E-DII™ scores) Outcome: DepS (CES-D scores) Type of data: Both binary and continuous	Model 1	Sex and age	Log-binomial regression [family=binomial (link='log')] Negative binomial regression [family=nbinomial (link=nbinomial')] Ordinal logistic regression [family=binomial (link='logit')]	Subgroup analysis
		Model 2	Model 1 + marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality		
		Model 3	Model 2 + BMI, bodily pain, anti-depressant use, HTN, T2DM and CVD		

The following chapters (Chapters 4-6) present the analyses which are the core part of this thesis followed by overall discussion, future recommendations and conclusions.

Chapter 4: Dietary patterns and Depressive symptoms

Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares

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4.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Shakya PR, Melaku YA, Page A, Gill TK. Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares. Clin Nutr. 2019. https://doi.org/10.1016/j.clnu.2019.12.011 (in press):00-000. Awaiting PMID: xxxxxx. Awaiting PMCID: PMCxxxxxxx.

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Name of Principal Author (Candidate)	Prem Raj Shakya		
Contribution to the Paper	Conception and design, organization and interpretation of data, manuscript preparation, contribution to the materials/analysis tools and critical revision and editing of the manuscript		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/03/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conception and design, statistical analysis, data interpretation, critical manuscript evaluation and editing and contribution to the materials/analysis tools		
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Name of Co-Author	Amanda Page		
Contribution to the Paper	Conception and design, interpretation of results, critical manuscript evaluation and editing, provide expert opinion and have given approval of the final version for publication		
Signature		Date	01/03/2020

Name of Co-Author	Tiffany K Gill		
Contribution to the Paper	Supervised the development of the work, conception and design, interpretation of results, critical manuscript evaluation and editing, contribution to the materials/analysis tools, provide expert opinion and have given approval of the final version for publication		
Signature		Date	01/03/2020

4.2 PUBLICATION

This result chapter is reproduced in the exact form as it appears in the manuscript:

Shakya PR, Melaku YA, Page A, Gill TK. Association between dietary patterns and adult depression symptoms based on principal component analysis, reduced-rank regression and partial least-squares. Clin Nutr. 2020. 39(9):2811-23. https://doi.org/10.1016/j.clnu.2019.12.011

In keeping with the style of this thesis, the tables and figures have been re-numbered, the references reformatted and incorporated into the thesis master reference list, and the manuscript repaginated.

4.3 ABSTRACT

Background and aims

There have been inconsistent findings on the association between dietary patterns and depressive symptoms (DepS). In addition, studies have used single analysis methods to identify dietary patterns. In the current study, we aimed to determine the association between dietary patterns, derived by principal component analysis (PCA), reduced-rank regression (RRR) and partial least-squares (PLS), and DepS among adults using a cohort study in Australia.

Methods

We examined a total of 1743 study participants (≥ 24 years, 48.9% males) using cross-sectional and longitudinal data from the North West Adelaide Health Study (NWAHS). The Center for Epidemiological Studies-Depression (CES-D) scale was used to assess DepS and a score ≥16 was considered as having depression. Dietary data were collected using a food frequency questionnaire. Eicosapentaenoic acid (EPA)/ Docosahexaenoic acid (DHA), folate, magnesium (Mg) and zinc (Zn) densities were chosen as the response variables for RRR and PLS analyses. Dietary patterns were identified by PCA, RRR and PLS. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated across quartiles (Q) using log-binomial logistic regression to assess the association between dietary patterns and DepS. Sensitivity analyses, including a longitudinal association between dietary patterns and DepS among 859 participants, were performed. Multiple imputation was performed to investigate the effect of missing data on the estimates.

Results

In this study, 16.9% (14.2% in men and 20.8% in women) of the participants had DepS. We retained two, four and four dietary patterns captured by PCA, RRR and PLS

respectively. The 'prudent' pattern determined by PCA [OR_{Q4VsQ1}=0.57; 95% CI: 0.35, 0.92] and RRR [OR_{Q4VsQ1}=0.66; 95% CI: 0.43, 1.00] together with the 'typical Australian' pattern determined by RRR [OR_{Q4VsQ1}=0.60; 95% CI: 0.40, 0.90] were inversely associated with DepS whereas the 'western' pattern derived by PCA [OR_{Q4VsQ1}=2.04; 95% CI: 1.12, 3.68] and PLS [OR_{Q4VsQ1}=1.62; 95% CI: 1.05, 2.50] was positively associated with DepS. In the longitudinal analysis, the 'prudent' pattern determined by PCA [OR_{Q4VsQ1}=0.52; 95% CI: 0.25, 1.09] tended to be inversely associated with DepS whereas 'western' patterns determined by PCA [OR_{Q4VsQ1}=3.47; 95% CI: 1.37, 8.78] and PLS [OR_{Q4VsQ1}=2.47; 95% CI: 1.24, 4.91] were positively associated with DepS. We found that a dietary pattern characterized by high intakes of fruits, vegetables, medium fat dairy, nuts, legumes, and fish was inversely associated with DepS in this population-based study. Contrary to this, a dietary pattern characterized by high intakes of processed and red meat, fast foods (snacks and takeaway foods), soft drinks, white bread and high-fat dairy products were significantly associated with DepS. Multiple imputation and sensitivity analysis identified similar patterns of association between dietary pattern and DepS.

Conclusions

The findings indicate that the 'western' pattern was consistently associated with an increased risk, and the 'prudent' pattern tended to be associated with a reduced risk of DepS. This suggests that dietary interventions may assist with the treatment of DepS. However, current evidence on the impact of diet on DepS should be supported using further longitudinal studies with extended follow up, larger sample sizes and repeated measures.

Keywords

Dietary pattern, depressive symptoms, principal component analysis, reduced-rank regression, partial least-squares

INTRODUCTION

Mental health problems are a major public health concern contributing to 14.4% of years lived with disability (YLD) globally in 2017 [383]. Depression is a common mental disorder affecting more than 300 million people of all ages with more women experiencing depression than men [5]. Depression is the third leading contributor to the current disease burden in terms of YLD globally (behind back pain and headache disorders) and Australia, accounting for 564 and 765 YLDs per 100,000 in 2017, respectively [383].

Depression has an increasing impact on economic loss due to both direct (treatment) and indirect (lost days of work and reduced productivity) costs [384] resulting in compromised quality of life and a reduced ability to undertake activities at work, school and/or in the family. In the worst cases, it can lead to suicide or attempted suicide [385].

Various risk factors are attributed to depression such as psychosocial, behavioural, metabolic, genetic and environmental factors. Key risk factors include major life stressors involving interpersonal stress and social rejection [386]. Behavioural risk factors including a less healthy diet [12, 13], smoking, obesity and limited physical activity also play a vital role in predicting the likelihood of depression [7] and, should, therefore, be targeted as part of the preventive measures [14]. Over the past decade, there has been increasing epidemiological evidence on the relationship between dietary patterns and mental health. Adherence to a healthy diet has been demonstrated to be associated with better mental health [43-46]. However, the findings are not consistent which may be due to methodological differences, including the use of various dietary pattern analysis methods [44, 47-49].

Limited studies have examined the association between dietary patterns and the risk of depression in Australian adults. [50, 51]. The majority of the current studies have focussed on a specific subset of the population, such as middle-aged women [50], adolescents [52] or the elderly population [53] but, dietary patterns are likely to vary according to gender, socioeconomic status, ethnic group and culture [42]. Some studies have focused on specific foods such as fruit and vegetables [54-56]. Furthermore, studies have used different approaches to the analysis of dietary data.

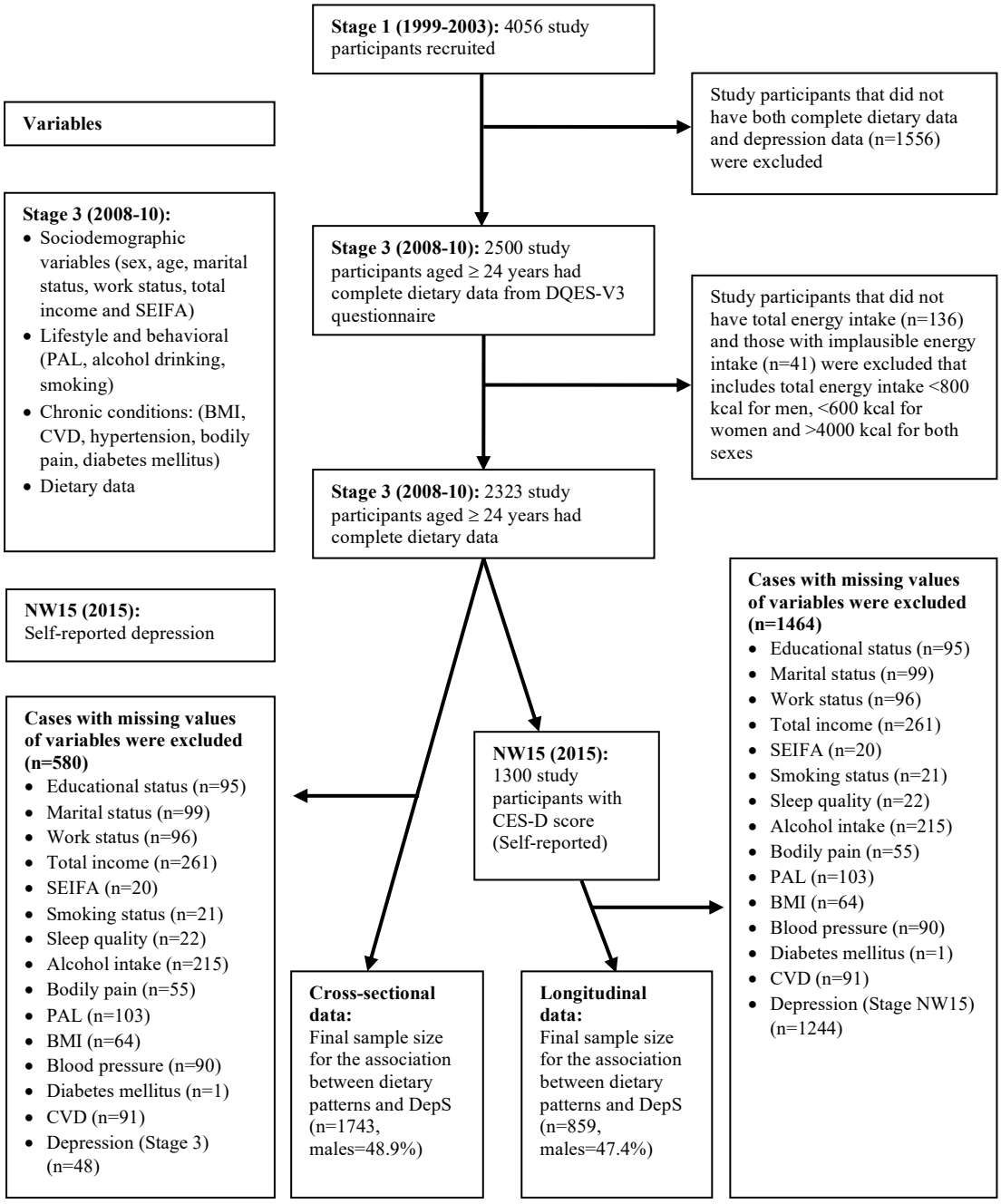
A priori (dietary quality indexes) and a posteriori (factor analysis or principal component analysis (PCA)) approaches are commonly used in dietary pattern analysis. Hybrid approaches, such as reduced-rank-regression (RRR) and reduced-rank-regression (PLS), are also widely used. RRR and PLS combine both a priori and a posteriori analysis approach [42, 58, 59]. Although previous studies have used PCA, RRR and PLS in identifying dietary patterns associated with cardiovascular disease (CVD) [60], type 2 diabetes [58] and musculoskeletal health [59], to our knowledge, the association of dietary patterns with depressive symptoms (DepS) derived by these three methods has not been comprehensively examined. Therefore, we aimed to use the three dietary pattern analysis methods to identify dietary patterns associated with DepS using data from the North West Adelaide Health Study (NWAHS).

METHODS

4.3.1 STUDY DESIGN AND POPULATION

The NWAHS is a longitudinal cohort study which recruited participants from the northern and western suburbs of Adelaide, South Australia. The region represents about one-third of the South Australian population and half of the metropolitan area of the capital city, Adelaide. The primary purpose of this population-based cohort study was to establish valid and reliable data on chronic diseases and their risk factors in South

Australia incorporating public health, clinical, social and biochemical parameters [375]. Three clinic-based stages of data collection have been conducted: 1999–2003, 2004–2006, and 2008–2010. Data were collected using a self-completed questionnaire, computer-assisted telephone interview (CATI) and clinical assessments. A self-complete survey (postal or online) was conducted in 2015 (NW15).



BMI - Body mass index; *CES-D* - Centre for Epidemiological Studies-Depression; CVD – Cardiovascular disease; *DepS*: depressive symptoms; *DQES-V3* – Dietary questionnaire for epidemiological studies version 3; *PAL* - Physical activity level; *SEIFA* - Socio-Economic Indexes for Areas

Figure 4.1. Sampling description of the study participants with dietary intake and depressive symptoms in the NWAHS

The recruitment details of this cohort are published elsewhere [375]. In brief, the study participants were adults aged 18 years and above when first recruited in Stage 1 from households with a landline which was randomly selected from the Electronic White pages. At the initial stage (Stage 1), 4056 males and females participated. Dietary data were collected as part of Stage 3 (2008-2010, n = 2323) and CES-D was included in Stage 3 and NW15 (2015, n = 1300). In total, 1743 participants were included in the cross-sectional study, and there were 859 participants included in the analysis of the longitudinal association between diet and DepS (*Figure 4.1*).

4.3.2 DIETARY ASSESSMENT AND FOOD GROUPS

Dietary intake was assessed using a validated dietary questionnaire for epidemiological studies (DQES-V3) which is an amendment of the food frequency questionnaire (FFQ) developed by Cancer Council Victoria. The questionnaire was self-completed and designed to assess intake over the previous 12 months. The completed forms were sent to Cancer Council Victoria for analysis of total daily intakes of food items and nutrients using the Australian NUTTAB95 (Australian Government Publishing Service, Canberra) food composition database [377]. Food items were categorized into thirty-nine food groups (Supplementary Table 4.1). The number of food items consumed per day in grams was calculated for each study participant.

4.3.3 ASSESSMENT OF OTHER COVARIATES

Sociodemographic characteristics such as educational status, marital status, work status, annual household income were collected at Stage 3. The socio-economic indexes for areas (SEIFA), an index developed by the Australian Bureau of Statistics (ABS) which ranks areas in Australia according to relative socio-economic advantage and disadvantage based on census collection districts was calculated [387]. The index used in this study is the Index of Relative Social Disadvantage (IRSD). The index values were

determined and then divided into quintiles, with the lowest representing greatest disadvantage. Annual household income was categorised as follows: up to $20,000, $20,001–$40,000, $40,001–$60,000, $60,001-$80,000 and more than $80,000. Marital status was categorized into married or living together with a partner (in a union), separated/divorced, widowed and never married. Alcohol intake was assessed using the frequency and number of standard drinks [388]. Smoking status was classified as non-smokers, ex-smokers and current smokers. A wall-mounted stadiometer measured height to the nearest 0.5 centimeters, and weight was measured using calibrated scales to the nearest 0.1 kilograms. BMI was then calculated (weight (kg)/ height (m^2)).We further classified BMI according to the WHO standard as underweight, normal weight, overweight and obese if BMI was <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, >30 kg/m^2 respectively [389]. Identification of participants with diabetes was either by clinician-diagnosed self-report of diabetes and/or laboratory diagnosis using blood samples collected during the clinic visit, with diabetes defined as fasting plasma glucose ≥7.0 mmol/L. Diagnosis of hypertension (high blood pressure) was made taking account of both systolic blood pressure (>140 mmHg) and diastolic blood pressure (>90 mmHg). Data on self-reported doctor-diagnosed CVD (including heart attack, stroke, angina and transient ischaemic attack) was collected.

Assessment of leisure-time PAL was performed using the Active Australia questions [390]. PAL was assessed considering the total amount of time spent walking for exercise and performing moderate and vigorous exercise. It was categorized into three categories; ‘No activity’, ‘Activity but not sufficient’ and ‘Sufficient activity’, with sufficient activity defined as at least 150 minutes of activity in the week with the time spent undertaking vigorous activity doubled to account for its higher intensity. Sleep quality was assessed by a self-reported questionnaire and categorized as ‘Very good’, ‘Fairly good’, ‘Fairly bad’ and ‘Very bad’. Participants were asked to indicate the

severity of any bodily pain using the relevant question from the Short Form (SF) 36 questionnaire [391]. This question asks how much bodily pain participants have had during the 4 weeks prior to interview. Responses are scored and these scores range from 0-100. A dichotomous variable was then created using the median value (74) as the cut-off score.

4.3.4 RESPONSE VARIABLES FOR RRR AND PLS ANALYSES

According to previously published literature, we chose the dietary intake of four nutrients; EPA and DHA (mg/d), folate (mg/d), Mg (mg/d) and Zn (mg/d) density from the FFQ as these nutrients have been shown to be strongly linked with DepS [20, 21, 23, 25, 36-40, 392]. The densities were calculated, dividing the nutrient intake in milligrams by total energy consumption multiplied by one hundred, which provides the density of a particular nutrient relative to energy consumption.

4.3.5 ASSESSMENT OF DEPS

The CES-D is a self-report scale designed to measure DepS in the general population [133] and has been validated against other scales [133]. The questionnaire addresses six symptoms of depression experienced during the preceding week, namely depressed mood, guilt or worthlessness, helplessness or hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Participants were asked to score the frequency of occurrence of specific symptoms during the previous week on a four-point scale (0, ‘rarely or none of the time’; 1, ‘some or little of the time’; 2, ‘occasionally or moderate amount of the time’; and 3, ‘most or all of the time). These were summed to yield a total score between 0 and 60. Participants with a CES-D score ≥16 were considered to have DepS [133].

4.3.6 DIETARY PATTERNS ANALYSIS

Factor scores and dietary patterns were calculated and constructed among 2323 study participants after excluding 136 participants who had missing data on energy intake and 41 cases with implausible energy intake. Total energy intake lower than 800 Kcal for men, 600 Kcal for female and higher than 4000 Kcal for both sexes were considered as implausible values for energy intake. Data reduction techniques using PCA, RRR and PLS were used to identify dietary patterns out of 39 food groups. We grouped food items based on their nutrient profile and taxonomy. The food groups used in the analysis are shown in Table 4.1. Thirty-nine dietary patterns were constructed using PCA. However, we retained only two factors, determined by the scree plot, an eigenvalue (>1) and interpretability. Varimax rotation was applied to attain optimal structure and increase the interpretability of factors. Factor scores for each of the participants and the retained factors were calculated as the sum of the products of factor loading coefficients, which was standardized by the daily intake of each food item. Quartiles were constructed for each of the dietary patterns based on the factor scores. Sample adequacy was checked using the Kaiser–Mayer–Olkin (KMO) test.

Table 4.1 Food groups used in the dietary analysis according to their nutritional composition and taxonomy.

No.	Food group	Foods items
1	Beer	Heavy beer, light beer, regular beer
2	Cabbages	Brussels, sprout, cauliflower, broccoli, coleslaw
3	Citrus fruit	oranges
4	Coffee	Coffee
5	Eggs	Eggs
6	Fish	Steamed fish, tinned fish
7	Flavoured milk	Flavoured milk
8	Fruity vegetables	Avocado, fresh tomatoes, tomato products, cucumber, green beans, zucchini, squash, mushrooms, pumpkin, cantaloupe, capsicum, eggplant
9	High-fat dairy	Full cream milk
10	High fibre bread	High fibre white bread, wholemeal bread, multi-grain bread, rye bread, soy and linseed bread
11	High-fibre cereals	Bran, sultana bran, other high fibre cereal
12	Jam and vegemite	Jam, vegemite
13	Juice	Orange juice, other fruit juice
14	Leafy vegetables	Iceberg lettuce, other lettuce, Asian greens, other cooked leafy vegetables
15	Legumes	Baked beans, dried beans, dried peas, chick dried beans, dried peas, chickpeas
16	Medium fat dairy	Reduced-fat milk, soymilk, skim milk, other milk, yoghurt, ricotta, cottage all other cheeses, cream, sour cream
17	Nuts	Other nuts
18	Other cereals	Sanitarium Weet-bix™, other weet-bix, regular cornflakes, commercial/homemade muesli (toasted or non-toasted), Just right®, sweet corn, other breakfast cereal
19	Other fruits	Tinned fruit salad, tinned peaches, apples, bananas, pineapple, strawberries, apricots, pears, peaches or nectarines, mango or pawpaw, berries, cherries, dried or tinned apricots, figs, grapes, other dried fruit plums, watermelon
20	Pasta and rice	Rice pasta, noodles, rice bubbles
21	Peanut butter	Peanuts, peanut butter
22	Potato with fat	Potato fat
23	Potato without fat	Potato no fat
24	Poultry	Chicken
25	Processed meat	Bacon, sausages, processed meat
26	Red meat	Beef or veal, pork lamb
27	Root vegetables	Beetroot, carrots
28	Saturated spread	Other margarine butter
29	Snacks	Cakes or sweet, pastries, chocolate, sweet biscuits, corn chips etc, ice cream, crackers not wholemeal, wholemeal crackers, other confectionery
30	Soft drinks	Soft drink, spirits premix, sports plus, diet soft drink
31	Spirits	Spirits
32	Stalk vegetables	Celery, onion or leeks, garlic, asparagus
33	Sugar	Sugar
34	Take away foods	Pizza, fried fish, pastries with cheese, pastries with meat
35	Tea and water	Tea, water, herbal tea
36	Tomato sauce	Tomato sauce or ketchup, canned tomatoes
37	Unsaturated spread	Olive margarine, margarine on vegetables, mayonnaise, miracles spread, canola margarine, cholesterol-lowering margarine, nut telex, poly margarine, soy margarine
38	White bread	White bread
39	Wine	White wine, red wine

The PROC PLS statement in SAS (SAS Institute Inc., Cary, NC, USA) was used to conduct both RRR and PLS analysis, defining 'METHOD=PLS' or 'METHOD=RRR' The details of this method are described by Hoffman *et al*. [58]. In this study, we used a dietary data file containing the 39 food groups coded as fg1-39 and four response variables, and the analysis identified four factors for each method. These four nutrients (response variables) have been consistently associated with DepS in previous studies [20, 21, 23, 25, 36-40, 392].

Quartiles [Q1 (lowest intake), Q2, Q3 and Q4 (highest intake)] of each of the factor scores were constructed. Factor loadings, which represent the standardized correlation between the factors and the food groups, were calculated. The proportion of factor-specific and all factor variances across all three methods that explained the response variables and food groups was also determined. The coefficient of determination (R^2) of a linear regression of the factor scores for dietary patterns derived by PCA against the nutrient densities (responses), was taken as the explained variance of PCA factors by response variables. Correlations (response scores) between the factors of each method and the response variables were computed.

4.3.7 DESCRIPTIVE ANALYSIS AND MODELLING

Descriptive analysis of sociodemographic and lifestyle characteristics and chronic conditions was performed across the factor quartiles. Mean values and standard deviations (continuous and normally distributed variables), medians and interquartile ranges (continuous and non-normally distributed variables) and proportions were calculated (categorical variables). Chi-square, Kruskal–Wallis tests for categorical variables and ANOVA were used to identify significant differences across different levels of dietary pattern scores.

Log-binomial logistic regression was used to assess the association between dietary patterns and DepS. We used a directed acyclic graph (DAG) to identify the covariates (*Supplementary Figure 4.1*). For the dietary patterns, three regression models were developed. The first model was adjusted for age, sex and total energy intake. Model two was additionally adjusted for marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, physical activity and self-reported sleep quality. In addition to the variables in the second model, BMI, bodily pain, hypertension, T2DM and CVD were adjusted for in the third model. We further assessed

the association between dietary patterns and incident cases (new cases between Stage 3 and NW15) of DepS using all the three models. The trend of associations was assessed using quartiles of dietary patterns as a continuous parameter. RRR and PLS analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All other analyses were conducted using STATA/SE version 15.1 (Stata, StataCorp LP, College Station, TX, USA).

4.3.8 SENSITIVITY AND SUBGROUP ANALYSES

Missing data were identified across all covariates. We conducted two sensitivity analyses: 1) by including antidepressant medication use as a covariate; 2) by performing multiple imputations on the covariates with missing values using the chained equation method [393]. Using the final models, subgroup analyses, using Poisson regression were performed to assess the association of dietary patterns with DepS in various subgroups of the study participants. Dietary patterns can also influence BMI [245, 394-396] through which diet could have an association with DepS. As a result, we did a mediation analysis [397] to investigate the extent of the association between diet and DepS that could be mediated by BMI.

4.3.9 ETHICAL CONSIDERATION

Ethics approval for NWAHS was obtained from the Human Ethics Research Committee, Queen Elizabeth Hospital, South Australia. All participants provided written informed consent.

RESULTS

A total of 2323 (46.6%, males) study participants had data on diet and DepS at Stage 3 of the NWAHS cohort after excluding the participants that did not have total energy intake and implausible energy intake values. However, the total number of study

participants in the multivariable analysis were 1743 (48.9%, males). Therefore, 580 (24.9%) cases had at least one missing value among the other covariates. Variables such as income per year (11.2%) and alcohol risk (9.2%) had the highest proportion of missing values (*Figure 4.1*).

4.3.10 SOCIODEMOGRAPHIC CHARACTERISTICS

The characteristics of the participants across the quartiles of the two dietary patterns derived from PCA are illustrated in Table 4.2. The mean age of the participants in Stage 3 was 57.5 (SD 14.1). More than two-thirds of the participants (1518, 68.3%) were married or living with a partner. Fourteen percent of participants were smokers at the time of data collection, whereas 39.8% of the participants were ex-smokers (Table 4.2).

The overall prevalence of DepS was 16.9% (14.2% in men and 20.8% in women). More than half (53.5%, n = 933) of the study participants were non-drinkers. More than two-third of the participants (74.6%, n = 1300) were overweight and obese. The prevalence of hypertension, T2DM and CVD was 26.9% (n = 469), 10% (n = 175), and 8.8% (n = 153) respectively (Table 4.2).

There were significant differences in the distribution of the covariates across quartiles of the ‘prudent’ and ‘western’ pattern by age, sex, educational status, marital status, work status, smoking status, alcohol intake risk and PAL (Table 4.2).

Table 4.2 Characteristics of study participants across quartiles of dietary patterns in Australian adults, South Australia (*n*=2323) (Frequency or numbers and percentages; mean values and standard deviations)

(table continues)

		Prudent pattern					Western pattern				
	Overall (*n* 2323)	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]
Age (years), mean (SD)	57.5 (±14.1)	56.1 (±15.1)	57.1 (±14.3)	57.4 (±13.9)	59.3 (±12.7)	**0.001**	59.3 (±13.7)	57.5 (±14.4)	58.2 (±13.9)	54.9 (±13.9)	**<0.001**
Sex (n, %)											
Male	1,083 (46.6)	346 (59.6)	265 (45.6)	238 (41.0)	234 (40.3)	**<0.001**	164 (28.2)	204 (35.1)	307 (52.8)	408 (70.3)	**<0.001**
Female	1,240 (53.4)	235 (40.4)	316 (54.4)	343 (59.0)	346 (59.7)		417 (71.8)	377 (64.9)	274 (47.2)	172 (29.7)	
Educational status (n, %)											
Did not complete school/ high school level	1,154 (49.7)	325 (55.9)	286 (49.2)	281 (48.4)	262 (45.2)	**<0.001**	296 (50.9)	272 (46.8)	291 (50.1)	295 (50.9)	**0.008**
Trade/ certificate/ diploma	698 (30.0)	184 (31.7)	170 (29.3)	175 (30.1)	169 (29.1)		155 (26.7)	169 (29.1)	172 (29.6)	202 (34.8)	
Degree or higher	376 (16.2)	45 (7.7)	104 (17.9)	97 (16.7)	130 (22.4)		107 (18.4)	105 (18.1)	95 (16.4)	69 (11.9)	
Missing	95 (4.1)	27 (4.6)	21 (3.6)	28 (4.8)	19 (3.3)		23 (4.0)	35 (6.0)	23 (4.0)	14 (2.4)	
Marital status (n, %)											
Married or living with partner	1,518 (65.3)	326 (56.1)	398 (68.5)	401 (69.0)	393 (67.8)	**<0.001**	338 (58.2)	366 (63.0)	416 (71.6)	398 (68.6)	**<0.001**
Separated/divorced	310 (13.3)	100 (17.2)	80 (13.8)	53 (9.1)	77 (13.3)		111 (19.1)	63 (10.8)	62 (10.7)	74 (12.8)	
Widowed	213 (9.2)	59 (10.2)	43 (7.4)	53 (9.1)	58 (10.0)		70 (12.0)	61 (10.5)	50 (8.6)	32 (5.5)	
Never married	183 (7.9)	66 (11.4)	38 (6.5)	46 (7.9)	33 (5.7)		38 (6.5)	56 (9.6)	29 (5.0)	60 (10.3)	
Missing	99 (4.3)	30 (5.2)	22 (3.8)	28 (4.8)	19 (3.3)		24 (4.1)	35 (6.0)	24 (4.1)	16 (2.8)	
Work status (n, %)											
Employed	1,224 (52.7)	312 (53.7)	324 (55.8)	306 (52.7)	282 (48.6)	**0.011**	284 (48.9)	299 (51.5)	304 (52.3)	337 (58.1)	**0.072**
Unemployed	32 (1.4)	13 (2.2)	2 (0.3)	10 (1.7)	7 (1.2)		12 (2.1)	8 (1.4)	4 (0.7)	8 (1.4)	
Retired	766 (33.0)	175 (30.1)	183 (31.5)	181 (31.2)	227 (39.1)		209 (36.0)	194 (33.4)	199 (34.3)	164 (28.3)	
Other	205 (8.8)	53 (9.1)	51 (8.8)	56 (9.6)	45 (7.8)		53 (9.1)	45 (7.7)	50 (8.6)	57 (9.8)	
Missing	96 (4.1)	28 (4.8)	21 (3.6)	28 (4.8)	19 (3.3)		23 (4.0)	35 (6.0)	24 (4.1)	14 (2.4)	
Income per year (n, %)											
Up to $20,000	315 (13.6)	98 (16.9)	53 (9.1)	75 (12.9)	89 (15.3)	**0.043**	95 (16.4)	79 (13.6)	73 (12.6)	68 (11.7)	**0.007**
$20,001-$40,000	536 (23.1)	140 (24.1)	138 (23.8)	131 (22.5)	127 (21.9)		131 (22.5)	145 (25.0)	124 (21.3)	136 (23.4)	
$40,001-$60,000	351 (15.1)	76 (13.1)	99 (17.0)	84 (14.5)	92 (15.9)		79 (13.6)	67 (11.5)	107 (18.4)	98 (16.9)	
$60,001-$80,000	289 (12.4)	68 (11.7)	79 (13.6)	73 (12.6)	69 (11.9)		54 (9.3)	71 (12.2)	72 (12.4)	92 (15.9)	
More than $80,000	571 (24.6)	129 (22.2)	148 (25.5)	149 (25.6)	145 (25.0)		147 (25.3)	141 (24.3)	144 (24.8)	139 (24.0)	
Missing	261 (11.2)	70 (12.0)	64 (11.0)	69 (11.9)	58 (10.0)		75 (12.9)	78 (13.4)	61 (10.5)	47 (8.1)	

Table 4.2 *(table continued)*
Characteristics of study participants across quartiles of dietary patterns in Australian adults, South Australia (*n*=2323) (Frequency or numbers and percentages; mean values and standard deviations)

(table continues)

		Prudent pattern					Western pattern				
	Overall (*n* 2323)	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]
SEIFA (n, %)											
Lowest quintile	599 (25.8)	171 (29.4)	153 (26.3)	150 (25.8)	125 (21.6)	**0.015**	136 (23.4)	149 (25.6)	152 (26.2)	162 (27.9)	0.4
Low quintile	567 (24.4)	159 (27.4)	143 (24.6)	119 (20.5)	146 (25.2)		143 (24.6)	134 (23.1)	141 (24.3)	149 (25.7)	
Middle quintile	498 (21.4)	114 (19.6)	132 (22.7)	126 (21.7)	126 (21.7)		120 (20.7)	134 (23.1)	123 (21.2)	121 (20.9)	
High quintile	495 (21.3)	104 (17.9)	117 (20.1)	136 (23.4)	138 (23.8)		124 (21.3)	132 (22.7)	130 (22.4)	109 (18.8)	
Highest quintile	144 (6.2)	27 (4.6)	34 (5.9)	43 (7.4)	40 (6.9)		48 (8.3)	29 (5.0)	32 (5.5)	35 (6.0)	
Missing	20 (0.9)	6 (1.0)	2 (0.3)	7 (1.2)	5 (0.9)		10 (1.7)	3 (0.5)	3 (0.5)	4 (0.7)	
Smoking status (n, %)											
Non-smoker	1,063 (45.8)	218 (37.5)	277 (47.7)	283 (48.7)	285 (49.1)	**<0.001**	282 (48.5)	289 (49.7)	268 (46.1)	224 (38.6)	**<0.001**
Ex-smoker	916 (39.4)	230 (39.6)	227 (39.1)	220 (37.9)	239 (41.2)		235 (40.4)	219 (37.7)	236 (40.6)	226 (39.0)	
Current smoker	323 (13.9)	127 (21.)	73 (12.6)	69 (11.9)	54 (9.3)		54 (9.3)	71 (12.2)	74 (12.7)	124 (21.4)	
Missing	21 (0.9)	6 (1.0%)	4 (0.7)	9 (1.5)	2 (0.3)		10 (1.7)	2 (0.3)	3 (0.5)	6 (1.0)	
Sleep quality (n, %)											
Very good	419 (18.0)	98 (16.9)	105 (18.1)	101 (17.4)	115 (19.8)	0.75	118 (20.3)	106 (18.2)	101 (17.4)	94 (16.2)	0.35
Fairly good	1,356 (58.4)	342 (58.9)	345 (59.4)	333 (57.3)	336 (57.9)		338 (58.2)	345 (59.4)	338 (58.2)	335 (57.8)	
Fairly bad	450 (19.4)	113 (19.4)	108 (18.6)	124 (21.3)	105 (18.1)		97 (16.7)	106 (18.2)	118 (20.)	129 (22.2)	
Very bad	76 (3.3)	23 (4.0)	19 (3.3)	14 (2.4)	20 (3.4)		20 (3.4)	18 (3.1)	23 (4.0)	15 (2.6)	
Missing	22 (0.9)	5 (0.9)	4 (0.7)	9 (1.5)	4 (0.7)		8 (1.4)	6 (1.0)	1 (0.2)	7 (1.2)	
Alcohol risk (n, %)											
Non-drinkers, no risk	1,152 (49.6)	318 (54.7)	283 (48.7)	264 (45.4)	287 (49.5)	**<0.001**	251 (43.2)	254 (43.7)	307 (52.8)	340 (58.6)	**<0.001**
Low risk	850 (36.6)	171 (29.4)	207 (35.6)	237 (40.8)	235 (40.5)		232 (39.9)	266 (45.8)	206 (35.5)	146 (25.2)	
Intermediate to very high risk	106 (4.6)	40 (6.9)	30 (5.2)	21 (3.6)	15 (2.6)		25 (4.3)	12 (2.1)	25 (4.3)	44 (7.6)	
Missing	215 (9.3)	52 (9.0)	61 (10.5)	59 (10.2)	43 (7.4)		73 (12.6)	49 (8.4)	43 (7.4)	50 (8.6)	
PAL (n, %)											
No activity	425 (18.3)	135 (23.2)	132 (22.7)	83 (14.3)	75 (12.9)	**<0.001**	89 (15.3)	99 (17.)	111 (19.1)	126 (21.7)	**0.025**
Activity but not sufficient	958 (41.2)	264 (45.4)	222 (38.2)	245 (42.2)	227 (39.1)		228 (39.2)	238 (41.0)	255 (43.9)	237 (40.9)	
Sufficient activity	837 (36.0)	153 (26.3)	205 (35.3)	222 (38.2)	257 (44.3)		238 (41.0)	208 (35.8)	190 (32.7)	201 (34.7)	
Missing	103 (4.4)	29 (5.0)	22 (3.8)	31 (5.3)	21 (3.6)		26 (4.)	36 (6.2)	25 (4.)	16 (2.8)	
BMI category (n, %)											
Normal/underweight	571 (24.6)	128 (22.0)	146 (25.1)	145 (25.0)	152 (26.2)	0.62	161 (27.7)	151 (26.0)	144 (24.8)	115 (19.8)	**0.001**
Overweight	911 (39.2)	235 (40.4)	234 (40.3)	217 (37.3)	225 (38.8)		237 (40.8)	220 (37.9)	234 (40.3)	220 (37.9)	
Obese	777 (33.4)	203 (34.9)	187 (32.2)	201 (34.6)	186 (32.1)		163 (28.1)	192 (33.0)	190 (32.7)	232 (40.0)	
Missing	64 (2.8)	15 (2.6)	14 (2.4)	18 (3.1)	17 (2.9)		20 (3.)	18 (3.1)	13 (2.2)	13 (2.2)	

Table 4.2 *(table continued)*
Characteristics of study participants across quartiles of dietary patterns in Australian adults, South Australia (*n*=2323) (Frequency or numbers and percentages; mean values and standard deviations)

		Prudent pattern					Western pattern				
	Overall (*n* 2323)	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]	Q1 (*n* 581)	Q2 (*n* 581)	Q3 (*n* 581)	Q4 (*n* 580)	P-value[a]
Bodily Pain (n, %)											
No	1,114 (48.0)	296 (50.9)	275 (47.3)	263 (45.3)	280 (48.3)	0.27	264 (45.4)	275 (47.3)	280 (48.2)	295 (50.9)	0.32
Yes	1,209 (52.0)	285 (49.1)	306 (52.7)	318 (54.)	300 (51.7)		317 (54.)	306 (52.7)	301 (51.8)	285 (49.1)	
Blood Pressure (n, %)											
Hypertension	609 (26.2)	161 (27.)	147 (25.3)	161 (27.7)	140 (24.1)	0.4	144 (24.8)	139 (23.9)	161 (27.7)	165 (28.4)	0.27
No Hypertension	1,624 (69.9)	399 (68.7)	415 (71.4)	395 (68.0)	415 (71.6)		411 (70.7)	418 (71.9)	398 (68.5)	397 (68.4)	
Missing	90 (3.9)	21 (3.6)	19 (3.3)	25 (4.3)	25 (4.3)		26 (4.5)	24 (4.1)	22 (3.8)	18 (3.1)	
Diabetes (n, %)											
No diabetes	2,076 (89.4)	511 (88.0)	530 (91.2)	527 (90.7)	508 (87.6)	0.11	525 (90.4)	523 (90.0)	518 (89.2)	510 (87.9)	0.5
Diabetes (diagnosed and undiagnosed)	246 (10.6)	69 (11.9)	51 (8.8)	54 (9.)	72 (12.4)		55 (9.5)	58 (10.0)	63 (10.8)	70 (12.1)	
Missing	1 (0.0)	1 (0.)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.)	0 (0.0)	0 (0.0)	0 (0.0)	
CVD (n, %)											
No CVD	2,026 (87.2)	497 (85.5)	510 (87.8)	505 (86.9)	514 (88.6)	0.68	500 (86.1)	508 (87.4)	502 (86.4)	516 (89.0)	0.26
CVD	206 (8.9)	58 (10.0)	52 (9.0)	48 (8.3)	48 (8.3)		58 (10.0)	40 (6.9)	57 (9.8)	51 (8.8)	
Missing	91 (3.9)	26 (4.5)	19 (3.3)	28 (4.8)	18 (3.1)		23 (4.0)	33 (5.7)	22 (3.8)	13 (2.2)	
Energy (kcal/day)	2042.87 (±579.90)	1754.91 (±537.33)	1914.86 (±488.36)	2102.94 (±522.09)	2399.40 (±562.86)	<0.001	1565.94 (±418.60)	1858.94 (±391.92)	2149.11 (±427.04)	2598.46 (±503.79)	<0.001
Depression (stage 3)											
No DepS	1,872 (80.6)	444 (76.4)	482 (83.0)	463 (79.7)	483 (83.3)	0.005	483 (83.1)	479 (82.4)	467 (80.4)	443 (76.4)	0.006
DepS	403 (17.3)	127 (21.9)	88 (15.1)	102 (17.6)	86 (14.8)		86 (14.8)	89 (15.3)	101 (17.4)	127 (21.9)	
Missing	48 (2.1)	10 (1.7)	11 (1.9)	16 (2.)	11 (1.9)		12 (2.1)	13 (2.2)	13 (2.2)	10 (1.7)	

P value < 0.05 are highlighted in bold.
Data from stage 3 are used.
Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures.
BMI - body mass index; SEIFA - Socio-Economic Indexes for Areas; PAL - physical activity level; CVD - cardiovascular disease.
[a] P value was from Chi-square for categorical variables and unadjusted ANOVA for a continuous variable
Depression was assessed by CES-D questionnaire: participants scoring ≥ 16 were classified as at risk of depression

4.3.11 DIETARY PATTERNS

We identified dietary patterns using three types of analysis (PCA = 2; RRR = 4 and PLS = 4 patterns). Among all the three analyses, there were two common patterns. The first pattern was termed a 'prudent' (or healthy) pattern and was characterized by high intake of fruit, vegetables, sugar, milk products containing medium fat, nut-based milk products, tea and water, nuts, fish, legumes, citrus fruit, tomato sauce, potato without fat and high-fibre bread. The second pattern, termed a 'western' (or unhealthy) pattern, was characterized by higher levels of sugary drinks, processed meat, take away foods, snacks, jam and Vegemite (a brewers' yeast extract commonly used as a spread in Australia), red meat, juice, beer, potato with fat, white bread, poultry, tomato sauces, peanut butter, high- fat dairy products and eggs (*Figure 4.2*).

We identified two more patterns from RRR and PLS. The first one was a diet typically consumed by the Australian population, i.e., high intake of red meat, jam and vegemite, unsaturated spreads, bread, vegetables, tomato sauces, fruits, juice, fish, processed meat and beer. We named this pattern as 'typical Australian'. The second pattern ('modern' pattern) was a diet typically rich in fish, coffee, fruits and vegetables, tea and water, take away foods, snacks and eggs (*Figure 4.2*). Intake of foods and nutrients across quartiles of dietary patterns are shown in Supplementary Table 4.1, 4.2 and 4.3.

Food groups	Principal component analysis		Reduced-rank regression				Partial least-square			
	Prudent	Western	Prudent	Western	Modern	Typical Australian	Prudent	Western	Modern	Typical Australian
Fruity vegetables	0.76	0.02	0.12	0.14	0.13	0.12	0.29	-0.29	0.20	0.20
Leafy vegetables	0.61	-0.06	0.12	0.08	0.15	0.09	0.22	-0.29	0.16	0.07
Stalk vegetables	0.61	-0.12	0.15	0.06	0.10	0.04	0.20	-0.29	0.14	0.12
Other fruits	0.57	0.06	0.02	-0.01	0.22	0.04	0.28	-0.16	0.20	-0.02
Root vegetables	0.57	0.08	0.04	0.21	0.01	0.16	0.25	-0.14	0.17	0.35
Cabbages	0.54	0.03	0.09	0.21	0.01	0.09	0.20	-0.18	0.12	0.31
Sugar	0.47	0.61	-0.17	-0.07	0.07	-0.06	0.22	0.07	0.31	0.12
Tea and water	0.43	0.40	0.00	0.17	0.14	-0.02	0.21	-0.07	0.14	0.13
Nuts	0.36	-0.11	0.08	0.12	0.02	-0.14	0.13	-0.16	0.01	0.05
Fish	0.34	-0.02	0.71	-0.29	0.28	0.10	-0.12	-0.45	0.26	-0.27
Medium fat dairy	0.33	-0.02	0.05	0.21	0.08	0.01	0.18	-0.13	-0.01	0.14
Legumes	0.32	-0.05	0.03	0.02	0.13	-0.02	0.15	-0.14	0.08	-0.09
High fibre bread	0.31	0.11	-0.08	0.03	0.14	0.25	0.24	-0.02	0.19	0.06
Tomato sauce	0.31	0.22	0.03	0.03	0.04	0.14	0.09	-0.11	0.17	0.06
Potato without fat	0.31	0.09	-0.03	0.17	-0.07	0.12	0.15	-0.01	0.10	0.34
Citrus fruit	0.29	-0.04	0.02	0.02	0.12	0.04	0.16	-0.09	0.09	-0.02
Other cereal	0.20	0.16	0.02	0.16	-0.24	0.02	0.02	0.02	0.06	0.28
Jam and vegemite	0.19	0.37	-0.14	0.09	0.11	0.75	0.17	0.10	0.34	0.15
Juice	0.15	0.30	-0.03	-0.08	0.02	0.11	0.03	0.03	0.20	0.02
Eggs	0.14	0.14	0.11	-0.15	0.04	0.03	-0.03	-0.10	0.16	-0.10
Pasta and rice	0.13	0.11	0.01	-0.10	-0.10	-0.12	-0.05	-0.05	0.06	-0.01
Poultry	0.12	0.17	0.20	0.02	-0.22	0.01	-0.22	-0.18	0.07	0.19
Peanut butter	0.12	0.19	-0.06	0.05	-0.03	0.07	0.05	0.03	0.09	0.11
High fibre cereal	0.09	-0.03	0.07	0.12	0.00	-0.02	0.03	-0.08	-0.05	0.06
Red meat	0.06	0.33	0.30	0.17	-0.59	0.16	-0.32	-0.14	0.10	0.43
Snacks	0.05	0.50	-0.19	-0.20	-0.09	-0.06	-0.01	0.20	0.22	0.08
Saturated spread	0.05	0.15	-0.08	-0.07	-0.08	-0.05	0.02	0.07	0.05	0.06
Wine	0.04	-0.07	0.10	0.05	0.00	0.01	-0.04	-0.13	-0.02	0.03
Coffee	0.01	0.19	0.04	0.59	0.28	-0.19	0.16	-0.03	-0.27	0.14
Potato with fat	-0.02	0.24	-0.18	-0.01	-0.01	0.01	0.04	0.15	0.06	0.12
Unsaturated spread	-0.03	0.41	-0.19	-0.09	0.04	0.28	0.07	0.20	0.27	0.06
Processed meat	-0.05	0.53	0.02	-0.04	-0.33	0.10	-0.23	0.06	0.19	0.26
Flavoured milk	-0.06	0.19	-0.02	0.04	-0.11	-0.01	-0.06	0.07	-0.01	0.04
Take away foods	-0.10	0.56	-0.03	-0.22	-0.13	0.06	-0.17	0.13	0.25	0.01
Spirits	-0.13	0.13	-0.04	-0.01	0.02	0.08	-0.05	0.07	0.03	-0.02
Beer	-0.14	0.29	-0.03	-0.07	-0.04	0.08	-0.11	0.07	0.10	0.00
Soft drinks	-0.16	0.41	-0.15	-0.19	-0.09	-0.02	-0.10	0.19	0.09	-0.02
High fat dairy	-0.18	0.22	-0.16	-0.11	0.00	-0.14	-0.04	0.18	-0.01	-0.06
White bread	-0.28	0.39	-0.20	-0.18	-0.11	0.16	-0.12	0.25	0.14	0.02

The colour gradation denotes the strength and direction of the correlation between the food groups and dietary patterns. Deep green colour represents a relatively higher correlation (a higher intake) of the food groups with the corresponding dietary patterns. Deep Red represents relatively a lower correlation (a lower intake) of the food groups with the corresponding patterns. Yellow and orange represent no correlation between the food groups with the corresponding dietary pattern.

Figure 4.2 Factor loadings of food groups in each dietary pattern identified using PCA, RRR and PLS (n = 1743).

Figure 4.3 depicts the correlation between factors and response variables estimated using PCA, PLS and RRR methods. Two additional factors from the PCA are included for comparison. 'Prudent', i.e. Factor 1 of the PCA, was positively correlated with folic acid, Mg and Zn densities. RRR analysis demonstrated a positive correlation between EPA/DHA, Mg and Zn densities in the 'prudent' dietary pattern whereas a 'typical

Australian' pattern was correlated with Mg and Zn densities. There is a significant negative correlation between Zn density and the 'western' pattern depicted in RRR. In contrast, PLS revealed a negative correlation between EPA/DHA, Mg and Zn densities with the 'prudent' pattern. We observed a negative linear relationship between folate and EPA/DHA and no association with other response variables (Supplementary Table 4.3).

4.3.12 CROSS-SECTIONAL ASSOCIATION BETWEEN DIETARY PATTERNS AND DEPS (STAGE 3)

The prevalence of DepS was 22.7%, 13.1%, 16.3% and 15.6% across the quartiles of the 'prudent' dietary pattern and 13.8%, 15.1%, 16.7% and 22.1% across the quartiles of the 'western' dietary pattern using the PCA method. In the multivariable regression analysis, those who had the highest adherence (Q4) to a prudent dietary pattern had a lower risk of DepS [OR_{Q4VsQ1} = 0.44; 95% confidence interval (CI): 0.30, 0.66; p < 0.001] compared to those with lowest adherence (Q1) (model 1). In the same model, an increased odd of DepS [OR_{Q4VsQ1} = 2.71; 95% CI: 1.66,4.42; p<0.001] for the 'western' dietary pattern were observed. In our last model (model 3) which was adjusted for all potential confounders, a significant inverse association was observed between the 'prudent' pattern and DepS, identified by PCA [OR_{Q4VsQ1} = 0.57; 95% CI: 0.35, 0.92; p = 0.021] and RRR [OR_{Q4VsQ1}=0.66; 95% CI: 0.43, 1.00; p = 0.048]. The 'western' pattern, identified by PCA [OR_{Q4VsQ1} = 2.04; 95% CI: 1.12, 3.68, p = 0.017] and PLS [OR_{Q4VsQ1} = 1.62; 95% CI: 1.05, 2.50; p = 0.030] showed a significant positive association with DepS. RRR also demonstrated a positive association but without statistical significance [OR_{Q4VsQ1} = 1.25; 95% CI: 0.82, 1.89, p = 0.293]. A 'typical Australian' pattern identified by RRR was inversely associated with DepS across all quartiles [OR_{Q2VsQ1} = 0.49; 95% CI: 0.32, 0.74; p = 0.001] [OR_{Q3VsQ1} = 0.52; 95% CI: 0.35, 0.79; p = 0.002] [OR_{Q4VsQ1} = 0.60; 95% CI: 0.40, 0.90; p = 0.014]. However, a

'typical Australian' pattern identified by PLS was not significantly associated with DepS [OR_{Q4VsQ1} = 0.90; 95% CI: 0.58, 1.39; p = 0.624]. Likewise, the 'modern' dietary pattern, identified by both RRR [OR_{Q4VsQ1} = 0.76; 95% CI: 0.50, 1.16; p = 0.204] and PLS [OR_{Q4VsQ1} = 0.71; 95% CI: 0.44, 1.16;1 p = 0.173], was not significantly associated with DepS (Table 4.3).

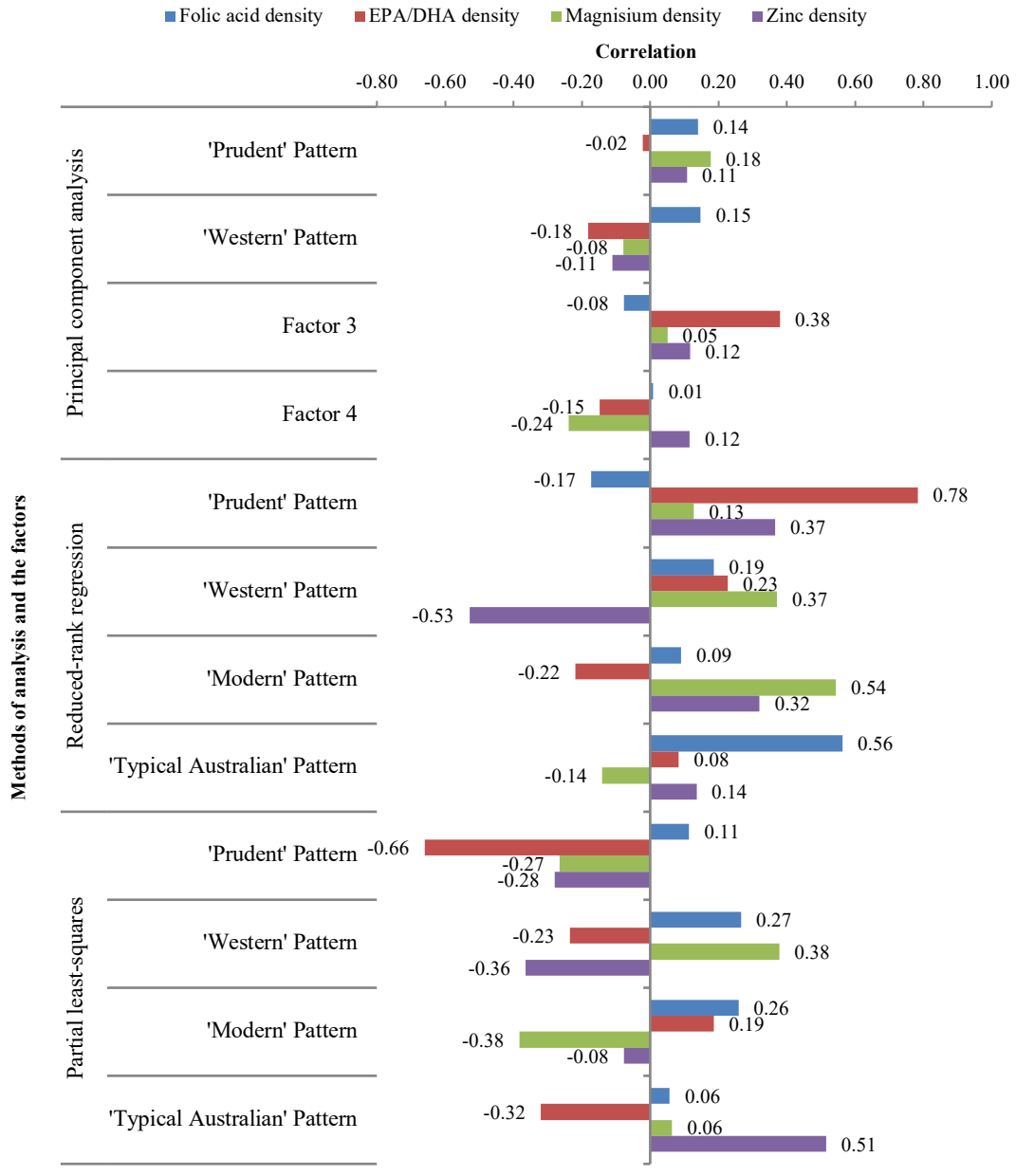


Figure 4.3. Correlation between factors and response variable obtained from principal component analysis, reduced-rank-regression and partial least squares.

Table 4.3 Odds ratio for the association between quartiles of dietary patterns and depressive symptoms among adults aged (≥24 years), South Australia (*n*=1743, Stage 3).

Odds ratio (95% confidence interval)					
	Q1 (reference)	Q2	Q3	Q4	P_{trend}
Principal component analysis					
Prudent dietary pattern					
Model 1	1.00	0.44(0.31-0.64) ***	0.51(0.36-0.74) ***	0.44(0.30-0.66) ***	<0.001
Model 2	1.00	0.49(0.32-0.75) **	0.64(0.41-0.97) *	0.56(0.35-0.90) *	0.052
Model 3	1.00	0.53(0.34-0.81) **	0.68(0.44-1.05)	0.57(0.35-0.92) *	0.060
Western dietary pattern					
Model 1	1.00	1.22(0.82-1.80)	1.63(1.07-2.48) *	2.71(1.66-4.42) ***	<0.001
Model 2	1.00	1.25(0.80-1.94)	1.56(0.97-2.51)	2.20(1.25-3.87) *	0.005
Model 3	1.00	1.23(0.78-1.94)	1.50(0.92-2.44)	2.04(1.13-3.68) *	0.016
Reduced rank regression					
Prudent dietary pattern					
Model 1	1.00	0.61(0.43-0.87) **	0.68(0.48-0.97) *	0.52(0.36-0.74) ***	0.001
Model 2	1.00	0.68(0.46-1.02)	0.91(0.61-1.35)	0.63(0.42-0.95) *	0.093
Model 3	1.00	0.72(0.48-1.09)	0.90(0.60-1.35)	0.66(0.43-1.00) *	0.117
Western dietary pattern					
Model 1	1.00	0.97(0.68-1.38)	0.88(0.61-1.27)	1.02(0.72-1.46)	0.963
Model 2	1.00	1.06(0.70-1.58)	1.15(0.77-1.73)	1.20(0.80-1.80)	0.337
Model 3	1.00	1.10(0.73-1.67)	1.15(0.75-1.75)	1.25(0.82-1.89)	0.288
Modern dietary pattern					
Model 1	1.00	0.77(0.54-1.11)	0.88(0.62-1.26)	0.96(0.67-1.36)	0.992
Model 2	1.00	0.67(0.44-1.00)	0.86(0.58-1.28)	0.79(0.53-1.19)	0.485
Model 3	1.00	0.71(0.47-1.07)	0.91(0.61-1.38)	0.76(0.50-1.16)	0.406
Typical Australian dietary pattern					
Model 1	1.00	0.54(0.38-0.76) **	0.54(0.38-0.76) **	0.68(0.48-0.96) *	0.018
Model 2	1.00	0.51(0.34-0.76) **	0.53(0.35-0.79) **	0.63(0.43-0.93) *	0.019
Model 3	1.00	0.49(0.32-0.74) **	0.52(0.35-0.79) **	0.60(0.40-0.90) *	0.013
Partial least square					
Prudent dietary pattern					
Model 1	1.00	0.91(0.64-1.30)	0.80(0.56-1.15)	0.85(0.59-1.22)	0.281
Model 2	1.00	0.87(0.58-1.30)	0.81(0.54-1.22)	0.82(0.54-1.25)	0.328
Model 3	1.00	0.85(0.56-1.28)	0.75(0.49-1.14)	0.85(0.55-1.30)	0.345
Western dietary pattern					
Model 1	1.00	1.32(0.91-1.94)	1.30(0.88-1.92)	2.31(1.60-3.33) ***	<0.001
Model 2	1.00	1.33(0.87-2.04)	1.17(0.76-1.82)	1.65(1.08-2.52) *	0.043
Model 3	1.00	1.34(0.87-2.07)	1.21(0.77-1.90)	1.62(1.05-2.50) *	0.054
Typical Australian dietary pattern					
Model 1	1.00	0.74(0.52-1.07)	0.94(0.67-1.33)	0.72(0.50-1.05)	0.216
Model 2	1.00	0.85(0.57-1.27)	1.23(0.83-1.83)	0.88(0.58-1.35)	0.986
Model 3	1.00	0.90(0.60-1.37)	1.27(0.84-1.91)	0.90(0.58-1.39)	0.966
Modern dietary pattern					
Model 1	1.00	0.69(0.49-1.00) *	0.65(0.45-0.94) *	0.81(0.54-1.22)	0.222
Model 2	1.00	0.78(0.52-1.18)	0.67(0.44-1.02)	0.77(0.48-1.23)	0.180
Model 3	1.00	0.76(0.50-1.15)	0.69(0.45-1.06)	0.71(0.44-1.16)	0.138

**P <0.05, **P<0.01, ***P <0.001*
Model 1 was adjusted for sex, age and total energy intake
Model 2 was additionally adjusted for marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality
Model 3 was additionally adjusted for BMI, bodily pain, hypertension, diabetes and CVD

4.3.13 LONGITUDINAL ASSOCIATION BETWEEN DIETARY PATTERN (STAGE 3) AND DEPS (STAGE NW15)

The incidence of DepS (the number of new reports of DepS between Stage 3 and NW15) was 19.1%, 12.6%, 8.8% and 9.8% across the quartiles of the 'prudent' dietary pattern and 11.6%, 13.5%, 11.2% and 14.0% across the quartiles of 'western' pattern identified by PCA. After adjusting for all potential confounders, an inverse trend was

found between the 'prudent' pattern and DepS [OR_{Q4VsQ1} = 0.52; 95% CI: 0.25, 1.09; p=0.084] [OR_{Q3VsQ1} = 0.46; 95% CI: 0.24, 0.90; p = 0.023] (model 3). The 'western' dietary pattern derived from PCA [OR_{Q4VsQ1} = 3.47; 95% CI: 1.37, 8.78; p = 0.009] and PLS [OR_{Q4VsQ1} = 2.47; 95% CI: 1.24, 4.91; p = 0.010] was positively associated with incident DepS (Supplementary Table 4.4). Results of the subgroup analyses are presented in *Supplementary Figure 4.2*.

4.3.14 SENSITIVITY AND MEDIATION ANALYSES

Sensitivity analyses by including antidepressant medication use as a covariate did not show any differences in the estimate of the association between dietary patterns and DepS (Supplementary Table 4.5 and Supplementary Table 4.6). Multiple imputation of covariates with missing values also showed minimal differences in the estimates of associations between dietary patterns and DepS in both cross-sectional and longitudinal analyses (Supplementary Table 4.7 and Supplementary Table 4.8). We did not find a significant interaction between dietary patterns and other covariates in predicting DepS. In the mediation analysis, only 4% of the association between western dietary pattern (Q4 vs. Q1) identified by PCA and DepS was through BMI *(Data not shown).*

DISCUSSION

This study provides evidence on the cross-sectional and longitudinal association between dietary patterns and DepS using PCA, RRR and PLS. To the best of our knowledge, this is the first study assessing the association between dietary patterns and DepS using PCA, RRR and PLS methods. Out of four dietary patterns identified by three methods, the 'western' pattern identified by PCA and PLS was associated with higher odds of DepS in both cross-sectional and longitudinal analyses whereas the 'prudent' pattern of PCA and RRR was inversely associated with DepS in the cross-sectional

analysis. A 'typical Australian' pattern from RRR was significantly associated with lower odds of DepS in the cross-sectional analysis.

4.3.15 COMPARISON WITH OTHER STUDIES

It has been claimed that diet and nutrition are key modifiable determinants that have a fundamental preventive role in mental disorders and promoting mental health [13]. Our findings from the PCA and RRR method support this claim and indicate that adherence to healthy diets was associated with a lower incidence of DepS. In addition, findings of this study are generally in line with a recent meta-analysis [46], which found a healthy or 'prudent' dietary pattern was inversely associated with the risk of DepS. Further, there are cohort [53, 55, 202, 398] and cross-sectional studies [52, 54] that have reported a significant inverse association between adherence to a 'prudent' diet pattern and DepS.

When considering direct effect of nutrients on DepS, higher consumption of fruit and vegetables has been found to lead to fewer DepS and better cognitive test scores [202, 247]. As fruit and vegetables are a rich source of folate, deficiency of this nutrient may cause an increase in homocysteine levels which has been associated with DepS [399]. Folate is required for the formation of methionine, in the form of methyl donor S-adenosyl-methionine (SAM), from homocysteine which is involved in the metabolism of neurotransmitters [399]. In the current study, dietary patterns higher in folate-rich foods were beneficial for DepS, as observed in the 'prudent' dietary pattern. Fish consumption, another principal constituent of a 'prudent' dietary pattern, is high in polyunsaturated ω-3 fatty acids (ω-3 PUFA) and can influence physiological pathways associated with DepS. Deficiency of this nutrient can induce modifications in neurotransmitter systems, which may be linked to the aetiology of DepS [262-264]. Moreover, it can reduce oxidative stress which is increased in depressed participants [268, 269]. Our results are in line with a

meta-analysis that revealed an inverse association between fish or ω-3 PUFA intake and risk of DepS [277].

4.3.16 POTENTIAL MECHANISM BETWEEN DIET AND DEPS

One of the potential underlying mechanisms that may mediate the link between diet and DepS is inflammation. Inflammation has been associated with depression [386], and it is possible that the anti-inflammatory properties of certain diets might reduce the level of depression [400, 401]. For example, fruit, vegetables, nuts and fish are characteristics food types for both prudent and anti-inflammatory diets. While BMI may be another possible mediator linking the 'western' dietary pattern and DepS [396], only 4% of the association was mediated by BMI in the current study. This is in contrast to previous evidence, linking a 'western' dietary pattern with higher BMI and obesity [245, 396]. Further comprehensive analysis is required to examine this association.

Some biological mechanisms have been suggested for the association between diet and DepS, including some that are consistent with the preventive role of a Mediterranean-style diet. Diet may affect brain functions that are involved in the aetiology of depression, including synthesis and regulation of neurotransmitters [402], synaptic plasticity, [146, 402, 403] membrane fluidity and neuroinflammation [392, 403]. For example, depression has been associated with low levels of the neurotransmitter 5HT [146, 404]. Dietary sources of tryptophan, the only precursor amino acid that aids the synthesis and production of 5HT [146, 404] contributing to positive mood, include fish, chicken, turkey, legumes, eggs, red meat, whole grains and nuts especially almonds. This is concordant with our findings that consumption of tryptophan-rich diets, such as the 'prudent' and 'typical Australian' dietary patterns, is beneficial for DepS.

4.3.17 THE ASSOCIATION BETWEEN THE WESTERN DIETARY PATTERN AND DEPRESSION

In contrast, there was a significant positive association between the 'western' diet and DepS with both PCA and PLS analysis. This was observed for all three models in PCA and PLS. A positive association was also captured by RRR analysis, but without statistical significance. A similar association has been reported in previous studies [51, 245, 405-407]. A possible mechanism may be the pro-inflammatory properties of this type of diet [386, 392, 400, 401]. In addition, western diets have a higher ratio of polyunsaturated ω-6 fatty acids (ω-6 PUFA) to ω-3 PUFA. ω-6 PUFA is associated with an increase in proinflammatory eicosanoids, a decrease in BDNF and a decrease in membrane fluidity [392]. Contrary to the effect of ω-6 PUFA, DHA, one of the important ω-3 PUFA, is abundant in the brain and decreases proinflammatory cytokines and increases brain-derived neurotrophic factor (BDNF). In addition to DHA, zinc and magnesium also promote the expression of BDNF, which in turn, enhances neuroplasticity [392, 402, 403]. It has been shown that in people with depression, inflammation is increased [403, 408] and BDNF is reduced [403]. Another important ω-3 PUFA, EPA, is present at levels several hundred-fold times lower than DHA but appears to have a more significant influence on final clinical efficacy than DHA [20] as evidenced by randomized controlled trials. EPA may exert its anti-inflammatory effects by reducing the inflammatory cytokines; particularly tumor necrosis factor-alpha (TNF-α), Interleukin 6 (IL-6) and Interleukin 1b (IL-1b) through inhibition of the activity of the nuclear factor kappa-B (NF-kB) pathway [20].

4.3.18 IMPLICATIONS OF THE STUDY

The findings of this study suggest that the promotion of healthy eating, particularly targeted at those with depression, through public health awareness campaigns, may contribute to reducing the current burden of DepS at the population level. In addition, information targeted at general practitioners, on the beneficial properties of healthy diets, for examples prudent or typical Australian diets, will increase awareness of the impact of diet on DepS.

4.3.19 STRENGTHS AND LIMITATION

The strength of our study includes the large sample size and the use of multiple methods to identify the dietary pattern that could be associated with DepS. The limitations of this study should also be considered. First, dietary intake was estimated by an FFQ. Recall bias and potential omission of food groups are significant limitations of the FFQ [230]. However, the FFQ is widely used to measure typical dietary exposures and behaviors in a large cohort-based study and taken as a reasonably reproducible and valid tool to assess the overall dietary consumption using dietary pattern methods [409]. Second, although the nutrients used as response variables have been consistently associated with DepS, they may not be the only nutrients that have high physiological impacts [20, 21, 23, 25, 36-40]. Third, we acknowledge that there is some subjective bias in interpreting the factor analysis, which is a typical limitation of factor analysis [410]. Fourth, although we used a DAG to map the potential confounders minimizing associated bias, confounding cannot be ruled out entirely [411]. Fifth, the main results in this study were presented from cross-sectional analysis which will prohibit claims of causality. Sixth, However, we used a longitudinal analysis, albeit with smaller sample size, as a sensitivity analysis. Sixth, we

acknowledge that we do not have any information on hormonal levels in our cohort, so we could not determine the impact of hormones on dietary patterns.

CONCLUSIONS

In conclusion, a 'prudent' dietary pattern, determined through the PCA approach, characterized by high intake of fruit, vegetables, nuts, fish, medium fat milk products, legumes and high fibre, tended to be inversely associated with depression. Similarly, the 'typical Australian' pattern depicted by RRR was also found to be associated with a significantly lower risk of DepS. However, current evidence on the impact of diet on DepS should be supported using further longitudinal studies with extended follow up, larger sample sizes and repeated measures.

Authors' contribution

All the authors conceived the study. PRS contributed to drafting the paper and interpretation of data. YAM analyzed data, reviewed and commented on all drafts. AP and TKG reviewed, gave their expert opinion and commented on all drafts and have given approval of the final version for publication.

Conflict of interest

The authors declared that there are no conflicts of interest.

Acknowledgments

The authors wish to acknowledge the contribution of North West Adelaide Health Study (NWAHS) participants as well as all the members of the study team for giving their substantial time and efforts. PRS was supported by ASI International scholarship provided by the University of Adelaide. Parts of the NWAHS project has been previously funded by the University of Adelaide, the South Australian Department of Health and

Wellbeing and the Premier's Science and Research fund (SA Government), for which authors are grateful.

SUPPLEMENTARY MATERIALS FOR CHAPTER 4

Supplementary Table 4.1 Food and nutrient intake across quartiles of dietary patterns derived by principal component analysis method

(table continues)

		Prudent					Western				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435		436	436	436	435	
Food groups (g/d)											
High fat dairy	90.7 (172.3)	151.3 (212.2)	80.7 (152.7)	68.0 (153.3)	62.6 (148.3)	<0.001	43.1 (108.5)	68.2 (139.7)	101.8 (177.3)	149.7 (223.4)	<0.001
Medium fat dairy	244.2 (221.3)	131.5 (162.1)	240.4 (209.2)	284.5 (231.6)	320.6 (229.0)	<0.001	251.2 (207.9)	248.1 (215.8)	247.1 (217.3)	230.4 (243.1)	0.51
Soft drinks	231.7 (341.1)	331.2 (449.8)	231.6 (315.9)	188.6 (258.3)	175.2 (286.8)	<0.001	115.0 (167.2)	166.7 (190.9)	208.0 (227.9)	437.5 (537.9)	<0.001
Processed meat	26.2 (21.8)	27.2 (24.1)	25.6 (19.9)	27.8 (21.2)	24.2 (21.6)	0.067	12.0 (11.1)	21.0 (15.0)	30.4 (19.2)	41.4 (26.6)	<0.001
High fibre cereal	1.9 (6.7)	1.1 (5.4)	2.0 (6.4)	1.7 (6.0)	2.6 (8.6)	0.010	2.2 (7.1)	1.4 (5.5)	2.2 (7.4)	1.7 (6.7)	0.16
Take away foods	37.8 (33.4)	42.4 (36.1)	37.1 (36.1)	37.9 (29.3)	33.7 (31.3)	0.002	19.5 (14.5)	28.0 (17.0)	38.3 (23.0)	65.3 (47.5)	<0.001
Citrus fruit	17.8 (25.7)	8.6 (12.6)	14.5 (22.3)	18.3 (23.5)	29.7 (34.7)	<0.001	19.3 (27.8)	16.8 (22.6)	17.5 (25.2)	17.4 (27.0)	0.50
Fruity vegetables	116.4 (70.8)	54.8 (30.1)	91.7 (40.7)	129.1 (47.1)	190.1 (72.8)	<0.001	115.3 (71.2)	115.4 (69.4)	114.7 (64.5)	120.2 (77.6)	0.63
Other fruits	205.3 (153.1)	109.5 (72.7)	167.0 (94.2)	220.8 (125.2)	324.0 (197.9)	<0.001	193.2 (122.1)	196.5 (131.5)	209.8 (150.9)	221.5 (196.2)	0.024
Root vegetables	14.5 (12.6)	6.5 (6.2)	10.8 (7.8)	16.1 (11.3)	24.7 (15.0)	<0.001	13.0 (11.4)	13.9 (11.1)	15.4 (13.4)	15.9 (14.2)	0.002
Leafy vegetables	27.6 (26.5)	10.6 (9.3)	20.7 (16.0)	29.5 (20.3)	49.8 (35.0)	<0.001	31.0 (29.9)	27.6 (25.6)	26.5 (24.3)	25.5 (25.6)	0.013
High fibre bread	51.2 (43.7)	34.4 (41.2)	46.8 (40.2)	54.2 (40.1)	69.5 (45.8)	<0.001	41.1 (32.0)	51.2 (40.8)	56.6 (43.4)	56.0 (54.1)	<0.001
Cabbages	32.2 (28.3)	14.6 (12.9)	25.1 (19.5)	35.9 (24.9)	53.1 (35.0)	<0.001	33.2 (30.2)	30.5 (26.7)	31.1 (24.7)	33.9 (31.1)	0.24
Legumes	36.1 (56.1)	18.8 (30.6)	25.3 (34.4)	36.2 (48.6)	64.3 (83.1)	<0.001	45.0 (69.8)	30.5 (44.0)	36.2 (56.3)	32.8 (49.8)	<0.001
Nutrients											
Protein (g/d)	95.1 (28.1)	79.5 (25.4)	89.3 (24.4)	99.8 (22.1)	111.7 (29.3)	<0.001	75.7 (21.7)	88.1 (19.4)	99.8 (21.6)	116.7 (30.5)	<0.001
Calcium (mg/d)	869 (327)	700 (295)	816 (287)	908 (310)	1051 (311)	<0.001	729 (294)	808 (289)	910 (292)	1027 (351)	<0.001
Potassium (mg/d)	3862 (1322)	2801 (871)	3467 (906)	4076 (943)	5106 (1286)	<0.001	3282 (1213)	3597 (1180)	4092 (1339)	4478 (1226)	<0.001
Vitamin D (µg/d)	3.5 (2.0)	3.4 (2.1)	3.1 (1.8)	3.4 (1.8)	3.9 (2.1)	<0.001	2.6 (1.4)	3.1 (1.5)	3.7 (1.9)	4.5 (2.3)	<0.001
Polyunsaturated fat (g/d)	15.59 (6.31)	13.70 (6.07)	14.69 (5.45)	15.78 (6.05)	18.18 (6.74)	<0.001	12.82 (6.15)	14.52 (5.63)	16.08 (5.24)	18.93 (6.51)	<0.001
Saturated fat (g/d)	28.76 (11.24)	27.32 (11.23)	28.01 (12.67)	28.95 (9.89)	30.79 (10.71)	<0.001	19.60 (5.69)	25.54 (6.32)	30.36 (7.11)	39.58 (13.01)	<0.001
Sodium (mg/d)	2415 (838)	2120 (774)	2262 (766)	2498 (770)	2781 (885)	<0.001	1694 (476)	2118 (484)	2565 (544)	3285 (817)	<0.001
Cholesterol (mg/d)	279 (106)	252 (101)	266 (95)	287 (94)	311 (123)	<0.001	219 (82)	256 (80)	293 (91)	350 (121)	<0.001

Supplementary Table 4.1 *(table continued)*
Food and nutrient intake across quartiles of dietary patterns derived by principal component analysis method

		Prudent					Western				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
Fat (g/d)	87.0 (27.6)	78.8 (27.3)	82.6 (24.3)	88.9 (26.8)	97.8 (28.2)	<0.001	67.0 (20.9)	79.6 (20.7)	90.9 (20.6)	110.6 (27.2)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	170.3 (64.7)	193.9 (71.1)	216.4 (78.9)	258.1 (99.3)	<0.001	159.8 (74.2)	189.2 (73.6)	225.1 (88.9)	264.6 (67.2)	<0.001
Fibre (g/d)	27.2 (10.6)	17.7 (5.9)	23.5 (6.2)	28.8 (6.6)	38.8 (9.7)	<0.001	24.3 (10.1)	25.9 (9.9)	28.6 (10.9)	30.0 (10.5)	<0.001
Zinc (mg/d)	10.58 (3.67)	8.96 (3.48)	9.97 (3.29)	11.20 (3.33)	12.21 (3.73)	<0.001	8.07 (2.85)	9.84 (2.66)	11.19 (2.99)	13.24 (3.94)	<0.001
Folic acid (µg/d)	173 (155)	164 (140)	173 (158)	163 (140)	194 (178)	0.067	97 (84)	149 (128)	181 (132)	274 (201)	<0.001
Magnesium (mg/d)	442 (157)	346 (138)	407 (130)	460 (127)	553 (151)	<0.001	370 (131)	415 (144)	470 (153)	511 (160)	<0.001
EPA and DHA (mg/d)	289.98 (236.37)	195.95 (160.30)	257.34 (193.03)	309.90 (208.20)	396.96 (309.65)	<0.001	295.66 (231.42)	265.57 (192.87)	289.73 (222.18)	308.98 (287.79)	0.052
Omega-3 fatty acid (mg/d)	3595 (1945)	3218 (1886)	3452 (1809)	3597 (1819)	4116 (2140)	<0.001	3037 (1739)	3343 (1704)	3733 (1784)	4271 (2278)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	18956 (10775)	20613 (9791)	21501 (10610)	24938 (11760)	<0.001	17827 (9686)	20342 (10075)	21834 (9827)	26007 (12441)	<0.001
Energy (kcal/day)	2063 (577)	1768 (534)	1934 (472)	2130 (518)	2422 (565)	<0.001	1589 (414)	1877 (395)	2177 (426)	2611 (503)	<0.001

Data are presented as mean (SD)

Supplementary Table 4.2 Food and nutrient intake across quartiles of dietary patterns derived by reduced rank regression method

		Prudent					Western				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435		436	436	436	435	
Food groups (g/d)											
High fat dairy	90.7 (172.3)	141.1 (215.8)	100.0 (177.0)	74.7 (149.9)	46.9 (117.1)	<0.001	122.4 (196.5)	88.6 (169.1)	81.1 (159.6)	70.6 (157.2)	<0.001
Medium fat dairy	244.2 (221.3)	223.9 (242.9)	232.7 (216.6)	254.9 (220.5)	265.4 (201.7)	0.020	173.6 (192.0)	239.2 (208.9)	257.1 (221.7)	306.9 (239.9)	<0.001
Soft drinks	231.7 (341.1)	347.8 (511.2)	224.2 (282.7)	181.8 (219.5)	172.8 (238.8)	<0.001	360.5 (474.8)	207.1 (315.0)	169.4 (210.2)	189.6 (272.5)	<0.001
Processed meat	26.2 (21.8)	26.7 (21.6)	28.0 (23.3)	25.3 (19.9)	24.8 (22.1)	0.13	30.0 (23.6)	24.2 (19.9)	25.4 (20.0)	25.2 (23.0)	<0.001
High fibre cereal	1.9 (6.7)	1.5 (6.2)	1.8 (6.5)	1.7 (5.8)	2.4 (8.1)	0.18	0.7 (3.7)	2.1 (7.3)	2.0 (7.0)	2.6 (7.9)	<0.001
Take away foods	37.8 (33.4)	40.8 (34.4)	39.6 (35.2)	34.4 (26.6)	36.3 (36.2)	0.017	50.8 (46.2)	36.0 (28.5)	31.8 (24.9)	32.6 (25.9)	<0.001
Citrus fruit	17.8 (25.7)	18.1 (28.4)	17.0 (24.6)	16.9 (25.0)	19.0 (24.7)	0.56	16.3 (23.7)	18.5 (28.0)	18.7 (26.2)	17.5 (24.8)	0.52
Fruity vegetables	116.4 (70.8)	111.3 (79.5)	104.9 (67.4)	117.6 (61.6)	131.8 (70.9)	<0.001	100.8 (65.9)	110.9 (64.8)	124.4 (72.3)	129.5 (76.3)	<0.001
Other fruits	205.3 (153.1)	217.7 (179.0)	197.7 (169.1)	195.5 (127.2)	210.2 (129.5)	0.10	202.0 (152.0)	210.5 (139.7)	208.6 (167.0)	200.0 (152.8)	0.70
Root vegetables	14.5 (12.6)	14.7 (13.3)	13.2 (11.0)	14.7 (12.7)	15.6 (13.3)	0.040	10.6 (9.2)	14.3 (12.6)	14.9 (11.2)	18.3 (15.3)	<0.001
Leafy vegetables	27.6 (26.5)	25.8 (29.8)	23.6 (23.3)	28.2 (23.2)	32.9 (28.2)	<0.001	24.5 (26.4)	26.6 (27.4)	28.6 (24.8)	30.8 (27.1)	0.003
High fibre bread	51.2 (43.7)	62.4 (53.8)	46.8 (40.7)	49.1 (39.4)	46.7 (37.2)	<0.001	47.8 (46.3)	51.0 (43.6)	53.1 (41.0)	53.1 (43.7)	0.23
Cabbages	32.2 (28.3)	30.1 (28.8)	29.3 (24.9)	32.0 (26.5)	37.3 (31.9)	<0.001	24.2 (23.8)	29.3 (24.5)	33.6 (26.8)	41.6 (34.1)	<0.001
Legumes	36.1 (56.1)	37.4 (63.0)	28.6 (42.2)	33.0 (53.2)	45.5 (62.1)	<0.001	37.6 (66.7)	36.3 (50.1)	32.0 (46.4)	38.7 (58.8)	0.32
Nutrients											
Protein (g/d)	95.1 (28.1)	89.1 (25.9)	87.6 (24.6)	94.2 (23.3)	109.4 (32.4)	<0.001	96.4 (31.0)	91.2 (26.0)	93.7 (25.6)	98.9 (28.8)	<0.001
Calcium (mg/d)	869 (327)	924 (355)	830 (313)	833 (314)	886 (316)	<0.001	824 (331)	842 (323)	863 (307)	946 (333)	<0.001
Potassium (mg/d)	3862 (1322)	3877 (1398)	3649 (1292)	3748 (1180)	4174 (1353)	<0.001	3511 (1287)	3701 (1360)	3935 (1221)	4302 (1288)	<0.001
Vitamin D (μg/d)	3.5 (2.0)	3.4 (2.1)	3.0 (1.8)	3.2 (1.6)	4.3 (2.0)	<0.001	4.4 (2.4)	3.3 (1.8)	3.2 (1.6)	3.0 (1.6)	<0.001
Polyunsaturated fat (g/d)	15.59 (6.31)	16.80 (6.71)	14.37 (5.92)	14.54 (5.59)	16.65 (6.57)	<0.001	16.71 (6.62)	15.21 (6.06)	15.32 (6.39)	15.11 (6.05)	<0.001
Saturated fat (g/d)	28.76 (11.24)	31.79 (13.84)	27.81 (10.35)	27.17 (9.21)	28.28 (10.46)	<0.001	32.64 (14.39)	27.64 (9.94)	27.54 (9.38)	27.23 (9.57)	<0.001
Sodium (mg/d)	2415 (838)	2593 (878)	2283 (828)	2289 (738)	2496 (861)	<0.001	2622 (944)	2303 (794)	2336 (755)	2399 (811)	<0.001
Cholesterol (mg/d)	279 (106)	259 (99)	261 (95)	275 (94)	323 (123)	<0.001	316 (124)	268 (96)	264 (91)	269 (103)	<0.001
Fat (g/d)	87.0 (27.6)	92.4 (29.6)	82.5 (25.9)	82.8 (24.6)	90.3 (28.8)	<0.001	94.3 (31.0)	84.5 (25.3)	84.7 (26.1)	84.6 (26.6)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	239.3 (88.2)	202.9 (85.1)	194.5 (73.6)	201.9 (88.7)	<0.001	216.8 (85.2)	208.7 (93.6)	207.8 (82.9)	205.4 (81.0)	0.22
Fibre (g/d)	27.2 (10.6)	28.1 (11.6)	25.5 (10.5)	26.3 (9.1)	28.9 (10.7)	<0.001	24.9 (10.3)	27.0 (10.8)	27.8 (10.1)	29.0 (10.9)	<0.001
Zinc (mg/d)	10.58 (3.67)	9.87 (3.54)	9.93 (3.41)	10.72 (3.14)	11.82 (4.18)	<0.001	10.12 (3.54)	9.95 (3.33)	10.76 (3.48)	11.50 (4.09)	<0.001
Folic acid (μg/d)	173 (155)	244 (193)	161 (133)	146 (122)	140 (137)	<0.001	189 (157)	158 (142)	164 (143)	183 (175)	0.051
Magnesium (mg/d)	442 (157)	447 (165)	421 (154)	428 (146)	471 (156)	<0.001	378 (138)	411 (144)	451 (134)	527 (168)	<0.001
EPA and DHA (mg/d)	289.98 (236.37)	134.55 (80.62)	184.38 (98.06)	276.56 (110.10)	565.05 (290.62)	<0.001	397.73 (330.87)	294.22 (212.43)	253.99 (175.42)	213.79 (140.18)	<0.001
Omega-3 fatty acid (mg/d)	3595 (1945)	3675 (1947)	3246 (1905)	3341 (1766)	4120 (2036)	<0.001	4100 (2245)	3571 (1775)	3367 (1858)	3343 (1771)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	23631 (11716)	20152 (10379)	19837 (10094)	22381 (11184)	<0.001	23174 (11604)	21263 (10278)	20880 (11283)	20680 (10506)	0.003
Energy (kcal/day)	2063 (577)	2205 (610)	1963 (552)	1964 (503)	2120 (600)	<0.001	2162 (638)	2015 (561)	2029 (545)	2046 (549)	<0.001

Data are presented as mean (SD)

(table continues)

Supplementary Table 4.2 (*table continued)*
Food and nutrient intake across quartiles of dietary patterns derived by reduced rank regression method

		Typical Australian					Modern				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435		436	436	436	435	
Food groups (g/d)											
High fat dairy	90.7 (172.3)	136.9 (215.7)	81.3 (155.6)	77.8 (162.3)	66.5 (137.3)	<0.001	91.2 (170.2)	94.8 (179.9)	83.2 (160.0)	93.6 (178.6)	0.75
Medium fat dairy	244.2 (221.3)	244.5 (237.8)	245.5 (208.7)	245.5 (220.9)	241.3 (217.8)	0.99	227.8 (217.0)	230.6 (210.7)	250.7 (227.5)	267.7 (228.1)	0.026
Soft drinks	231.7 (341.1)	253.9 (434.6)	173.2 (200.6)	234.1 (318.8)	265.6 (360.9)	<0.001	292.2 (406.8)	240.2 (338.8)	211.8 (282.9)	182.4 (314.9)	<0.001
Processed meat	26.2 (21.8)	23.5 (21.2)	24.9 (20.9)	26.5 (20.2)	29.9 (24.2)	<0.001	37.7 (27.1)	26.9 (18.9)	22.4 (18.3)	17.8 (16.2)	<0.001
High fibre cereal	1.9 (6.7)	1.8 (6.3)	2.3 (7.7)	1.7 (6.1)	1.6 (6.7)	0.36	1.9 (6.9)	1.5 (5.2)	1.8 (6.9)	2.2 (7.6)	0.51
Take away foods	37.8 (33.4)	37.8 (34.9)	34.3 (29.7)	35.4 (28.1)	43.6 (39.1)	<0.001	46.5 (39.8)	36.5 (28.6)	34.3 (30.8)	33.8 (31.9)	<0.001
Citrus fruit	17.8 (25.7)	16.5 (24.1)	17.0 (25.1)	19.1 (27.2)	18.4 (26.3)	0.40	13.1 (19.5)	15.6 (20.9)	19.7 (30.6)	22.6 (29.0)	<0.001
Fruity vegetables	116.4 (70.8)	108.6 (69.6)	113.9 (63.7)	114.6 (67.3)	128.6 (80.4)	<0.001	104.1 (64.4)	111.9 (64.1)	117.1 (71.4)	132.5 (79.4)	<0.001
Other fruits	205.3 (153.1)	208.3 (156.2)	198.1 (136.8)	200.1 (137.0)	214.5 (178.6)	0.36	162.3 (111.1)	186.0 (120.7)	215.8 (145.7)	257.1 (202.1)	<0.001
Root vegetables	14.5 (12.6)	13.8 (12.9)	12.6 (11.3)	13.9 (10.9)	17.8 (14.5)	<0.001	15.1 (13.0)	13.4 (10.8)	13.8 (12.4)	15.9 (14.0)	0.015
Leafy vegetables	27.6 (26.5)	24.4 (22.9)	25.9 (22.2)	30.6 (29.0)	29.8 (30.5)	<0.001	22.8 (21.9)	24.6 (22.5)	27.1 (23.6)	36.1 (34.1)	<0.001
High fibre bread	51.2 (43.7)	37.7 (37.7)	45.6 (38.1)	55.5 (41.6)	66.1 (51.1)	<0.001	41.3 (41.0)	51.0 (42.4)	54.2 (42.7)	58.4 (46.9)	<0.001
Cabbages	32.2 (28.3)	30.2 (27.8)	30.8 (28.0)	32.0 (26.0)	35.6 (31.0)	0.024	30.8 (27.6)	32.9 (29.6)	30.8 (26.1)	34.1 (29.8)	0.23
Legumes	36.1 (56.1)	41.5 (66.3)	37.3 (59.4)	32.0 (44.7)	33.7 (51.1)	0.061	27.0 (44.0)	30.0 (44.9)	35.7 (52.3)	51.9 (74.5)	<0.001
Nutrients											
Protein (g/d)	95.1 (28.1)	93.3 (27.4)	90.0 (24.6)	92.9 (25.8)	104.2 (31.9)	<0.001	107.4 (29.5)	93.0 (24.6)	89.5 (26.5)	90.5 (27.9)	<0.001
Calcium (mg/d)	869 (327)	922 (329)	831 (316)	844 (331)	878 (325)	<0.001	870 (334)	835 (318)	854 (328)	916 (323)	0.002
Potassium (mg/d)	3862 (1322)	4103 (1527)	3650 (1170)	3582 (1099)	4113 (1360)	<0.001	3728 (1152)	3648 (1251)	3825 (1369)	4247 (1422)	<0.001
Vitamin D (µg/d)	3.5 (2.0)	3.5 (2.1)	3.2 (1.8)	3.3 (1.9)	3.8 (2.0)	<0.001	3.3 (1.8)	3.2 (1.9)	3.4 (1.9)	4.0 (2.2)	<0.001
Polyunsaturated fat (g/d)	15.59 (6.31)	15.15 (6.64)	14.43 (5.69)	15.18 (5.79)	17.59 (6.63)	<0.001	15.89 (6.08)	15.27 (6.03)	15.06 (6.28)	16.13 (6.79)	0.038
Saturated fat (g/d)	28.76 (11.24)	30.29 (13.33)	26.72 (9.54)	27.32 (10.64)	30.73 (10.56)	<0.001	33.01 (11.11)	28.25 (10.15)	27.08 (9.53)	26.71 (12.78)	<0.001
Sodium (mg/d)	2415 (838)	2209 (775)	2225 (742)	2352 (748)	2874 (901)	<0.001	2687 (859)	2341 (750)	2282 (795)	2349 (882)	<0.001
Cholesterol (mg/d)	279 (106)	280 (106)	266 (92)	278 (111)	293 (113)	0.002	317 (116)	275 (96)	262 (97)	263 (107)	<0.001
Fat (g/d)	87.0 (27.6)	87.9 (28.7)	81.2 (24.2)	83.9 (26.8)	95.1 (28.7)	<0.001	95.2 (27.7)	85.3 (26.2)	83.4 (26.6)	84.1 (28.4)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	231.1 (107.0)	194.9 (79.5)	189.4 (63.1)	223.3 (80.5)	<0.001	213.4 (78.7)	201.9 (82.7)	206.9 (90.2)	216.5 (90.6)	0.054
Fibre (g/d)	27.2 (10.6)	28.0 (12.3)	25.9 (9.7)	25.6 (8.7)	29.3 (11.0)	<0.001	25.7 (9.2)	25.9 (9.6)	26.9 (11.0)	30.3 (11.8)	<0.001
Zinc (mg/d)	10.58 (3.67)	10.43 (3.64)	9.93 (3.27)	10.12 (3.24)	11.85 (4.15)	<0.001	13.07 (3.76)	10.52 (3.04)	9.74 (3.20)	9.00 (3.29)	<0.001
Folic acid (µg/d)	173 (155)	92 (82)	110 (70)	159 (98)	331 (202)	<0.001	161 (149)	172 (144)	172 (151)	186 (172)	0.31
Magnesium (mg/d)	442 (157)	489 (173)	422 (137)	403 (146)	452 (154)	<0.001	412 (140)	414 (144)	440 (156)	500 (168)	<0.001
EPA and DHA (mg/d)	289.98 (236.37)	254.89 (217.08)	286.79 (227.33)	290.72 (210.15)	327.59 (279.82)	<0.001	237.04 (168.12)	242.92 (172.57)	283.92 (223.76)	396.26 (315.43)	<0.001
Omega-3 fatty acid (mg/d)	3595 (1945)	3172 (1706)	3398 (1854)	3594 (1831)	4219 (2201)	<0.001	3419 (1856)	3430 (1767)	3470 (1780)	4064 (2263)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	20363 (11253)	20137 (10298)	21391 (10037)	24113 (11769)	<0.001	21275 (10811)	21097 (9926)	20685 (10811)	22947 (12112)	0.013
Energy (kcal/day)	2063 (577)	2133 (606)	1932 (531)	1952 (529)	2236 (584)	<0.001	2205 (556)	2011 (559)	1993 (580)	2043 (590)	<0.001

Data are presented as mean (SD)

		Prudent					Western				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435		436	436	436	435	
Food groups (g/d)											
High fat dairy	90.7 (172.3)	106.6 (181.8)	86.6 (165.0)	83.4 (168.5)	86.0 (173.0)	0.17	36.0 (103.7)	61.5 (137.1)	90.4 (159.9)	174.9 (230.1)	<0.001
Medium fat dairy	244.2 (221.3)	163.5 (169.1)	226.9 (214.3)	267.9 (222.4)	318.7 (243.7)	<0.001	298.7 (223.1)	269.4 (204.1)	238.7 (223.9)	169.8 (213.5)	<0.001
Soft drinks	231.7 (341.1)	312.5 (407.3)	241.0 (337.1)	204.7 (300.2)	168.4 (291.7)	<0.001	141.8 (206.8)	177.7 (214.8)	208.5 (251.0)	399.1 (524.4)	<0.001
Processed meat	26.2 (21.8)	36.4 (26.7)	26.1 (18.8)	22.9 (19.0)	19.3 (17.5)	<0.001	22.9 (20.9)	25.2 (20.6)	26.7 (21.0)	30.0 (24.0)	<0.001
High fibre cereal	1.9 (6.7)	1.4 (6.0)	1.7 (5.8)	2.0 (7.4)	2.4 (7.5)	0.20	2.6 (8.4)	2.2 (6.7)	1.5 (5.8)	1.2 (5.5)	0.008
Take away foods	37.8 (33.4)	49.2 (43.8)	37.4 (32.1)	34.4 (26.8)	30.1 (24.7)	<0.001	30.5 (30.6)	34.2 (25.1)	37.6 (31.6)	48.9 (41.4)	<0.001
Citrus fruit	17.8 (25.7)	10.9 (16.6)	15.2 (21.7)	16.0 (20.9)	29.0 (35.8)	<0.001	22.7 (28.7)	18.6 (26.2)	17.3 (25.9)	12.5 (20.4)	<0.001
Fruity vegetables	116.4 (70.8)	84.5 (53.8)	98.0 (54.8)	119.1 (62.0)	164.0 (82.0)	<0.001	159.9 (77.7)	125.8 (62.2)	98.5 (59.5)	81.3 (55.8)	<0.001
Other fruits	205.3 (153.1)	143.5 (101.7)	166.0 (100.5)	203.4 (118.9)	308.4 (208.4)	<0.001	253.8 (186.8)	219.4 (142.3)	186.5 (131.9)	161.3 (128.7)	<0.001
Root vegetables	14.5 (12.6)	9.8 (9.4)	12.2 (10.0)	14.9 (11.2)	21.3 (15.8)	<0.001	18.7 (14.4)	14.9 (12.1)	12.9 (11.3)	11.6 (11.2)	<0.001
Leafy vegetables	27.6 (26.5)	18.7 (19.0)	22.3 (21.5)	29.6 (24.9)	40.0 (33.3)	<0.001	44.5 (34.5)	29.6 (23.2)	20.8 (18.3)	15.6 (16.4)	<0.001
High fibre bread	51.2 (43.7)	32.7 (34.9)	40.5 (37.6)	60.5 (42.1)	71.2 (48.0)	<0.001	51.2 (36.7)	52.0 (39.6)	51.2 (43.7)	50.6 (53.2)	0.97
Cabbages	32.2 (28.3)	22.3 (21.1)	28.0 (23.7)	32.1 (26.6)	46.3 (34.4)	<0.001	44.1 (33.2)	32.9 (26.5)	27.4 (24.0)	24.3 (24.5)	<0.001
Legumes	36.1 (56.1)	26.6 (42.6)	28.4 (44.8)	32.5 (43.6)	57.0 (79.2)	<0.001	56.7 (75.2)	40.3 (57.2)	26.0 (41.2)	21.6 (34.8)	<0.001
Nutrients											
Protein (g/d)	95.1 (28.1)	103.1 (33.1)	90.6 (25.3)	91.4 (26.3)	95.2 (25.2)	<0.001	109.0 (31.2)	95.5 (24.3)	86.9 (24.4)	88.8 (26.4)	<0.001
Calcium (mg/d)	869 (327)	767 (305)	803 (314)	890 (314)	1015 (318)	<0.001	932 (338)	856 (295)	820 (314)	866 (349)	<0.001
Potassium (mg/d)	3862 (1322)	3332 (1085)	3490 (1159)	3951 (1288)	4676 (1316)	<0.001	4481 (1408)	3932 (1237)	3522 (1168)	3512 (1224)	<0.001
Vitamin D (µg/d)	3.5 (2.0)	3.9 (2.2)	3.2 (1.8)	3.4 (1.9)	3.4 (1.9)	<0.001	4.0 (2.0)	3.1 (1.7)	3.0 (1.7)	3.7 (2.2)	<0.001
Polyunsaturated fat (g/d)	15.59 (6.31)	15.48 (6.40)	14.53 (5.76)	15.53 (6.32)	16.82 (6.55)	<0.001	16.68 (6.65)	14.93 (5.48)	14.38 (6.14)	16.36 (6.63)	<0.001
Saturated fat (g/d)	28.76 (11.24)	31.41 (11.55)	27.37 (9.86)	27.87 (10.42)	28.39 (12.52)	<0.001	27.06 (9.59)	27.00 (9.09)	27.60 (10.50)	33.40 (13.87)	<0.001
Sodium (mg/d)	2415 (838)	2567 (904)	2243 (755)	2357 (799)	2494 (851)	<0.001	2486 (877)	2333 (734)	2273 (835)	2569 (867)	<0.001
Cholesterol (mg/d)	279 (106)	329 (125)	270 (89)	261 (97)	258 (94)	<0.001	316 (122)	275 (98)	256 (90)	270 (104)	<0.001
Fat (g/d)	87.0 (27.6)	91.0 (28.8)	82.8 (26.3)	85.4 (27.9)	88.9 (26.9)	<0.001	89.2 (27.9)	83.8 (24.6)	81.8 (26.9)	93.4 (29.5)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	188.7 (69.7)	192.3 (79.2)	215.4 (92.3)	242.2 (89.6)	<0.001	209.2 (92.2)	204.9 (85.6)	197.0 (76.6)	227.5 (85.5)	<0.001
Fibre (g/d)	27.2 (10.6)	21.6 (8.0)	23.9 (8.5)	28.1 (9.6)	35.1 (10.8)	<0.001	32.2 (11.4)	28.0 (9.9)	24.6 (9.5)	23.9 (9.4)	<0.001
Zinc (mg/d)	10.58 (3.67)	11.72 (4.15)	10.25 (3.31)	10.09 (3.44)	10.27 (3.49)	<0.001	11.60 (4.01)	10.69 (3.38)	9.88 (3.41)	10.15 (3.62)	<0.001
Folic acid (µg/d)	173 (155)	146 (130)	155 (141)	188 (158)	203 (180)	<0.001	142 (149)	146 (122)	171 (144)	235 (181)	<0.001
Magnesium (mg/d)	442 (157)	376 (134)	403 (139)	459 (151)	528 (157)	<0.001	497 (158)	443 (144)	411 (152)	416 (158)	<0.001
EPA and DHA (mg/d)	289.98 (236.37)	369.29 (319.90)	264.50 (195.36)	279.07 (209.72)	246.94 (174.34)	<0.001	523.56 (311.59)	281.55 (143.66)	199.92 (119.66)	154.56 (102.43)	<0.001
Omega-3 fatty acid (mg/d)	3595 (1945)	3686 (2141)	3294 (1692)	3603 (1894)	3799 (1994)	0.001	4016 (2050)	3466 (1803)	3229 (1810)	3671 (2021)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	21180 (10791)	19795 (10093)	21415 (10995)	23615 (11629)	<0.001	22965 (11465)	20639 (9949)	19584 (10544)	22815 (11489)	<0.001
Energy (kcal/day)	2063 (577)	2056 (594)	1937 (543)	2045 (571)	2216 (566)	<0.001	2137 (586)	2018 (526)	1934 (556)	2163 (608)	<0.001

Data are presented as mean (SD)

(table continues)

Supplementary Table 4.3 *(table continued)*
Food and nutrient intake across quartiles of dietary patterns derived by partial least square method

		Typical Australian					Modern				
	Total	Q1	Q2	Q3	Q4	P-value	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435		436	436	436	435	
Food groups (g/d)											
High fat dairy	90.7 (172.3)	110.3 (197.0)	94.5 (170.7)	86.3 (161.7)	71.5 (155.0)	0.009	105.8 (191.6)	80.8 (161.7)	73.1 (147.2)	103.1 (183.3)	0.009
Medium fat dairy	244.2 (221.3)	192.2 (191.4)	218.9 (199.1)	259.4 (228.9)	306.4 (245.4)	<0.001	242.3 (220.6)	249.1 (226.7)	242.7 (216.6)	242.7 (222.0)	0.96
Soft drinks	231.7 (341.1)	246.0 (389.1)	250.5 (397.7)	206.1 (276.0)	224.1 (281.0)	0.19	168.3 (235.9)	220.7 (328.2)	240.7 (328.9)	297.1 (431.5)	<0.001
Processed meat	26.2 (21.8)	17.6 (16.1)	23.5 (19.0)	29.4 (20.4)	34.3 (26.6)	<0.001	18.5 (16.2)	22.8 (19.9)	27.6 (20.9)	35.8 (25.4)	<0.001
High fibre cereal	1.9 (6.7)	1.6 (6.0)	1.7 (6.1)	1.8 (6.6)	2.3 (7.9)	0.38	2.3 (7.4)	2.5 (7.7)	1.4 (6.2)	1.2 (5.3)	0.005
Take away foods	37.8 (33.4)	36.8 (36.2)	36.3 (31.8)	38.1 (33.2)	39.9 (32.3)	0.38	26.8 (20.9)	31.5 (23.0)	38.3 (32.3)	54.7 (45.0)	<0.001
Citrus fruit	17.8 (25.7)	19.6 (28.5)	17.3 (26.8)	16.5 (23.0)	17.7 (24.2)	0.32	13.2 (21.6)	16.7 (23.2)	18.7 (27.1)	22.4 (29.4)	<0.001
Fruity vegetables	116.4 (70.8)	91.5 (61.6)	105.3 (61.1)	126.6 (71.7)	142.2 (76.9)	<0.001	88.5 (54.8)	110.2 (63.4)	123.1 (67.8)	143.8 (82.8)	<0.001
Other fruits	205.3 (153.1)	212.2 (161.9)	203.2 (172.6)	204.7 (125.9)	200.9 (148.4)	0.72	151.5 (109.2)	190.7 (122.6)	216.8 (138.7)	262.1 (203.3)	<0.001
Root vegetables	14.5 (12.6)	8.5 (8.0)	11.5 (9.5)	15.2 (11.5)	23.0 (15.3)	<0.001	10.3 (9.1)	13.4 (11.3)	15.5 (13.0)	19.0 (14.7)	<0.001
Leafy vegetables	27.6 (26.5)	25.0 (27.5)	26.4 (24.7)	27.6 (26.0)	31.6 (27.3)	0.002	20.2 (20.2)	27.0 (23.0)	28.5 (25.6)	34.9 (33.4)	<0.001
High fibre bread	51.2 (43.7)	45.7 (42.9)	49.0 (42.3)	52.5 (39.6)	57.7 (48.8)	<0.001	36.7 (33.7)	45.5 (38.1)	53.8 (42.4)	68.9 (52.1)	<0.001
Cabbages	32.2 (28.3)	20.3 (20.8)	26.3 (22.1)	32.9 (23.5)	49.2 (35.6)	<0.001	26.8 (25.5)	28.7 (24.3)	34.8 (29.1)	38.5 (32.1)	<0.001
Legumes	36.1 (56.1)	45.5 (71.5)	38.3 (55.3)	32.5 (49.8)	28.2 (42.0)	<0.001	31.5 (54.0)	32.5 (43.1)	32.8 (46.2)	47.8 (74.2)	<0.001
Nutrients											
Protein (g/d)	95.1 (28.1)	82.1 (28.9)	89.1 (24.3)	97.2 (20.5)	111.8 (28.8)	<0.001	79.5 (21.8)	89.2 (23.2)	95.7 (23.9)	115.9 (29.4)	<0.001
Calcium (mg/d)	869 (327)	776 (314)	829 (302)	888 (315)	982 (340)	<0.001	791 (304)	834 (318)	861 (324)	988 (329)	<0.001
Potassium (mg/d)	3862 (1322)	3407 (1384)	3612 (1262)	3959 (1125)	4471 (1255)	<0.001	3381 (1099)	3655 (1328)	3830 (1200)	4583 (1341)	<0.001
Vitamin D (µg/d)	3.5 (2.0)	3.9 (2.3)	3.4 (2.0)	3.3 (1.7)	3.2 (1.7)	<0.001	2.7 (1.7)	3.0 (1.7)	3.4 (1.7)	4.7 (2.2)	<0.001
Polyunsaturated fat (g/d)	15.59 (6.31)	14.82 (6.21)	15.34 (6.58)	15.48 (5.94)	16.71 (6.37)	<0.001	12.74 (5.76)	14.15 (5.15)	15.86 (5.68)	19.60 (6.42)	<0.001
Saturated fat (g/d)	28.76 (11.24)	25.70 (13.25)	27.58 (10.47)	29.72 (9.24)	32.06 (10.61)	<0.001	23.15 (7.94)	26.21 (8.54)	29.35 (11.77)	36.37 (11.62)	<0.001
Sodium (mg/d)	2415 (838)	2093 (812)	2310 (791)	2494 (749)	2764 (851)	<0.001	1822 (560)	2165 (596)	2467 (621)	3208 (844)	<0.001
Cholesterol (mg/d)	279 (106)	268 (121)	264 (102)	280 (83)	306 (112)	<0.001	229 (79)	262 (93)	280 (90)	347 (122)	<0.001
Fat (g/d)	87.0 (27.6)	78.9 (27.2)	84.7 (28.2)	88.5 (24.3)	95.9 (28.0)	<0.001	71.7 (22.8)	80.1 (21.6)	88.2 (23.7)	108.1 (28.0)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	192.5 (93.3)	202.3 (83.5)	213.4 (78.1)	230.5 (83.3)	<0.001	168.3 (67.6)	195.9 (88.5)	211.2 (69.8)	263.4 (86.3)	<0.001
Fibre (g/d)	27.2 (10.6)	24.0 (11.0)	25.7 (10.2)	27.6 (9.3)	31.4 (10.4)	<0.001	22.2 (8.4)	25.6 (10.1)	27.5 (9.5)	33.4 (11.0)	<0.001
Zinc (mg/d)	10.58 (3.67)	8.14 (3.04)	9.71 (2.92)	11.04 (2.61)	13.45 (3.77)	<0.001	9.02 (3.14)	9.99 (3.29)	10.59 (3.46)	12.74 (3.73)	<0.001
Folic acid (µg/d)	173 (155)	145 (127)	168 (151)	176 (151)	213 (186)	<0.001	97 (81)	129 (98)	180 (136)	289 (203)	<0.001
Magnesium (mg/d)	442 (157)	392 (153)	418 (147)	448 (143)	508 (159)	<0.001	430 (158)	420 (160)	429 (153)	487 (147)	<0.001
EPA and DHA (mg/d)	289.98 (236.37)	400.37 (333.69)	283.71 (207.67)	248.29 (156.72)	227.39 (163.86)	<0.001	186.80 (121.94)	253.80 (162.89)	300.61 (220.40)	418.99 (324.45)	<0.001
Omega-3 fatty acid (mg/d)	3595 (1945)	3794 (2140)	3586 (1909)	3456 (1776)	3545 (1925)	0.068	2838 (1673)	3240 (1538)	3664 (1746)	4643 (2266)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	20944 (10973)	21495 (10780)	21475 (10952)	22088 (11168)	0.50	17581 (10030)	19661 (9239)	22038 (10291)	26731 (11984)	<0.001
Energy (kcal/day)	2063 (577)	1857 (586)	1983 (564)	2107 (503)	2307 (556)	<0.001	1690 (429)	1911 (482)	2088 (461)	2564 (539)	<0.001

Data are presented as mean (SD)

Supplementary Table 4.3 Pearson correlation coefficients among response variables

Response variables	Folic acid density (mg/day/Kcal)	EPA DHA (mg/day/Kcal)	Magnesium density(mg/day/Kcal)	Zinc density(mg/day/Kcal)
Folic acid density (mg/day/Kcal)	1			
EPA DHA (mg/day/Kcal)	-0.0657	1		
Magnesium density (mg/day/Kcal)	0.133	0.0778	1	
Zinc density (mg/day/Kcal)	-0.1062	0.1631	0.0112	1

Supplementary Table 4.4 Odds ratio for the association between quartiles of food patterns and depression among adults aged (≥ 24 years), South Australia (*n* = 859), Data from the longitudinal analysis between Stage 3 and NW15

Odds ratio (OR) and 95% confidence intervals					
	Q1	Q2	Q3	Q4	P_{trend}
Principal component Analysis					
Prudent dietary pattern					
Model 1	1.00	0.59(0.34-1.01)	0.40(0.22-0.73) **	0.48(0.25-0.91) *	0.007
Model 2	1.00	0.66(0.37-1.17)	0.44(0.23-0.85) *	0.58(0.29-1.19)	0.053
Model 3	1.00	0.65(0.36-1.16)	0.46(0.24-0.90) *	0.52(0.25-1.09)	0.039
Western dietary pattern					
Model 1	1.00	1.54(0.85-2.80)	1.71(0.86-3.40)	3.31(1.46-7.52) **	0.007
Model 2	1.00	1.57(0.83-2.98)	1.57(0.74-3.30)	2.95(1.21-7.20) *	0.031
Model 3	1.00	1.66(0.86-3.20)	1.78(0.83-3.83)	3.47(1.37-8.78) **	0.014
Reduced rank regression					
Prudent dietary pattern					
Model 1	1.00	0.74(0.42-1.29)	0.77(0.44-1.35)	0.57(0.31-1.03)	0.088
Model 2	1.00	0.80(0.45-1.45)	0.79(0.44-1.42)	0.63(0.33-1.19)	0.168
Model 3	1.00	0.82(0.45-1.51)	0.78(0.43-1.42)	0.61(0.32-1.19)	0.153
Western dietary pattern					
Model 1	1.00	0.61(0.33-1.10)	0.96(0.56-1.66)	0.77(0.44-1.36)	0.703
Model 2	1.00	0.64(0.34-1.21)	1.10(0.61-1.97)	0.87(0.48-1.59)	0.945
Model 3	1.00	0.70(0.37-1.34)	1.13(0.62-2.06)	0.90(0.48-1.67)	0.906
Modern dietary pattern					
Model 1	1.00	1.25(0.70-2.23)	0.92(0.49-1.70)	1.33(0.74-2.38)	0.549
Model 2	1.00	1.37(0.74-2.53)	1.04(0.54-1.99)	1.39(0.74-2.59)	0.496
Model 3	1.00	1.39(0.74-2.60)	1.11(0.57-2.14)	1.31(0.69-2.49)	0.591
Typical Australian dietary pattern					
Model 1	1.00	1.08(0.62-1.90)	1.20(0.69-2.09)	0.69(0.36-1.31)	0.417
Model 2	1.00	1.06(0.58-1.93)	1.12(0.62-2.01)	0.70(0.36-1.36)	0.403
Model 3	1.00	1.05(0.57-1.93)	1.13(0.62-2.05)	0.73(0.37-1.43)	0.495
Partial least square					
Prudent dietary pattern					
Model 1	1.00	0.74(0.42-1.29)	0.72(0.41-1.28)	0.79(0.45-1.41)	0.413
Model 2	1.00	0.75(0.41-1.37)	0.74(0.41-1.36)	0.84(0.45-1.55)	0.558
Model 3	1.00	0.70(0.38-1.30)	0.75(0.41-1.40)	0.86(0.46-1.60)	0.652
Western dietary pattern					
Model 1	1.00	1.32(0.69-2.53)	1.68(0.89-3.20)	2.67(1.44-4.96) **	0.001
Model 2	1.00	1.28(0.64-2.53)	1.52(0.77-3.02)	2.36(1.21-4.62) *	0.009
Model 3	1.00	1.33(0.66-2.67)	1.70(0.84-3.44)	2.47(1.24-4.91) *	0.007
Modern dietary pattern					
Model 1	1.00	0.88(0.52-1.49)	0.51(0.27-0.95) *	0.76(0.39-1.47)	0.149
Model 2	1.00	0.88(0.50-1.55)	0.51(0.27-0.99) *	0.75(0.37-1.51)	0.169
Model 3	1.00	0.85(0.48-1.52)	0.52(0.27-1.01)	0.73(0.35-1.50)	0.168
Typical Australia dietary pattern					
Model 1	1.00	0.32(0.17-0.60) ***	0.47(0.27-0.84) *	0.80(0.46-1.37)	0.438
Model 2	1.00	0.32(0.17-0.63) **	0.52(0.28-0.97) *	0.87(0.48-1.56)	0.773
Model 3	1.00	0.35(0.18-0.69) **	0.57(0.31-1.07)	0.89(0.49-1.62)	0.839

**P <0.05, **P<0.01, ***P <0.001*

Model 1 was adjusted for sex, age and total energy intake

Model 2 was additionally adjusted for marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality

Model 3 was additionally adjusted for BMI, bodily pain, hypertension, T2DM and CVD

Supplementary Table 4.5 Odds ratio for the association between quartiles of food patterns and depression among adults aged (≥ 24 years), South Australia (n = 1743)[a]

**P <0.05, **P<0.01, ***P <0.001*

Odds ratio (95% confidence interval)					
	Q1 (reference)	Q2	Q3	Q4	P_{trend}
Principal component analysis					
Prudent dietary pattern					
Model 3	1.00	0.48(0.31-0.75) **	0.68(0.44-1.07)	0.56(0.34-0.91) *	0.072
Western dietary pattern					
Model 3	1.00	1.26(0.79-2.00)	1.46(0.88-2.41)	1.98(1.08-3.61) *	0.028
Reduced rank regression					
Prudent dietary pattern					
Model 3	1.00	0.73(0.48-1.12)	0.90(0.59-1.36)	0.63(0.41-0.96)	0.079
Western dietary pattern					
Model 3	1.00	1.16(0.76-1.77)	1.31(0.85-2.01)	1.33(0.87-2.03)	0.162
Modern dietary pattern					
Model 3	1.00	0.67(0.44-1.02)	0.87(0.57-1.31)	0.73(0.48-1.12)	0.323
Typical Australian dietary pattern					
Model 3	1.00	0.50(0.33-0.75) **	0.51(0.33-0.77) **	0.61(0.40-0.92) *	0.014
Partial least square					
Prudent dietary pattern					
Model 3	1.00	0.79(0.52-1.20)	0.73(0.47-1.11)	0.83(0.53-1.28)	0.332
Western dietary pattern					
Model 3	1.00	1.36(0.87-2.12)	1.22(0.77-1.93)	1.61(1.03-2.51) *	0.063
Typical Australian dietary pattern					
Model 3	1.00	0.94(0.61-1.44)	1.33(0.88-2.03)	0.94(0.60-1.47)	0.795
Modern dietary pattern					
Model 3	1.00	0.80(0.52-1.23)	0.73(0.47-1.13)	0.65(0.40-1.08)	0.086

Model 3 was adjusted sex, age and total energy intake, for marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality, BMI, bodily pain, hypertension, diabetes, CVD and antidepressant intake

[a] *Sensitivity analysis with including antidepressant*

Supplementary Table 4.6 Odds ratio for the association between quartiles of food patterns and depression among adults aged (≥ 24 years), South Australia (n = 859)[a], Data from the longitudinal analysis between Stage 3 and NW15

Odds ratio (OR) and 95% confidence intervals					
	Q1 (Reference)	Q2	Q3	Q4	P_{trend}
Principal component Analysis					
Prudent dietary pattern					
Model 3	1.00	0.64(0.35-1.16)	0.47(0.24-0.92)	0.51(0.24-1.06)	0.038
Western dietary pattern					
Model 3	1.00	1.58(0.81-3.05)	1.74(0.80-3.77)	3.35(1.32-8.54)	0.017
Reduced rank regression					
Prudent dietary pattern					
Model 3	1.00	0.81(0.44-1.51)	0.78(0.43-1.44)	0.62(0.32-1.20)	0.165
Western dietary pattern					
Model 3	1.00	0.70(0.36-1.34)	1.12(0.61-2.05)	0.85(0.45-1.60)	0.970
Modern dietary pattern					
Model 3	1.00	1.39(0.74-2.63)	1.05(0.54-2.05)	1.29(0.67-2.48)	0.676
Typical Australian dietary pattern					
Model 3	1.00	1.10(0.59-2.03)	1.12(0.61-2.05)	0.73(0.36-1.45)	0.463
Partial least square					
Prudent dietary pattern					
Model 3	1.00	0.63(0.34-1.18)	0.74(0.40-1.39)	0.74(0.39-1.41)	0.450
Western dietary pattern					
Model 3	1.00	1.33(0.66-2.68)	1.59(0.78-3.25)	2.42(1.21-4.83) *	0.010
Modern dietary pattern					
Model 3	1.00	0.92(0.51-1.65)	0.58(0.29-1.14)	0.76(0.36-1.57)	0.239
Typical Australia dietary pattern					
Model 3	1.00	0.35(0.18-0.69) **	0.56(0.30-1.04)	0.88(0.48-1.61)	0.786

**P <0.05, **P<0.01, ***P <0.001*

Model 3 was adjusted sex, age and total energy intake, for marital status, educational status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality, BMI, bodily pain, hypertension, T2DM, CVD and antidepressant intake

[a] *Sensitivity analysis with including antidepressant*

Supplementary Table 4.7 Associations of dietary patterns with prevalent depression (n = 2,323)[a] in the Australian adults participating in the NWAHS

	Odds ratio (95% confidence interval)				
	Q1 (Reference)	Q2	Q3	Q4	P_{trend}
Principal Component analysis					
Prudent dietary pattern					
Model 1	1.00	0.55(0.40-0.74) **	0.59(0.43-0.80) *	0.42(0.30-0.59) ***	0.000
Model 2	1.00	0.63(0.44-0.91) *	0.76(0.53-1.09)	0.60(0.40-0.89) *	0.036
Model 3	1.00	0.67(0.47-0.97) *	0.78(0.54-1.13)	0.60(0.40-0.91) *	0.041
Western dietary pattern					
Model 1	1.00	1.11(0.79-1.54)	1.53(1.07-2.17) **	2.29(1.51-3.46) ***	0.000
Model 2	1.00	0.97(0.67-1.41)	1.27(0.85-1.88)	1.66(1.04-2.66) *	0.024
Model 3	1.00	0.95(0.64-1.39)	1.18(0.78-1.77)	1.54(0.94-2.51)	0.069
Reduced rank regression					
Prudent dietary pattern					
Model 1	1.00	0.65(0.48-0.89) *	0.62(0.46-0.84) *	0.57(0.42-0.78) *	0.000
Model 2	1.00	0.77(0.55-1.08)	0.79(0.56-1.11)	0.72(0.51-1.02)	0.084
Model 3	1.00	0.82(0.58-1.17)	0.79(0.56-1.13)	0.76(0.53-1.09)	0.133
Western dietary pattern					
Model 1	1.00	0.88(0.65-1.19)	0.76(0.56-1.04)	0.85(0.63-1.15)	0.207
Model 2	1.00	0.98(0.70-1.38)	1.05(0.74-1.49)	0.99(0.71-1.40)	0.925
Model 3	1.00	1.02(0.72-1.45)	1.06(0.74-1.52)	1.02(0.72-1.46)	0.843
Modern dietary pattern					
Model 1	1.00	0.84(0.61-1.14)	0.91(0.67-1.24)	0.98(0.72-1.34)	0.943
Model 2	1.00	0.75(0.53-1.05)	0.93(0.66-1.32)	0.86(0.61-1.23)	0.692
Model 3	1.00	0.80(0.56-1.14)	0.98(0.69-1.40)	0.84(0.58-1.21)	0.583
Typical Australian dietary pattern					
Model 1	1.00	0.63(0.47-0.85) *	0.61(0.45-0.82) *	0.70(0.52-0.94) *	0.012
Model 2	1.00	0.58(0.42-0.82) *	0.63(0.45-0.88) *	0.66(0.47-0.93) *	0.021
Model 3	1.00	0.56(0.40-0.80) **	0.64(0.45-0.90) *	0.65(0.46-0.93) *	0.027
Partial least square					
Prudent dietary pattern					
Model 1	1.00	1.00(0.74-1.35)	0.83(0.61-1.13)	0.85(0.62-1.17)	0.186
Model 2	1.00	1.07(0.77-1.51)	0.88(0.62-1.25)	0.95(0.66-1.35)	0.526
Model 3	1.00	1.02(0.72-1.44)	0.80(0.56-1.16)	0.92(0.64-1.33)	0.415
Western dietary pattern					
Model 1	1.00	1.34(0.97-1.85)	1.30(0.93-1.80)	2.20(1.61-3.02) **	0.000
Model 2	1.00	1.18(0.83-1.70)	1.07(0.74-1.55)	1.52(1.05-2.18) *	0.044
Model 3	1.00	1.17(0.81-1.70)	1.08(0.74-1.58)	1.46(1.01-2.12) *	0.074
Typical Australian dietary pattern					
Model 1	1.00	0.72(0.53-0.98)	0.83(0.61-1.12)	0.70(0.51-0.97) *	0.071
Model 2	1.00	0.84(0.59-1.18)	1.07(0.76-1.50)	0.83(0.58-1.19)	0.603
Model 3	1.00	0.90(0.63-1.28)	1.09(0.77-1.55)	0.83(0.57-1.20)	0.560
Modern dietary pattern					
Model 1	1.00	0.77(0.56-1.04)	0.71(0.52-0.98)	0.88(0.62-1.26)	0.351
Model 2	1.00	0.85(0.60-1.20)	0.77(0.54-1.11)	0.83(0.56-1.25)	0.286
Model 3	1.00	0.82(0.58-1.18)	0.77(0.53-1.12)	0.81(0.53-1.22)	0.262

**P <0.05, **P<0.01, ***P <0.001*

Model 1 was adjusted for sex, age and total energy intake

Model 2 was additionally adjusted for marital status, educational status, employment status, income, Socio-Economic Indexes for Areas, alcohol risk, smoking status, physical activity and self-reported sleep quality

Model 3 was additionally adjusted for body mass index, bodily pain, hypertension, diabetes and cardiovascular disease

[a] *Multiple imputation was performed*

Supplementary Table 4.8 Associations of dietary patterns with incident depression (n = 1344)[a] in the Australian adults participating in the NWAHS

	Odds ratio (95% confidence interval)				
	Q1 (Reference)	Q2	Q3	Q4	Ptrend
Principal Component Analysis					
Prudent dietary pattern					
Model 1	1.00	0.67(0.42-1.09)	0.49(0.29-0.80) *	0.52(0.29-0.92) *	0.010
Model 2	1.00	0.86(0.51-1.45)	0.62(0.35-1.10)	0.75(0.39-1.47)	0.241
Model 3	1.00	0.90(0.52-1.56)	0.67(0.38-1.20)	0.75(0.38-1.48)	0.256
Western dietary pattern					
Model 1	1.00	1.29(0.78-2.13)	1.66(0.92-2.99)	3.07(1.56-6.06) **	0.002
Model 2	1.00	1.22(0.71-2.11)	1.48(0.79-2.76)	2.45(1.15-5.24) **	0.025
Model 3	1.00	1.20(0.68-2.10)	1.50(0.79-2.84)	2.44(1.11-5.37) **	0.029
Reduced rank regression					
Prudent dietary pattern					
Model 1	1.00	0.65(0.42-1.01)	0.72(0.46-1.12)	0.55(0.33-0.90) *	0.032
Model 2	1.00	0.80(0.50-1.28)	0.81(0.50-1.32)	0.71(0.42-1.22)	0.243
Model 3	1.00	0.85(0.53-1.37)	0.82(0.50-1.34)	0.73(0.42-1.25)	0.260
Western dietary pattern					
Model 1	1.00	0.76(0.48-1.19)	0.82(0.52-1.29)	0.78(0.49-1.23)	0.361
Model 2	1.00	0.89(0.54-1.46)	1.07(0.65-1.76)	0.92(0.55-1.52)	0.917
Model 3	1.00	0.92(0.55-1.53)	1.08(0.64-1.80)	0.93(0.56-1.55)	0.935
Modern dietary pattern					
Model 1	1.00	1.19(0.73-1.94)	0.93(0.58-1.49)	1.35(0.83-2.18)	0.379
Model 2	1.00	1.26(0.75-2.12)	0.95(0.57-1.58)	1.36(0.81-2.28)	0.436
Model 3	1.00	1.33(0.78-2.27)	1.03(0.61-1.72)	1.43(0.85-2.40)	0.340
Typical Australian dietary pattern					
Model 1	1.00	1.12(0.70-1.78)	1.05(0.65-1.71)	0.80(0.49-1.30)	0.392
Model 2	1.00	1.16(0.70-1.92)	1.08(0.63-1.83)	0.78(0.45-1.35)	0.400
Model 3	1.00	1.11(0.67-1.85)	1.07(0.62-1.82)	0.81(0.47-1.41)	0.498
Partial least square					
Prudent dietary pattern					
Model 1	1.00	0.85(0.52-1.37)	0.69(0.43-1.10)	0.78(0.47-1.29)	0.217
Model 2	1.00	0.91(0.54-1.53)	0.74(0.45-1.22)	0.83(0.49-1.43)	0.365
Model 3	1.00	0.86(0.50-1.45)	0.74(0.44-1.23)	0.85(0.49-1.47)	0.441
Western dietary pattern					
Model 1	1.00	1.36(0.82-2.26)	1.65(0.99-2.74)	2.47(1.46-4.18) **	0.001
Model 2	1.00	1.22(0.71-2.11)	1.42(0.81-2.46)	1.85(1.02-3.33) *	0.035
Model 3	1.00	1.24(0.71-2.16)	1.52(0.87-2.66)	1.84(1.01-3.36) *	0.034
Typical Australian dietary pattern					
Model 1	1.00	0.54(0.34-0.86) *	0.45(0.27-0.75) *	0.73(0.45-1.19)	0.113
Model 2	1.00	0.61(0.37-0.99) *	0.56(0.33-0.95) *	0.87(0.52-1.47)	0.464
Model 3	1.00	0.62(0.38-1.02)	0.56(0.33-0.95) *	0.87(0.51-1.47)	0.435
Modern dietary pattern					
Model 1	1.00	0.92(0.59-1.43)	0.64(0.40-1.02)	0.81(0.47-1.40)	0.190
Model 2	1.00	0.96(0.60-1.53)	0.61(0.37-1.01)	0.67(0.36-1.21)	0.065
Model 3	1.00	0.93(0.58-1.50)	0.62(0.37-1.05)	0.66(0.36-1.23)	0.076

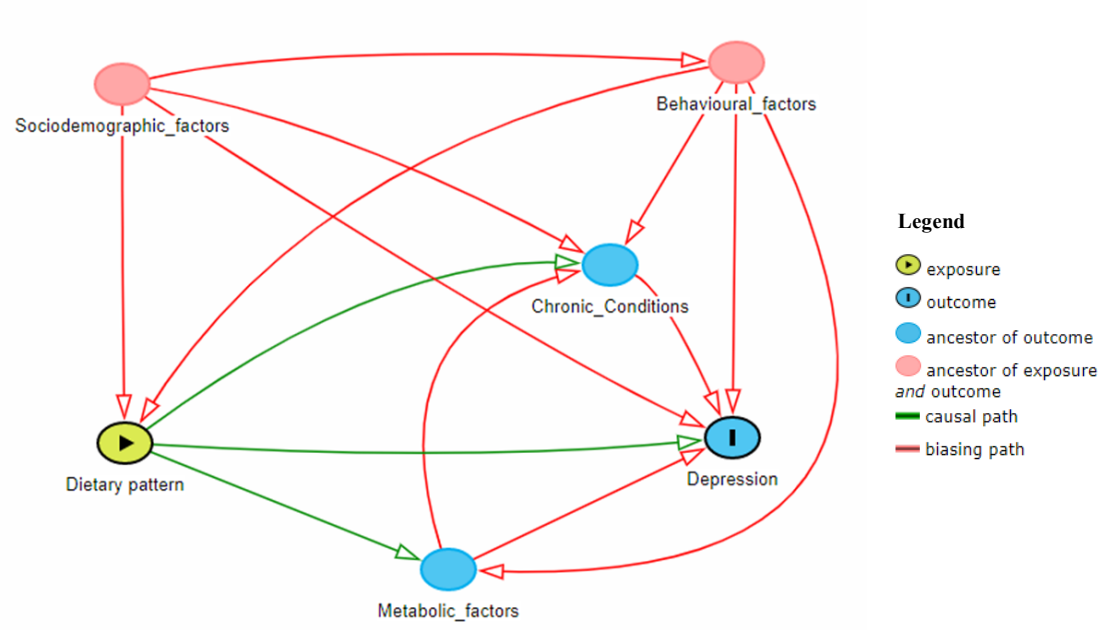
**P <0.05, **P<0.01, ***P <0.001*

Model 1 was adjusted for sex, age and total energy intake

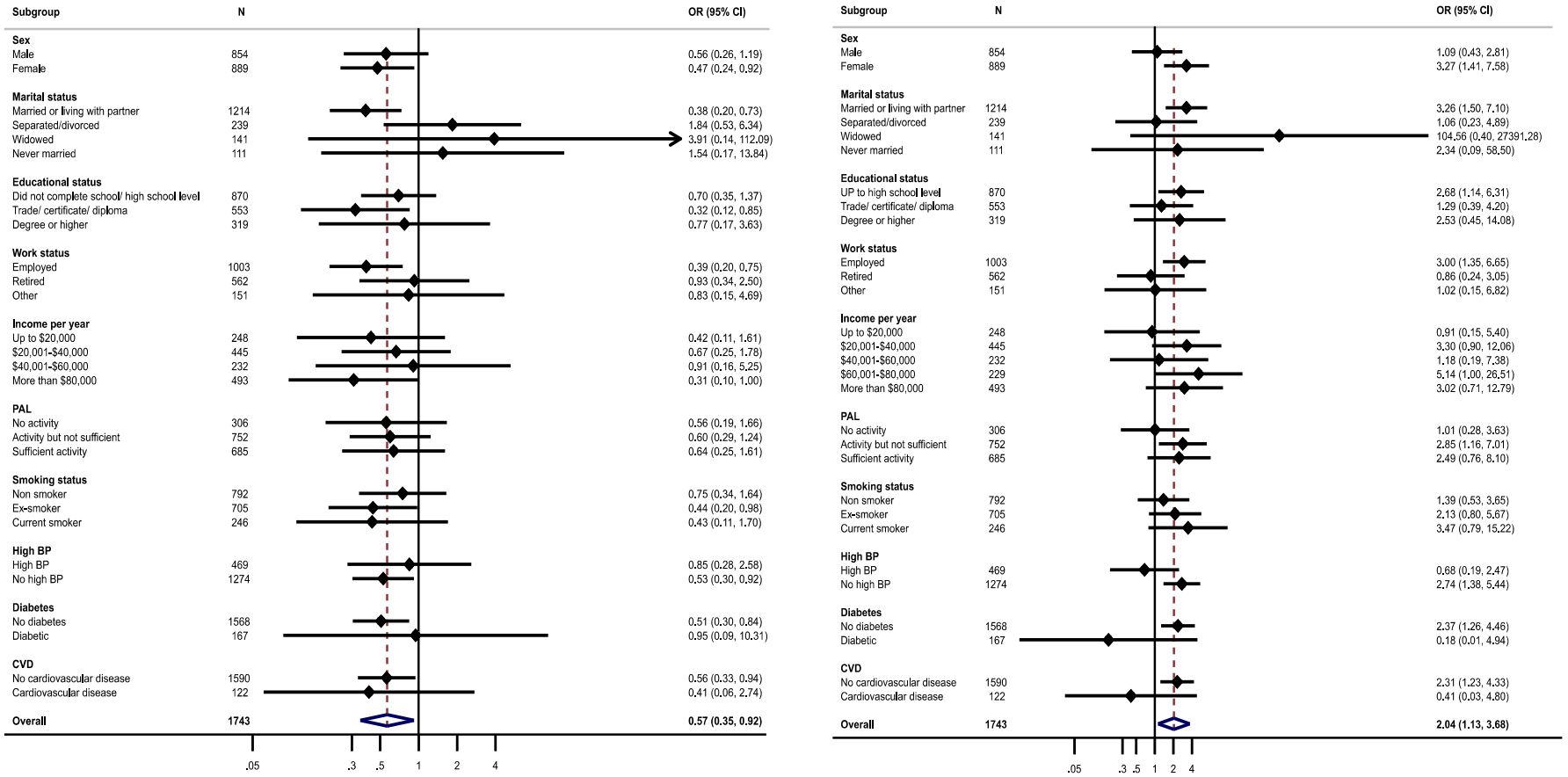
Model 2 was additionally adjusted for marital status, educational status, employment status, income, Socio-Economic Indexes for Areas, alcohol risk, smoking status, physical activity and self-reported sleep quality

Model 3 was additionally adjusted for body mass index, body pain, hypertension, diabetes and cardiovascular disease

[a]*Multiple imputations was performed*



Supplementary Figure 4.1 Directed Acyclic Graph for dietary pattern and DepS



Supplementary Figure 4.2. Subgroup analysis of the association of fourth quartiles (highest intake) of prudent (left) and Western (right) dietary patterns with depressive symptoms by PCA method, South Australia

The first quartile (lowest intake of prudent food pattern) was the reference. Poisson's regression was used to compute Odds ratio (OR).

Chapter 5: Nutrient patterns and depressive symptoms

Nutrient patterns and depressive symptoms among Australian adults

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5.1 PUBLICATION

This result chapter is reproduced in the exact form as it appears in the manuscript:

Shakya PR, Melaku YA, Page AJ, Gill TK. Nutrient patterns and depressive symptoms among Australian adults. Eur J Nutr. 2020. https://doi.org/10.1007/s00394-020-02243-y

In keeping with the style of this thesis, the tables and figures have been re-numbered, the references reformatted and incorporated into the thesis master reference list, and the manuscript repaginated.

5.2 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Nutrient patterns and depressive symptoms among Australian adults
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Shakya PR, Melaku YA, Page AJ, Gill TK. Nutrient patterns and depressive symptoms among Australian adults. Eur J Nutr. 2020. 10.1007/s00394-020-02243-y. (in press):00-000. Awaiting PMID: xxxxxx. Awaiting PMCID: PMCxxxxxxx.

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Name of Principal Author (Candidate)	Prem Raj Shakya		
Contribution to the Paper	Conception and design, statistical analysis, interpretation of data, manuscript preparation, contribution to the materials/analysis tools, critical revision and editing of the manuscript		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	15/06/20

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Supervised the development of the work, conception and design, interpretation of results, contribution to the materials/analysis tools, interpretation of results and critical revision of the manuscript and approved the final version for publication		
Signature		Date	15/6/20

5.3 ABSTRACT

Purpose

Much of the current literature on the associations between diet and depression focus on single nutrients, rather than nutrient patterns (NPs). We investigated the association between NPs and depressive symptoms (DepS) in an Australian adult population.

Methods

DepS were examined at two different time points, in 2010 (Stage 3, *n* = 1743, 49.0% males) and 2015 [North West (NW15), *n* = 1,024, 46.6% males] of the NWAHS. Dietary habits were evaluated using a food frequency questionnaire (FFQ) at Stage 3. DepS were assessed using the Center for Epidemiological Studies-Depression (CES-D) scale at Stage 3 and NW15. Principal component analysis was used to identify NPs as well as the factor structure of the CES-D. Log- and negative-binomial regression analyses were used to assess the association between NPs and DepS scores. Ordinal logistic regression analysis was undertaken between the NPs and factor structure of the CES-D score.

Results

Three NPs (from the FFQ) and two-factors (from CES-D score) were obtained. After adjusting for known confounding variables, a 'plant-sourced' NP (β-carotene, fibre, VC, potassium and α-carotene) was inversely associated with DepS at Stage 3 [Prevalence ratio $(PR)_{Q4VsQ1}$, 0.78; 95% CI, 0.66-0.92; p = 0.003] whereas an 'animal-sourced' (ω-3 PUFA, MUFA, VE and cholesterol) or 'mixed-source' [phosphorous, protein, vitamin B2, iodine and zinc] NP was not associated with DepS. There was an

inverse relationship between the ‘plant-sourced’ NP and the ‘(absence of) positive-affect’ factor from the CES-D in both stages.

Conclusions

The ‘plant-sourced’ NP is consistently and inversely associated with DepS; however, longitudinal studies are recommended to confirm these results.

Keywords

Nutrient patterns, Depressive symptoms, Principal component analysis, CES-D factor structure

INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder and has the largest share of the world's burden of disease in terms of disability, mortality and healthcare costs. According to the Global Burden of Disease (GBD) 2017 estimates, MDD is ranked as the third contributor to year lived with disability (YLD) after low back pain and headache disorders [412]. The WHO reported that 322 million people suffered from depression globally, with a prevalence of 4.4% (5.1% in females and 3.6% in males) in 2015 [413]. In Australia, the prevalence of MDD was 3.4% in 2015, 3.3% in 2016 and 3.3% in 2017 [383]. Depression is a complex multifactorial disorder, where the risk factors from multiple domains are related and interact with each other [146]. In addition to genetic, biological, and environmental risk factors, diet has been suggested to be associated with depression [43].

Evidence indicates that individual nutrients may play a role in reducing depressive symptoms (DepS). For example, ω-3 fatty acids [277, 414, 415], total carotenoids [416], beta-carotene [27], vitamin C [28], potassium [32], magnesium [33, 305], and zinc [33, 305, 417] have been shown to reduce DepS. However, in recent years, there is an increasing interest in determining the combined effect of the whole diet and the nutrients that are consumed on depression [79]. Previous observational studies have mainly focussed on the association between dietary patterns and depression based upon food groups rather than nutrients as summarised in various systematic reviews and meta-analyses [43, 46, 234, 235].

Dietary patterns based upon food groups provide an improved general understanding about the connections between diet and disease [42] and might predict chronic disease risk with improved accuracy rather than examining individual foods [62], however, the underlying mechanisms are difficult to ascertain using this method.

Nutrient patterns (NPs), sometimes referred to as nutrient-based dietary patterns, may provide more realistic data on the possible biological mechanisms linking diet and depression [64]. Furthermore, compared to dietary patterns, nutrients are functionally non-exchangeable with the same nutrients consumed across populations. This should facilitate the use and generalizability of the NP approach across populations [63], whereas, dietary patterns may be affected by social, cultural and geographical scenarios [74]. However, it should be noted that challenges exist to translate findings from NP analysis and providing advice on nutrient intakes based on this analysis despite NPs are more comprehensive than studying individual nutrients in association with disease outcomes. Supplementing NP with dietary pattern is imperative to tackle this challenge. Related to this, we have previously published a study on dietary patterns and DepS in the same study population as that presented here [418].

Existing studies investigating the combination of nutrients, have focused on cancer patients [66-69], bone mineral density [70-73], obesity [74, 75], metabolic syndrome [77], brain and cognitive health [78, 364] and inflammation [76]. Only one study has assessed the association of NPs with psychological disorders, including depression [79]. However, the study did not explore the association between NPs and depression by focusing on identifying specific DepS that could plausibly be associated with NPs. To the best of our knowledge, this is the first study which aims to investigate the association between NPs and DepS in the Australian adult population, providing insight into the possible relationship between specific nutrients and DepS.

METHODS

5.3.1 STUDY DESIGN AND PARTICIPANTS

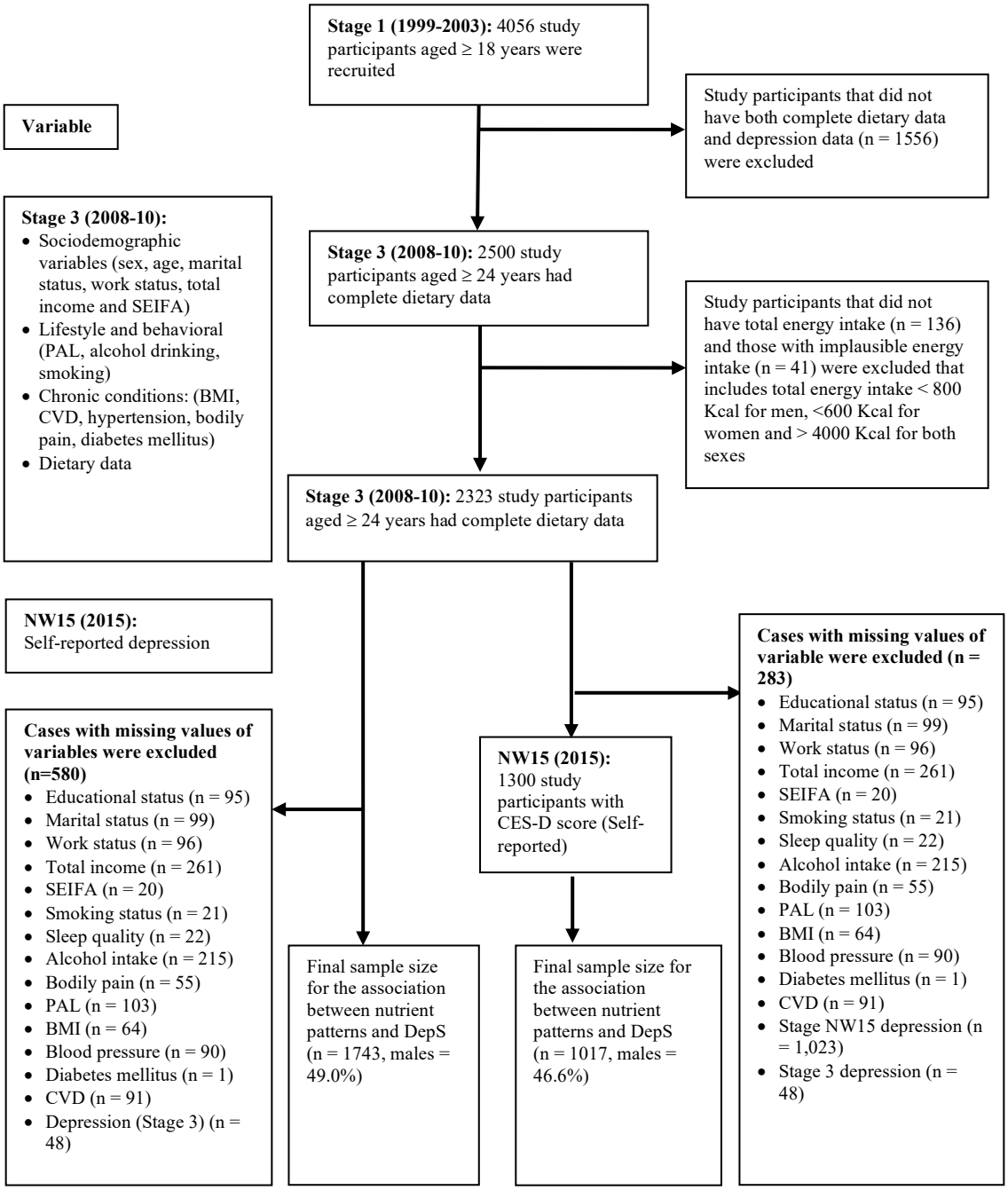
The current study utilised data from the North West Adelaide Health Study (NWAHS), which is a longitudinal cohort that recruited study participants from the northern and western suburbs of Adelaide, South Australia. Three clinic-based stages of data collection have been conducted: 1999–2003, 2004–2006, and 2008–2010. Data were collected using self-completed questionnaires, computer-assisted telephone interviews and the clinical assessments. In addition, a self-complete survey (postal or online) was conducted in 2015 (NW15).

The details of this cohort are published elsewhere [375]. In brief, the eligible study participants were adults aged 18 years and over when first recruited in Stage 1 from households with a landline that were randomly selected from the electronic White Pages®. At Stage 1, a total of 4056 participants were initially enrolled. Data from Stage 3 and NW15 were used in this study. Dietary data were collected as part of Stage 3. In NW15, the point prevalence for the CES-D was determined. Dietary data were only available at Stage 3 and thus used these data to examine associations with DepS at the two-time points. Participants with missing data were excluded and full data sets were used. A summary of the stages is presented in *Figure 5.1*. Ethical approval for each stage of the NWAHS project was obtained from the Human Ethics Research Committee, Queen Elizabeth Hospital, South Australia. All participants provided written informed consent.

5.3.2 MEASURES OF DEPS AT STAGE 3 AND NW15

DepS were measured by the Center for Epidemiologic Studies Depression Scale (CES-D) [133]. This screening instrument is widely used to assess DepS frequency using

20 items [133, 419, 420]. Participants indicated how much of the time during the past week they experienced each symptom on a 4-point scale [rarely or none of the time (0), some or little of the time (1), occasionally or moderate amount of the time (2) and most or all of the time (3)] allowing a maximum score of 60, with higher scores reflecting more significant DepS. Radloff et al. suggested a cut-off score of 16, indicating further clinical evaluation for depression was required [133].



***BMI**: body mass index; **CES-D**: Center for Epidemiological Studies-Depression; **CVD:** cardiovascular disease; **DepS**: Depressive symptoms; **PAL**: physical activity level; **SEIFA**: socio-economic index for Area*

Figure 5.1. Flowchart of participants included in the study design in the NWAHS, South Australia

5.3.3 DIETARY AND NUTRIENT INTAKE ASSESSMENTS AT STAGE 3

Dietary intake was assessed using the validated Dietary Questionnaire for Epidemiological Studies Version 3 (DQESV3), which is a revision of the Food Frequency Questionnaire (FFQ) developed by Cancer Council Victoria [421]. The details

of the questionnaire have been published elsewhere [422]. In short, the semi-quantitative DQESV3 is categorised into three parts: 1) a series of question about the quantity and type of commonly consumed items which are used to provide additional detail for some of the 74 food frequency items; 2) questions based on a series of portion size photos for different food types used to scale intake data; 3) a list of 74 food or beverage items categorized under 'cereal foods, sweets and snacks' (21 items), 'daily products, meat and fish' (15 items), 'fruit' (13 items) and 'vegetables including fresh, frozen and tinned' (25 items) with ten frequency responses ranging from 'never' to '3 or more times per day', followed by three additional questions to quantify intake of alcoholic beverages, over the previous 12 months. The completed DQESV3 forms were sent to Cancer Council Victoria for the calculation of total daily intake of food items and nutrients. Estimated total daily intakes of foods/nutrients were computed using Australian NUTTAB95 (Australian Government Publishing Service, Canberra) food composition database [377]. Nutrients from each food item were categorised into thirty-one nutrient groups which were as follows: phosphorous, protein, vitamin B2, iodine, zinc, vitamin B3, saturated fat, calcium, sodium, vitamin B12, retinol, iron, cholesterol, starch and dextrin, vitamin B1, vitamin D, vitamin B7, folic acid, β-carotene, fibre, vitamin C, potassium, α-carotene, lutein and zeaxanthin (LZ), magnesium, lycopene, vitamin B6, ω-3 fatty acid, ω-6 fatty acid, monounsaturated acid (MUFA) and vitamin E.

5.3.4 COVARIATES ASSESSMENT AT STAGE 3

We identified potential confounders (socio-demographic, behaviours, metabolic and chronic conditions) which may have a link with diet and depression. These were included in the multivariable models. The Socio-Economic Index For Areas (SEIFA), an index developed by the Australian Bureau of Statistics (ABS) that ranks areas in Australia according to relative socio-economic advantage and disadvantage based on

Census collection districts, was calculated as an indicator of socio-economic status [387]. Marital status was categorised into married or living together with a partner, separated/divorced, widowed and never married. Annual household income was categorised as follows: up to $20,000, $20,001–$40,000, $40,001–$60,000, $60,001-$80,000 and more than $80,000.

The Active Australia questions were used to assess leisure-time physical activity level (PAL) [390]. PAL was assessed considering the number of times a person exercised in the previous week and the total amount of time spent walking for exercise and performing moderate and vigorous exercise. Responses were categorised into three categories: 'no activity', 'activity but not sufficient' and 'sufficient activity', with sufficient activity defined as at least 150 minutes of activity in the week with the time spent undertaking vigorous activity doubled to account for its higher intensity. Sleep quality was assessed by a self-reported questionnaire and categorised as 'very good', 'fairly good', 'fairly bad' and 'very bad'. Smoking status was classified as non-smokers, ex-smokers and current smokers. Alcohol risk was calculated based on the 1989 National Heart Foundation Risk Factor Prevalence study classification formulae [388]. Respondents were categorised as non-drinkers, no risk drinkers, low-risk drinkers, intermediate-risk drinkers, high-risk drinkers and very high-risk drinkers. These categories were further collapsed into non-drinkers or no risk drinkers; low risk; and intermediate to very high risk for analysis.

Metabolic factors and chronic conditions included in this analysis were diabetes, hypertension, cardiovascular disease (CVD), as well as body mass index (BMI) [423]. Standard protocols were followed to measure height and weight. The measured height and weight were converted into BMI, which was further classified into underweight, normal weight, overweight and obese categories if BMI was < 18.5 kg/m^2, 18.5-24.9

kg/m^2, 25-29.9 kg/m^2, > 30 kg/m^2 respectively based on the WHO classification [389]. Identification of participants with diabetes was either by clinician-diagnosed self-report and/or laboratory diagnosis using blood samples collected during the clinic visit, with diabetes defined as fasting plasma glucose ≥ 7.0 mmol/L. Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated and relaxed for at least 5 min before the measurement. Diagnosis of hypertension (high blood pressure) was made taking account of both systolic (>140 mmHg) and diastolic (> 90 mmHg) blood pressure. Data on self-reported doctor-diagnosed CVD was collected. Data on bodily pain was collected based on the Short Form (SF) 36 Health Survey questionnaire [391]. Participants were asked to rate the severity of bodily pain (from none to very severe) they had experienced in the last four weeks. They were then asked about the extent of interference in their usual work routine that could be attributed to the pain.

5.3.5 IDENTIFICATION OF NPS

NPs were identified by principal component analysis (PCA) using the 31 nutrient groups determined from all measured nutrients. Varimax rotation was used to improve interpretability, reduce the correlation between the factors and to attain optimal structure. Eigenvalues > 1, scree plots and interpretability were used to determine and retain factors. Factor loadings of each nutrient were calculated within each factor. For each participant, factor scores were computed by summing the products of factor loading coefficients and standardising it by the daily intake of each nutrient. The nomenclature of NP was based upon the nutrient groups with the higher loading on each of the factors. In addition, Pearson's correlation coefficient was determined between the continuous factors of each NP and the 39 food groups obtained in the same data.

5.3.6 IDENTIFICATION OF CES-D FACTOR STRUCTURE AT STAGE 3 AND NW15

CES-D factor structures were identified by a PCA technique using the 20 items of the CES-D questionnaire. A similar analysis to that undertaken for NPs was conducted, in order to retain the factor structures.

5.3.7 DATA ANALYSES AT STAGE 3 AND NW15

Data were summarized using means and standard deviations (for continuous normally distributed variables), medians and interquartile ranges (for continuous non-normally distributed variables) and proportions (for categorical variables). The chi-square test was used to compare the difference between categorical variables, and ANOVA was used to compare differences in continuous variables. The Kruskal Wallis test was used for variables which were continuous but not normally distributed. Factor scores of NPs and depression patterns were categorised into quartiles [Q1 (lowest), Q2, Q3 and Q4 (highest)].

To determine the association between NPs and DepS, three approaches were undertaken depending on the nature of the outcome variable. Log-binomial regression was used in the model where DepS determined from the CES-D was a binary outcome variable. Negative binomial regression was used when DepS were a count variable which was over-dispersed. Ordinal logistic regression analysis was used to determine the association between quartiles of both NPs and CES-D factor structure. Results are reported in odds ratio (OR) for log-binomial and ordinal logistic regression and prevalence ratio (PR) for negative binomial regression models.

Two analyses were performed: 1) dietary data, covariates and DepS were used from Stage 3; 2) In the second analysis, the outcome variable (DepS) was used from

NW15. The first model was adjusted for age, sex and total energy intake; the second model was further adjusted for educational status, marital status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL, self-reported sleep quality, BMI, bodily pain, hypertension, diabetes and CVD in addition to the variables included in the first model. Further, in the second model using DepS from NW15, a continuous score obtained from the Stage 3 depression score was added as a covariate, as an indicator of baseline depression in the first two approaches, i.e. log- and negative binomial regression, however, this covariate was not adjusted for in the ordinal logistic regression approach. The trend of associations, as a continuous parameter, was assessed across the quartiles of NPs. Subgroup analyses (sex, educational status, work status, income status, PAL, smoking status, hypertension, diabetes and CVD) were performed using the fully adjusted log-binomial model to assess the association of NPs with DepS in various subgroups of the study participants. All the analyses were performed using STATA/SE version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

The total number of participants in Stage 3 who had complete dietary data from DQESV3 was 2500, 7.1% (n = 177) participants were excluded as either they did not have data on total energy intake, or the energy intake was implausible (outside of the normal range)[1,2,*]. Among the remaining 2323 study participants with complete dietary data, 30.0% (n = 580) had at least one missing value for the covariates. A high proportion of missing values were observed in the following variables: total income (11.2%, n = 261),

[1] Banna JC, McCrory MA, Fialkowski MK, Boushey C. Examining Plausibility of Self-Reported Energy Intake Data: Considerations for Method Selection. Front Nutr. 2017. 4:45.
[2] Willett W. Nutritional epidemiology. Oxford, United Kingdom: Oxford University Press 1998.
* In our study, we excluded the participants with total energy intake < 800 Kcal for men, <600 Kcal for women and > 4000 Kcal for both sexes

alcohol intake (9.2%, n = 215), PAL (4.4%, n = 103), marital status (4.3%, n = 99), work status (4.1%, n=96), educational status (4.1%, n = 95), CVD (3.9%, n = 91) and blood pressure (3.9%, n = 90). Similarly, of the 1300 study participants included from NW15 who had complete self-reported CES-D score, 21.8% (n = 283) had at least one missing value of the covariates, and a high proportion of the missing values were from variables such as total income and alcohol intake (*Figure 5.1*). The detailed baseline characteristics of missing values are presented in Supplementary Table 5.1. The total number of included participants for the log-and negative binomial models were: Stage 3; n = 1,743 and Stage NW15; n = 1,017 and for ordinal logistic regression: Stage 3; n = 1,525 and Stage NW15; n = 891.

Table 5.1 Characteristics of study participants according to sex in Stage 3 [2008-10; *n* = 1,743] of the adult Australian in NWAHS

	Male (*n*=854)	**Female (*n*=889)**	**Total (*n*=2.323)**	**P-value**
Age, Mean (SD)	57.1 (13.9)	56.1 (13.3)	56.6 (13.6)	0.14
Educational status (n %)				
Did not complete school/ high school level	342 (40.0)	528 (59.4)	870 (49.9)	<0.001
Trade/ certificate/ diploma	354 (41.5)	200 (22.5)	554 (31.8)	
Degree or higher	158 (18.5)	161 (18.1)	319 (18.3)	
Marital status (n %)				
Married or living with partner	632 (74.0)	582 (65.5)	1,214 (69.7)	<0.001
Separated/divorced	107 (12.5)	132 (14.8)	239 (13.7)	
Widowed	46 (5.4)	105 (11.8)	151 (8.7)	
Never married	69 (8.1)	70 (7.9)	139 (8.0)	
Work status[a] (n %)				
Employed	525 (61.5)	478 (53.8)	1,003 (57.5)	<0.001
Unemployed	10 (1.2)	13 (1.5)	23 (1.3)	
Retired	278 (32.6)	284 (31.9)	562 (32.2)	
Other	41 (4.8)	114 (12.8)	155 (8.9)	
Income per year[a] (n %)				
Up to $20,000	105 (12.3)	143 (16.1)	248 (14.2)	0.012
$20,001-$40,000	203 (23.8)	246 (27.7)	449 (25.8)	
$40,001-$60,000	153 (17.9)	150 (16.9)	303 (17.4)	
$60,001-$80,000	123 (14.4)	122 (13.7)	245 (14.1)	
More than $80,000	270 (31.6)	228 (25.6)	498 (28.6)	
SEIFA[a] (n %)				
Lowest quintile	202 (23.7)	241 (27.1)	443 (25.4)	0.56
Low quintile	212 (24.8)	218 (24.5)	430 (24.7)	
Middle quintile	191 (22.4)	187 (21.0)	378 (21.7)	
High quintile	193 (22.6)	190 (21.4)	383 (22.0)	
Highest quintile	56 (6.6)	53 (6.0)	109 (6.3)	
Smoking status[a] (n %)				
Non-smoker	351 (41.1)	441 (49.6)	792 (45.4)	<0.001
Ex-smoker	380 (44.5)	325 (36.6)	705 (40.4)	
Current smoker	123 (14.4)	123 (13.8)	246 (14.1)	
Sleep quality[a] (n %)				
Very good	160 (18.7)	159 (17.9)	319 (18.3)	0.12
Fairly good	518 (60.7)	505 (56.8)	1,023 (58.7)	
Fairly bad	150 (17.6)	197 (22.2)	347 (19.9)	
Very bad	26 (3.0)	28 (3.1)	54 (3.1)	

(table continues)

Table 5.1 *(table continued)*

Characteristics of study participants according to sex in Stage 3 [2008-10; *n* = 1,743] of the adult Australian in NWAHS

	Male (*n*=854)	Female (*n*=889)	Total (*n*=2.323)	P-value
Alcohol risk[a] (n %)				
Non-drinkers, no risk	693 (81.1)	240 (27.0)	933 (53.5)	<0.001
Low risk	113 (13.2)	607 (68.3)	720 (41.3)	
Intermediate to very high risk	48 (5.6)	42 (4.7)	90 (5.2)	
PAL[a] (n %)				
No activity	146 (17.1)	160 (18.0)	306 (17.6)	0.65
Activity but not sufficient	363 (42.5)	389 (43.8)	752 (43.1)	
Sufficient activity	345 (40.4)	340 (38.2)	685 (39.3)	
BMI[a] (n %)				
Normal_underweight	164 (19.2)	279 (31.4)	443 (25.4)	<0.001
Overweight	398 (46.6)	304 (34.2)	702 (40.3)	
Obese	292 (34.2)	306 (34.4)	598 (34.3)	
Bodily pain[a] (n %)				
No	393 (46.0)	444 (49.9)	837 (48.0)	0.1
Yes	461 (54.0)	445 (50.1)	906 (52.0)	
BP[a] (n %)				
High BP	258 (30.2)	211 (23.7)	469 (26.9)	0.002
No high BP	596 (69.8)	678 (76.3)	1,274 (73.1)	
Diabetes[a] (n %)				
No diabetes	745 (87.2)	823 (92.6)	1,568 (90.0)	<0.001
Diabetes	109 (12.8)	66 (7.4)	175 (10.0)	
CVD[a] (n %)				
No CVD	752 (88.1)	838 (94.3)	1,590 (91.2)	<0.001
CVD (inc TIA)	102 (11.9)	51 (5.7)	153 (8.8)	
Depression (Stage 3)[a] (n %)				
No depressive symptoms	733 (85.8)	715 (80.4)	1,448 (83.1)	0.003
Depressive symptoms	121 (14.2)	174 (19.6)	295 (16.9)	
Energy (kcal/day)[b]				
Mean (SD)	2175 (587)	1956 (546)	2063 (577)	<0.001
Scores for Animal NP[b] Mean (SD)	0.12 (0.97)	-0.16 (0.93)	-0.02 (0.96)	<0.001
Scores for Plant NP[b] Mean (SD)	-0.05 (1.01)	0.10 (0.99)	0.02 (1.00)	0.002
Scores for Mixed NP[b], Mean (SD)	0.19 (1.01)	-0.10 (0.93)	0.04 (0.98)	<0.001

BMI body mass index*; BP* blood pressure*; CVD* cardiovascular disease*; PAL* physical activity level*; SEIFA* socio-economic index for areas*; TIA* transient ischaemic attack

[a]*Pearson's chi-squared test;*

[b]*Two sample t-test*

5.3.8 SOCIODEMOGRAPHIC CHARACTERISTICS

The characteristics of the participants stratified by sex are illustrated in Table 5.1. The mean age (SD) of male (n = 854) and female (n = 889) participants at Stage 3 was 57.1 (13.9) years and 56.1 (13.3) years respectively. The majority of participants rated their sleep as fairly good (58.4%, n=1,356). Alcohol risk, after combining low, intermediate to high risk, was higher in females (72%, n = 649) than male (18.8%, n = 161). Overall, 82.4% of participants undertook some physical activity; however, only 39.3% of participants had sufficient physical activity to provide a health benefit. More than two-thirds of the participants (74.6%, n = 1300) were overweight or obese. The overall prevalence of DepS was 16.9% (n = 295) [Males, 14.2% (n = 121); Females

19.6% (n = 174)] (Table 5.1). Anthropometric, socioeconomic and clinical characteristics based on the quartiles of the NPs are shown in Supplementary table 5.2, 5.3 and 5.4.

5.3.9 NUTRIENT PATTERNS (NPS)

Figure 5.2 represents the three identified NPs among the 2323 participants who provided valid FFQ data. For the NP analysis, three primary factors were retained from the PCA. Among the identified NPs, the high positive loadings indicate strong associations between the nutrients and patterns, whereas negative loadings indicate negative associations with the pattern. The 'mixed-source' NP was characterised by a high intake of phosphorus, protein, vitamin B2, iodine, zinc, vitamin B3, saturated (SFA), calcium, vitamin B12, vitamin A, iron, cholesterol, potassium, starch and dextrin, vitamin B1, vitamin D, vitamin B7 and magnesium. The 'plant-sourced' NP represented a high intake of β-carotene, fibre, vitamin C, potassium, α–carotene, lutein and zeaxanthin (LZ), iron and magnesium. The 'animal-sourced' NP was characterised by a high intake of polyunsaturated fatty acid (PUFA) containing ω-3 PUFA and ω-6 fatty acid, MUFA and vitamin E. These NPs accounted for 29.5%, 18.5% and 12.2% of the variance in nutrient intake respectively and accounted for 60.2% of the total variance. Nutrient intake across quartiles for each NPs are presented in Supplementary Table 5, 6, 7. Overall, mean (SD) energy intake was 2063.1 (SD 577) kcal/day and varied significantly across the quartiles of the NPs. Across quartiles of the plant-sourced pattern, higher consumption of fibre, VC, magnesium, potassium, β-carotene, α-carotene, lycopene and LZ ($p < 0.001$) and lower consumption of cholesterol and iodine were observed.

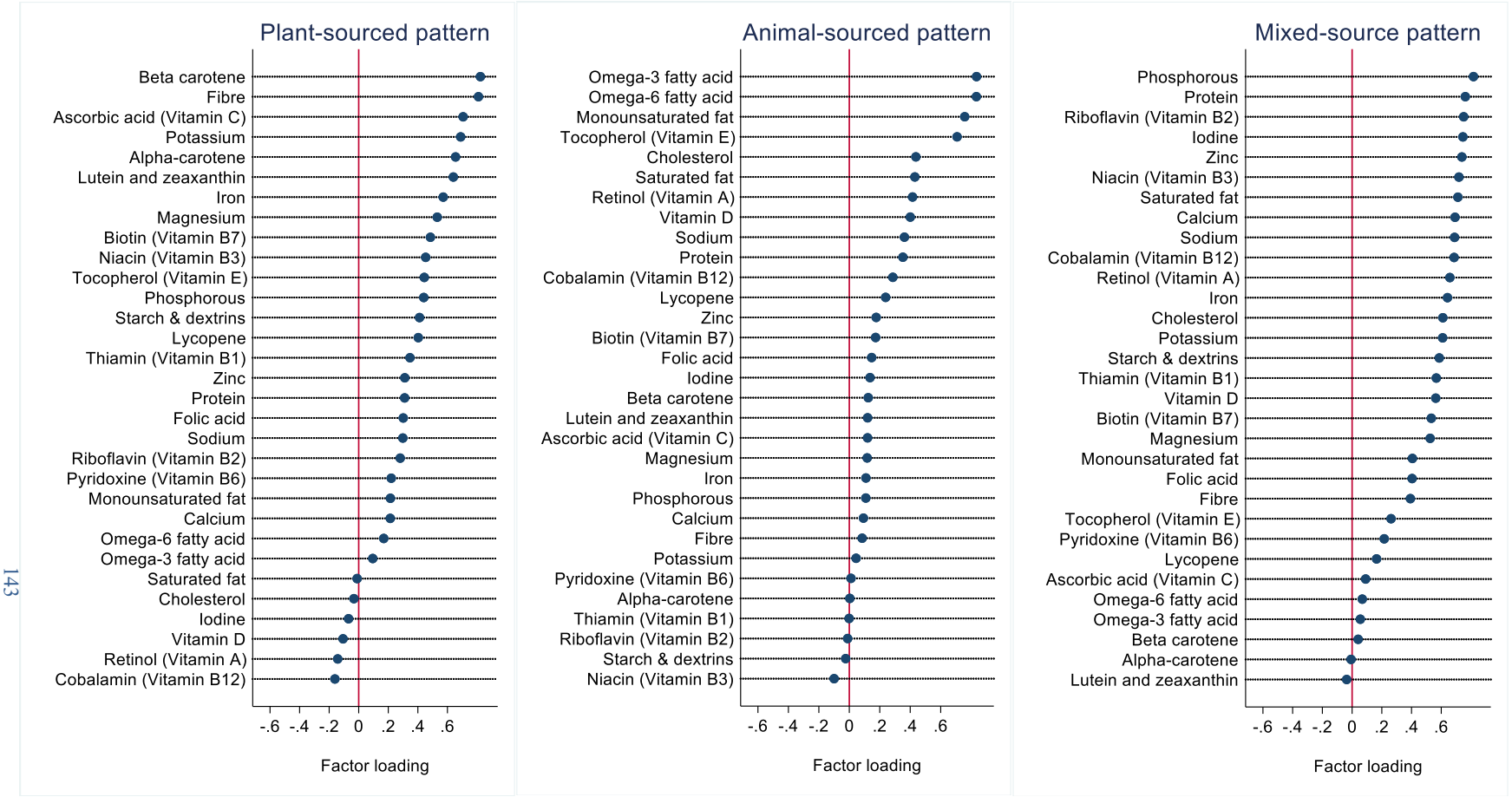


Figure 5.2. Factor loading of nutrient patterns according to factor analysis among NWAHS participants

5.3.10 CORRELATION WITH FOOD SOURCES OF EACH NUTRIENT PATTERNS AT STAGE 3

The Pearson's correlation coefficient was determined between the continuous factors of each NP and the 39 food groups obtained from the same data. The results are shown in Supplementary Table 5.8 and demonstrate that, for the 'plant-sourced' NP, a very strong correlation was observed with fruity vegetables (r = 0.69), a moderate correlation with root vegetables (r = 0.61), a fair correlation with leafy vegetables (r = 0.53), cabbages (r = 0.52), other fruits (r = 0.50) and stalk vegetables (r = 0.42). In addition, potential sources of fatty acids were checked through the correlation between MUFA, ω-3 fatty acid, ω-6 fatty acid, saturated fat, Vitamin E and NPs (Supplementary table 5.9) which identified the sources of this fatty acids comes from both animal and plant sources.

5.3.11 EXPLAINED VARIATIONS OF CES-D FACTOR STRUCTURE AT STAGE 3 AND NW15

Table 5.2 represents the two identified CES-D factor structures. The first factor was named the 'depressed-affect' and characterised by 'felt depressed', 'everything an effort', 'could not get going', 'bothered by things' and 'felt sad'. The second factor, '(absence of) positive-affect', is characterised by a low score for items such as 'hopeful about future', 'feel as good as other', 'feel happy' and 'enjoy life'. These CES-D factor structures accounted for 28.7% and 19.4% respectively of the variance in item score in Stage 3 (48.0% of the total variance) and 29.9% and 16.7%, respectively in NW15 (46.7% of the total variance).

Table 5.2 Factor loadings among CES-D factor structure in Stage 3 (2008-10; *n* =1937) and Stage NW15 (2015; *n* =1,115) in the Australian adults participating in the NWAHS

Loadings higher than 0.57 are typed in bold

	Depressed affect		(Absence of) Positive-affect	
Items	Stage 3	Stage NW15	Stage 3	Stage NW15
Felt depressed	0.69	0.67	0.49	0.39
Everything an effort	0.68	0.53	0.35	0.24
Could not get going	0.66	0.54	0.27	0.18
Bothered by things	0.65	0.66	0.20	0.11
Felt sad	0.65	0.69	0.46	0.37
Cannot keep mind on tasks	0.62	-0.61	-0.01	-0.37
Could not shake blues	0.61	0.60	0.44	0.36
Felt fearful	0.61	0.58	0.29	0.19
Restless sleep	0.58	0.51	0.02	0.01
Talked less than usual	0.57	0.64	0.33	0.24
Felt lonely	0.54	0.56	0.48	0.39
Life is a failure	0.50	0.72	0.52	0.40
Appetite poor	0.47	0.61	0.10	0.03
Crying spells	0.46	0.41	0.31	0.22
People dislike me	0.45	0.66	0.36	0.35
People were unfriendly	0.38	0.44	0.25	0.15
Did not enjoy life	0.46	0.12	0.67	0.65
Did not feel happy	0.44	0.39	0.69	0.72
Did not feel as good as other	-0.01	0.39	0.72	0.73
Not hopeful about future	0.09	0.06	0.75	0.80
Variance (%)	28.7	29.9	19.4	16.7
Cumulative variance (%)	28.7	29.9	48	46.7

5.3.12 ASSOCIATION BETWEEN NPS AND DEPS (STAGE 3 AND NW15)

In the fully adjusted model, log-binomial regression analysis showed that there was an inverse association between the plant-sourced NP and DepS at both Stage 3 and NW15 (Table 5.3). There was a 24% (OR_{Q4vsQ1} = 0.76; 95% CI: 0.48-1.20) and a 37% (OR_{Q4vsQ1} = 0.63; 95% CI: 0.34-1.17) reduction in odds of DepS among participants in the fourth quartile compared to those in the first quartile at Stages 3 and NW15, respectively.

The negative binomial regression showed that there was a significant inverse association between the plant-sourced NP and CES-D score (PR_{Q4vsQ1}, 0.78; 95% CI, 0.66-0.92; p = 0.006) in Stage 3. In NW15, this inverse association was also observed,

but it was not statistically significant (PR_{Q4vsQ1}, 0.89; 95% CI, 0.71-1.10; p = 0.290). No consistent associations were observed between animal- and mixed sourced NP and DepS, either at Stage 3 or NW15 (Table 5.3).

The results of ordinal logistic regression analysis for the association between quartiles of NPs and the CES-D factors showed a reduction in '(absence of) positive-affect' with higher consumption of plant-sourced NP (Supplementary Table 5.10).

5.3.13 SENSITIVITY AND SUBGROUP ANALYSES

As part of a sensitivity analysis, in our final model, we checked the association between DepS and NPs after including familial status as this could be associated with depression, however, the inclusion of this covariate had little impact on the results (Appendix D). We also checked the association after multiple imputations for the missing data. However, it showed minimal differences in the estimates of the associations between NPs and DepS (Appendix E). A significant interaction between NPs and other covariates in predicting depression was not observed. Results of the subgroup analyses for each derived NPs for various parameters (sex, educational status, marital status, work status, income status, PAL, smoking status, hypertension, diabetes and CVD) are presented in *Supplementary Figure 5.1*.

Table 5.3 Associations of nutrient pattern with depression score and prevalent depression at Stage 3 (2008-10; *n*=1,743) and Stage NW15 (2015; *n*=1,017) in the Australian adults participating in the NWAHS

	PR (95% confidence interval)[a]					OR (95% confidence interval)[b]			
	Q1 (Reference)	Q2	Q3	Q4 (Highest)	P for trend	Q2	Q3	Q4 (Highest)	P for trend
Stage 3									
Plant-sourced nutrient pattern									
Model 1	1.00	0.75(0.65-0.87) ***	0.77(0.66-0.89) ***	0.66(0.57-0.77) ***	0.000	0.68(0.47-0.96) **	0.70(0.49-1.00) *	0.54(0.37-0.79) ***	0.004
Model 2	1.00	0.88(0.76-1.02) *	0.89(0.77-1.04)	0.78(0.66-0.92) **	0.006	0.85(0.57-1.29)	0.95(0.62-1.44)	0.76(0.48-1.20)	0.342
Animal-sourced nutrient pattern									
Model 1	1.00	0.91(0.79-1.05)	1.03(0.89-1.19)	1.05(0.90-1.23)	0.312	0.78(0.53-1.13)	1.10(0.77-1.57)	1.12(0.77-1.64)	0.289
Model 2	1.00	0.97(0.84-1.13)	1.04(0.90-1.21)	1.04(0.89-1.22)	0.478	0.81(0.53-1.25)	1.13(0.75-1.71)	1.00(0.64-1.56)	0.653
Mixed-sourced nutrient pattern									
Model 1	1.00	1.07(0.92-1.24)	0.97(0.83-1.13)	1.11(0.91-1.34)	0.613	1.03(0.71-1.48)	0.76(0.51-1.15)	0.93(0.57-1.52)	0.449
Model 2	1.00	1.09(0.94-1.27)	0.96(0.81-1.13)	1.05(0.86-1.28)	0.949	1.04(0.67-1.60)	0.73(0.45-1.18)	0.84(0.47-1.48)	0.281
Stage NW15									
Plant-sourced nutrient pattern									
Model 1	1.00	0.79(0.66-0.95) **	0.76(0.63-0.91) ***	0.69(0.56-0.84)***	0.000	0.61(0.40-0.92) **	0.62(0.41-0.95)**	0.41(0.25-0.66) ***	0.001
Model 2	1.00	0.96(0.79-1.16)	0.95(0.78-1.16)	0.89(0.71-1.10)	0.29	0.85(0.51-1.44)	0.96(0.56-1.66)	0.63(0.34-1.17)	0.228
Animal-sourced nutrient pattern									
Model 1	1.00	1.02(0.85-1.22)	0.85(0.70-1.02)	1.04(0.85-1.27)	0.792	1.13(0.74-1.72)	0.88(0.56-1.38)	1.07(0.67-1.70)	0.937
Model 2	1.00	1.02(0.84-1.23)	0.87(0.71-1.05)	0.88(0.71-1.08)	0.101	1.22(0.71-2.08)	0.89(0.51-1.56)	0.79(0.43-1.46)	0.307
Mixed-sourced nutrient pattern									
Model 1	1.00	0.83(0.69-1.01)	0.94(0.77-1.15)	0.93(0.73-1.19)	0.823	0.62(0.39-0.97)	0.84(0.53-1.34)	0.71(0.39-1.27)	0.443
Model 2	1.00	0.79(0.65-0.97)	0.91(0.73-1.12)	0.96(0.74-1.25)	0.971	0.47(0.27-0.83)	0.71(0.39-1.28)	0.54(0.26-1.12)	0.237

Model 1 was adjusted for sex, age and total energy intake

Model 2 was additionally adjusted for marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, PAL, self-reported sleep quality, BMI, bodily pain, hypertension, diabetes and CVD

**** p<0.01, ** p<0.05, * p<0.1*

[a]Negative binomial regression analysis; [b]Log-binomial regression analysis

PR: Prevalence ratio; OR: Odds ratio

DISCUSSION

In this study, we explored the association between NPs and depression, focusing on identifying specific DepS that could plausibly be associated with NPs. This approach enabled us to identify NPs that have a physiological role in predicting specific DepS. To date, no study has explored if NPs could potentially impact specific DepS. Our study identified three NPs, 'plant-sourced', 'animal-sourced' and 'mixed-source' accounting for 60.2% of the total variance in the nutrient intake. After adjusting for potential confounders, 'plant-sourced' NPs, characterised by high intake of β-carotene, fibre, vitamin C, potassium, α-carotene and LZ, were inversely associated with DepS, whereas no significant association was observed with 'animal-source' and 'mixed-source' NPs.

To our knowledge, there is only one cross-sectional study investigating the role of NPs, as identified by factor analysis, on DepS [79]. These results were contradictory to our findings as this study found that 'omnivore'-like NPs (similar to the 'animal-sourced' NP in our study), high in amino acids, cobalamin, zinc, phosphorus, SFA, cholesterol and pantothenic acid, were inversely associated with psychological disorders including DepS [79]. One possible explanation for this inconsistency may be that the participants were Iranian University employees aged 18-55 years and not a population-based cohort of all ages. There is, however, evidence to support our findings. For instance, it has been shown that serum levels of carotenoids were inversely associated with DepS [416, 424] and β-carotene has been explored as a novel anti-depressants agent [27]. In addition, a recent study has demonstrated an inverse association between DepS with folate and β-carotene and a positive association with vitamin B12 and vitamin A [425].

Many epidemiological and randomized controlled trial (RCT) nutrition intervention studies indicate that consumption of a Mediterranean diet [233, 239, 426, 427] or a

healthy diet [234] has a protective effect on the onset of DepS, although, a recent study has revealed that this effect is not observed in longitudinal studies [428]. However, to date, it is still not clear whether there is any particular component of the 'healthy diet' that is responsible for this protective effect. Two recent meta-analyses on fruit and vegetables consumption and risk of depression have speculated that high intake of fruit and vegetables may be one protective factor [56, 315]. Our research supports this hypothesis with a consistent inverse association with 'plant-sourced' NP and DepS.

A possible biological explanation for the protective effect of 'plant-sourced' NP may come from the beneficial properties of nutrients with high loadings on this NP; β-carotene [27, 425, 429], fruit and vegetables dietary fibre [430, 431], vitamin C [432], β-carotene [429] and LZ [429, 433] may affect DepS via their antioxidant capability by reducing brain damage due to reactive oxygen species (ROS) [429, 434]. A link has been found between oxidative stress and the pathophysiology of many neuropsychiatric disorders, including major depression [435-437]. High levels of aerobic respiration, as well as a high content of PUFA and lower antioxidant activity compared to other tissues, may make the brain more susceptible to oxidative stress [438]. Furthermore, there is evidence to indicate that antioxidants have beneficial effects upon inflammatory markers such as interleukin (IL)-1, IL-6, and interferon γ (IFN-γ) [439].

Carotenoids, with their antioxidant properties, have been linked to reducing inflammation, associated with depression [416]. This antioxidant can reduce the risk of depression by protecting against the generation of free radicals produced via the inflammatory pathway, mediated by IL-1 [416, 437]. Interestingly, in one experimental animal study, it was found that β-carotene has anti-depressant like effects significantly increasing the levels of norepinephrine in the brain [27]. Norepinephrine along with 5-hydroxytrptamine (5HT, serotonin) and dopamine, increased the expression of brain-

derived neurotrophic factor (BDNF) in the hippocampus, which results in increased neurogenesis by up-regulating synaptic functions and neuron cell survival, in the central nervous systems, thus reducing DepS [440].

Alternatively, the observed associations may be enhanced by other dietary factors such as dietary fibre [430, 441] and polyphenols [442] possibly as a consequence of their anti-inflammatory, neuroprotective and prebiotic properties, which are also found in fruit and vegetables [15]. A study, in Japanese employees, found that DepS were only inversely associated with fibre from fruit and vegetables but not with other fibres such as total fibre, soluble, insoluble and cereal fibre [430]. Likewise, the beneficial effects of highly loaded minerals in this NP, such as potassium [32], iron [34] and magnesium [305] could also have played a role in lowering DepS.

In our study, unlike the plant-sourced NP, we found an inconsistent association between the animal-sourced NP and DepS. This might be because unhealthy (such as SFA) and healthy (ω-3 fatty acids and MUFA) nutrients are also highly correlated which could have a deleterious effect if included under the same NP. Some of the nutrients in 'animal-sourced' NP, have been considered key protective nutrients for DepS such as ω-3 fatty acids [277, 415], vitamin E [443] and vitamin D [29, 30] while some of these nutrients such as ω-6 fatty acids [444, 445] and SFA [446] are positively associated with depression when they are consumed in excessive. The second highest factor loading for the 'animal-sourced' NP was obtained from ω-6 PUFAs, possibly sourced from vegetable oils, nuts and seeds that are used in snacks and take away foods [279, 447]. In our study, the highest intake levels of ω-6 PUFAs were observed in quartiles of the 'animal-sourced' NP rather than other NPs. Furthermore, the correlation between this NP with fish, red meat, eggs and processed meat from the same dataset was in general poor ($r < 0.3$) and a fair correlation with unsaturated spread.

Some physiological and clinical implications can be extracted from this study. The physiological role of nutrients in DepS could be explored more precisely using factor analysis of the CES-D scale and using continuous data rather than a binary outcome variable. Since dichotomising an outcome variable may lead to some loss of information and overall reduced statistical power [448], future research should also focus on finding out the exact components that could potentially be associated with NPs. In terms of clinical implications, these findings may also assist in promoting increased consumption of foods rich in antioxidants to alleviate DepS in the clinical settings.

The strength of our study includes the large sample size and the multiple statistical models used to identify specific components of DepS that could plausibly be associated with NPs. Several limitations also need to be considered when interpreting our findings. First, due to the cross-sectional nature of the study, causality cannot be inferred. Second, we used FFQ for dietary intake, which may give rise to recall bias and some degree of misclassification that must be considered when interpreting our findings [230]. However, the FFQ (i.e. DQESV3) used was a well-validated and standardised tool, used to measure dietary exposures in the large epidemiological studies as well as having been tested within various age groups and population [421, 422]. Third, we used a self-reported rating scale CES-D questionnaire as a measurement tool for DepS and, therefore, this should not be considered as clinically diagnosed depression. However, the CES-D is a commonly used scale to measure DepS and has been widely used in population-based studies [133]. Fourth, residual confounding cannot be ruled out. Fifth, the subjective or arbitrary decisions in factor analysis, such as choice of nutrients to be included in the analysis, the number of factors to be extracted and preference of rotation method in the analysis, should be considered while interpreting the results [410].

In conclusion, the 'plant-sourced' NP characterised by high intake of β-carotene, fibre, vitamin C, potassium, α-carotene, lutein and zeaxanthin are inversely associated with DepS. While a significant association was not observed in a fully adjusted model between nutrient patterns and CES-D factor structure of DepS, it appears that a diet high in plant-sourced nutrients and antioxidants may reduce DepS, more specifically '(absence of) positive-affect' or anhedonic state. Large scale longitudinal studies are recommended to confirm these results.

Acknowledgements

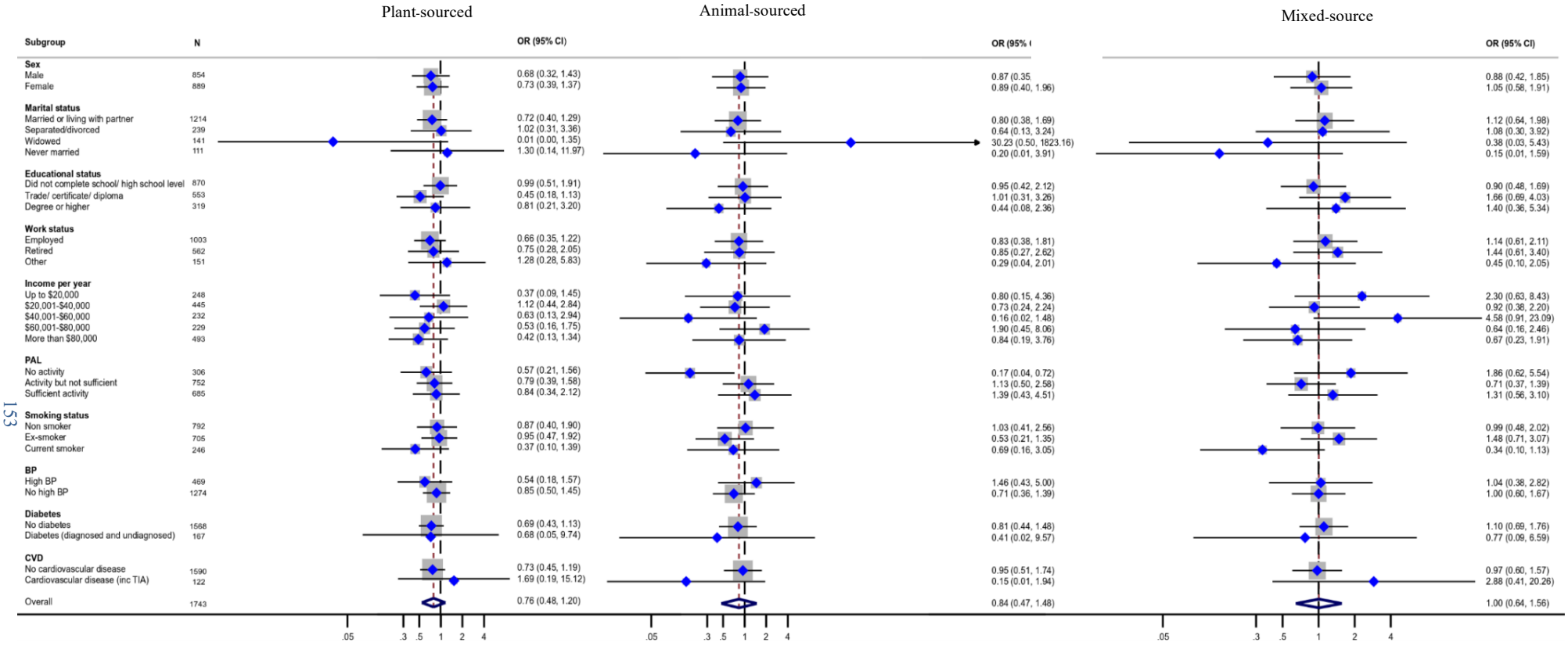
We are most grateful for the generosity of the cohort participants from the North West Adelaide Health Study (NWAHS) as well as all the members of the study team for giving their substantial time and efforts. PRS was supported by Adelaide Scholarship International (ASI) scholarship provided by the University of Adelaide. Authors are also grateful to all of the providers of research funds for this project including the University of Adelaide, the South Australian Department of Health and Wellbeing, the Premier's Science and Research fund (SA Government). The authors' responsibilities were as followed. All the authors conceived the study. PRS contributed to the literature search, data analysis and manuscript drafting. YAM contributed to the study design, data interpretation, and providing feedback. AP and TKG reviewed and critically appraised the manuscript, commenting on all drafts. All authors have read and approved the final version of the manuscript for publication.

Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS FOR CHAPTER 5



Supplementary Figure 5.1. Subgroup analysis of nutrient patterns

Supplementary Table 5.1 Characteristics of all study participants in the NWAHS Stage 3 (2008-10; *n* = 2,323)

	Male (*n*=1,083)	**Female (*n*=1,240)**	**Total (*n*=2.323)**	**P-value**
Age, Mean (SD)	57.7 (14.3)	57.2 (13.9)	57.5 (14.1)	0.4
Educational status[a] (n %)				
Did not complete school/ high school level	426 (39.3)	728 (58.7)	1,154 (49.7)	<0.001
Trade/ certificate/ diploma	429 (39.6)	269 (21.7)	698 (30.0)	
Degree or higher	180 (16.6)	196 (15.8)	376 (16.2)	
Missing	48 (4.4)	47 (3.8)	95 (4.1)	
Marital status[a] (n %)				
Married or living with partner	751 (69.3)	767 (61.9)	1,518 (65.3)	<0.001
Separated/divorced	135 (12.5)	175 (14.1)	310 (13.3)	
Widowed	59 (5.4)	154 (12.4)	213 (9.2)	
Never married	87 (8.0)	96 (7.7)	183 (7.9)	
Missing	51 (4.7)	48 (3.9)	99 (4.3)	
Work status[a] (n %)				
Employed	619 (57.2)	605 (48.8)	1,224 (52.7)	<0.001
Unemployed	13 (1.2)	19 (1.5)	32 (1.4)	
Retired	348 (32.1)	418 (33.7)	766 (33.0)	
Other	54 (5.0)	151 (12.2)	205 (8.8)	
Missing	49 (4.5)	47 (3.8)	96 (4.1)	
Income per year[a] (n %)				
Up to $20,000	130 (12.0)	185 (14.9)	315 (13.6)	<0.001
$20,001-$40,000	230 (21.2)	306 (24.7)	536 (23.1)	
$40,001-$60,000	183 (16.9)	168 (13.5)	351 (15.1)	
$60,001-$80,000	147 (13.6)	142 (11.5)	289 (12.4)	
More than $80,000	299 (27.6)	272 (21.9)	571 (24.6)	
Missing	94 (8.7)	167 (13.5)	261 (11.2)	
SEIFA[a] (n %)				
Lowest quintile	255 (23.5)	344 (27.7)	599 (25.8)	0.26
Low quintile	268 (24.7)	299 (24.1)	567 (24.4)	
Middle quintile	240 (22.2)	258 (20.8)	498 (21.4)	
High quintile	237 (21.9)	258 (20.8)	495 (21.3)	
Highest quintile	71 (6.6)	73 (5.9)	144 (6.2)	
Missing	12 (1.1)	8 (0.6)	20 (0.9)	
Smoking status[a] (n %)				
Non-smoker	437 (40.4)	626 (50.5)	1,063 (45.8)	<0.001
Ex-smoker	483 (44.6)	433 (34.9)	916 (39.4)	
Current smoker	155 (14.3)	168 (13.5)	323 (13.9)	
Missing	8 (0.7)	13 (1.0)	21 (0.9)	
Sleep quality[a] (n %)				
Very good	210 (19.4)	209 (16.9)	419 (18.0)	0.093
Fairly good	640 (59.1)	716 (57.7)	1,356 (58.4)	
Fairly bad	189 (17.5)	261 (21.0)	450 (19.4)	
Very bad	33 (3.0)	43 (3.5)	76 (3.3)	
Missing	11 (1.0)	11 (0.9)	22 (0.9)	
Alcohol risk[a] (n %)				
Non-drinkers, no risk	821 (75.8)	331 (26.7)	1,152 (49.6)	<0.001
Low risk	129 (11.9)	721 (58.1)	850 (36.6)	
Intermediate to very high risk	57 (5.3)	49 (4.0)	106 (4.6)	
Missing	76 (7.0)	139 (11.2)	215 (9.3)	
PAL[a] (n %)				
No activity	195 (18.0)	230 (18.5)	425 (18.3)	0.78
Activity but not sufficient	438 (40.4)	520 (41.9)	958 (41.2)	
Sufficient activity	396 (36.6)	441 (35.6)	837 (36.0)	
Missing	54 (5.0)	49 (4.0)	103 (4.4)	
BMI[a] (n %)				
Normal_underweight	209 (19.3)	362 (29.2)	571 (24.6)	<0.001
Overweight	506 (46.7)	405 (32.7)	911 (39.2)	
Obese	347 (32.0)	430 (34.7)	777 (33.4)	
Missing	21 (1.9)	43 (3.5)	64 (2.8)	
Bodily pain[a] (n %)				
No	481 (44.4)	633 (51.0)	1,114 (48.0)	0.001
Yes	602 (55.6)	607 (49.0)	1,209 (52.0)	

(table continues)

Supplementary table 5.1 (*table continued)*

Characteristics of all study participants in the NWAHS Stage 3 (2008-10; *n* = 2,323)

	Male (*n*=1,083)	**Female (*n*=1,240)**	**Total (*n*=2.323)**	**P-value**
BP[a] (n %)				
High BP	316 (29.2)	293 (23.6)	609 (26.2)	0.006
No high BP	736 (68.0)	888 (71.6)	1,624 (69.9)	
Missing	31 (2.9)	59 (4.8)	90 (3.9)	
Diabetes[a] (n %)				
No diabetes	940 (86.8)	1,136 (91.6)	2,076 (89.4)	<0.001
Diabetes	143 (13.2)	103 (8.3)	246 (10.6)	
Missing	0 (0.0)	1 (0.1)	1 (0.0)	
CVD[a] (n %)				
No CVD	908 (83.8)	1,118 (90.2)	2,026 (87.2)	<0.001
CVD (inc TIA)	128 (11.8)	78 (6.3)	206 (8.9)	
Missing	47 (4.3)	44 (3.5)	91 (3.9)	
Depression (Stage 3)[a] (n %)				
No depressive symptoms	907 (83.7)	965 (77.8)	1,872 (80.6)	<0.001
Depressive symptoms	150 (13.9)	253 (20.4)	403 (17.3)	
Missing	26 (2.4)	22 (1.8)	48 (2.1)	
Energy (kcal/day)[b]				
Mean (SD)	2162 (595)	1939 (546)	2043 (580)	<0.001
Scores for Animal NP[b] Mean (SD)	0.17 (1.05)	-0.15 (0.93)	0.00 (1.00)	<0.001
Scores for Plant NP[b] Mean (SD)	-0.07 (1.00)	0.06 (1.00)	-0.00 (1.00)	<0.001
Scores for Mixed NP[b], Mean (SD)	0.15 (1.03)	-0.13 (0.95)	-0.00 (1.00)	<0.001

[a]Pearson's chi-squared test; [b]Two sample t-test

BMI - body mass index; BP: blood pressure; CVD - cardiovascular disease; PAL - physical activity level; SEIFA - socio-economic indexes for areas; TIA - transient ischaemic attack

Supplementary Table 5.2 Characteristics of all study participants within each quartile of the plant-sourced nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	Q2 (*n*=581)	Q3 (*n*=581)	Q4 (*n*=580)	P-value
Age, Mean (SD)	57.1 (15.1)	56.8 (14.7)	57.7 (13.9)	58.2 (12.4)	0.32
Sex[a] (n %) Male	309 (53.2)	264 (45.4)	260 (44.8)	250 (43.1)	0.003
Female	272 (46.8)	317 (54.6)	321 (55.2)	330 (56.9)	
Educational status[a] (n %)					
Did not complete school/ high school level	315 (54.2)	299 (51.5)	289 (49.7)	251 (43.3)	<0.001
Trade/ certificate/ diploma	182 (31.3)	169 (29.1)	171 (29.4)	176 (30.3)	
Degree or higher	54 (9.3)	88 (15.1)	101 (17.4)	133 (22.9)	
Missing	30 (5.2)	25 (4.3)	20 (3.4)	20 (3.4)	
Marital status[a] (n %)					
Married or living with partner	327 (56.3)	392 (67.5)	388 (66.8)	411 (70.9)	<0.001
Separated/divorced	101 (17.4)	69 (11.9)	66 (11.4)	74 (12.8)	
Widowed	55 (9.5)	56 (9.6)	60 (10.3)	42 (7.2)	
Never married	66 (11.4)	38 (6.5)	45 (7.7)	34 (5.9)	
Missing	32 (5.5)	26 (4.5)	22 (3.8)	19 (3.3)	
Work status[a] (n %)					
Employed	306 (52.7)	301 (51.8)	316 (54.4)	301 (51.9)	0.25
Unemployed	12 (2.1)	3 (0.5)	7 (1.2)	10 (1.7)	
Retired	175 (30.1)	195 (33.6)	197 (33.9)	199 (34.3)	
Other	57 (9.8)	57 (9.8)	41 (7.1)	50 (8.6)	
Missing	31 (5.3)	25 (4.3)	20 (3.4)	20 (3.4)	
Income per year[a] (n %)					
Up to $20,000	89 (15.3)	67 (11.5)	76 (13.1)	83 (14.3)	0.14
$20,001-$40,000	143 (24.6)	145 (25.0)	128 (22.0)	120 (20.7)	
$40,001-$60,000	79 (13.6)	77 (13.3)	100 (17.2)	95 (16.4)	
$60,001-$80,000	72 (12.4)	70 (12.0)	75 (12.9)	72 (12.4)	
More than $80,000	117 (20.1)	153 (26.3)	146 (25.1)	155 (26.7)	
Missing	81 (13.9)	69 (11.9)	56 (9.6)	55 (9.5)	
SEIFA[a] (n %)					
Lowest quintile	166 (28.6)	152 (26.2)	161 (27.7)	120 (20.7)	0.023
Low quintile	157 (27.0)	145 (25.0)	118 (20.3)	147 (25.3)	
Middle quintile	115 (19.8)	120 (20.7)	132 (22.7)	131 (22.6)	
High quintile	114 (19.6)	117 (20.1)	129 (22.2)	135 (23.3)	
Highest quintile	25 (4.3)	42 (7.2)	36 (6.2)	41 (7.1)	
Missing	4 (0.7)	5 (0.9)	5 (0.9)	6 (1.0)	
Smoking status[a] (n %)					
Non-smoker	227 (39.1)	274 (47.2)	278 (47.8)	284 (49.0)	<0.001
Ex-smoker	236 (40.6)	223 (38.4)	219 (37.7)	238 (41.0)	
Current smoker	112 (19.3)	79 (13.6)	76 (13.1)	56 (9.7)	
Missing	6 (1.0)	5 (0.9)	8 (1.4)	2 (0.3)	
Sleep quality[a] (n %)					
Very good	103 (17.7)	93 (16.0)	113 (19.4)	110 (19.0)	0.081
Fairly good	320 (55.1)	363 (62.5)	326 (56.1)	347 (59.8)	
Fairly bad	131 (22.5)	105 (18.1)	117 (20.1)	97 (16.7)	
Very bad	22 (3.8)	17 (2.9)	13 (2.2)	24 (4.1)	
Missing	5 (0.9)	3 (0.5)	12 (2.1)	2 (0.3)	
Alcohol risk[a] (n %)					
Non-drinkers, no risk	301 (51.8)	290 (49.9)	282 (48.5)	279 (48.1)	0.19
Low risk	187 (32.2)	207 (35.6)	225 (38.7)	231 (39.8)	
Intermediate to very high risk	33 (5.7)	22 (3.8)	26 (4.5)	25 (4.3)	
Missing	60 (10.3)	62 (10.7)	48 (8.3)	45 (7.8)	
PAL[a] (n %)					
No activity	143 (24.6)	107 (18.4)	91 (15.7)	84 (14.5)	<0.001
Activity but not sufficient	250 (43.0)	252 (43.4)	245 (42.2)	211 (36.4)	
Sufficient activity	156 (26.9)	195 (33.6)	221 (38.0)	265 (45.7)	
Missing	32 (5.5)	27 (4.6)	24 (4.1)	20 (3.4)	
BMI[a] (n %)					
Normal_underweight	133 (22.9)	147 (25.3)	149 (25.6)	142 (24.5)	0.81
Overweight	243 (41.8)	226 (38.9)	215 (37.0)	227 (39.1)	
Obese	192 (33.0)	190 (32.7)	198 (34.1)	197 (34.0)	
Missing	13 (2.2)	18 (3.1)	19 (3.3)	14 (2.4)	
Bodily pain[a] (n %)					
No	297 (51.1)	284 (48.9)	271 (46.6)	262 (45.2)	0.19
Yes	284 (48.9)	297 (51.1)	310 (53.4)	318 (54.8)	

(table continues)

Supplementary Table 5.2 *(table continued)*

Characteristics of all study participants within each quartile of the plant-sourced nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	**Q2 (*n*=581)**	**Q3 (*n*=581)**	**Q4 (*n*=580)**	**P-value**
BP[a] (n %)					
High BP	162 (27.9)	145 (25.0)	154 (26.5)	148 (25.5)	0.71
No high BP	399 (68.7)	412 (70.9)	402 (69.2)	411 (70.9)	
Missing	20 (3.4)	24 (4.1)	25 (4.3)	21 (3.6)	
Diabetes[a] (n %)					
No diabetes	521 (89.7)	517 (89.0)	524 (90.2)	514 (88.6)	0.81
Diabetes	59 (10.2)	64 (11.0)	57 (9.8)	66 (11.4)	
Missing	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	
CVD[a] (n %)					
No CVD	490 (84.3)	508 (87.4)	511 (88.0)	517 (89.1)	0.28
CVD (inc TIA)	62 (10.7)	49 (8.4)	50 (8.6)	45 (7.8)	
Missing	29 (5.0)	24 (4.1)	20 (3.4)	18 (3.1)	
Depression (Stage 3)[a] (n %)					
No depressive symptoms	450 (77.5)	471 (81.1)	473 (81.4)	478 (82.4)	0.073
Depressive symptoms	121 (20.8)	95 (16.4)	99 (17.0)	88 (15.2)	
Missing	10 (1.7)	15 (2.6)	9 (1.5)	14 (2.4)	
Energy (kcal/day)[b]					
Mean (SD)	1793.85 (525.15)	1922.07 (517.61)	2108.76 (520.82)	2347.34 (598.46)	<0.001

[a]Pearson's chi-squared test ; [b]Two sample t-test

BMI - body mass index; BP: blood pressure; CVD - cardiovascular disease; PAL - physical activity level; SEIFA - socio-economic indexes for areas; TIA - transient ischaemic attack

Supplementary Table 5.3 Characteristics of all study participants within each quartile of the animal-sourced nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	Q2 (*n*=581)	Q3 (*n*=581)	Q4 (*n*=580)	P-value
Age, Mean (SD)	57.9 (14.5)	56.4 (14.1)	58.1 (13.7)	57.6 (13.9)	0.17
Sex[a] (n %) Male	227 (39.1)	244 (42.0)	276 (47.5)	336 (57.9)	<0.001
Female	354 (60.9)	337 (58.0)	305 (52.5)	244 (42.1)	
Educational status[a] (n %)					
Did not complete school/ high school level	305 (52.5)	286 (49.2)	285 (49.1)	278 (47.9)	0.62
Trade/ certificate/ diploma	165 (28.4)	168 (28.9)	179 (30.8)	186 (32.1)	
Degree or higher	92 (15.8)	104 (17.9)	91 (15.7)	89 (15.3)	
Missing	19 (3.3)	23 (4.0)	26 (4.5)	27 (4.7)	
Marital status[a] (n %)					
Married or living with partner	400 (68.8)	399 (68.7)	382 (65.7)	337 (58.1)	0.003
Separated/divorced	66 (11.4)	63 (10.8)	80 (13.8)	101 (17.4)	
Widowed	52 (9.0)	52 (9.0)	55 (9.5)	54 (9.3)	
Never married	44 (7.6)	43 (7.4)	36 (6.2)	60 (10.3)	
Missing	19 (3.3)	24 (4.1)	28 (4.8)	28 (4.8)	
Work status[a] (n %)					
Employed	295 (50.8)	325 (55.9)	308 (53.0)	296 (51.0)	0.45
Unemployed	12 (2.1)	6 (1.0)	7 (1.2)	7 (1.2)	
Retired	207 (35.6)	176 (30.3)	192 (33.0)	191 (32.9)	
Other	47 (8.1)	51 (8.8)	48 (8.3)	59 (10.2)	
Missing	20 (3.4)	23 (4.0)	26 (4.5)	27 (4.7)	
Income per year[a] (n %)					
Up to $20,000	97 (16.7)	67 (11.5)	70 (12.0)	81 (14.0)	0.025
$20,001-$40,000	130 (22.4)	139 (23.9)	136 (23.4)	131 (22.6)	
$40,001-$60,000	80 (13.8)	76 (13.1)	100 (17.2)	95 (16.4)	
$60,001-$80,000	69 (11.9)	64 (11.0)	79 (13.6)	77 (13.3)	
More than $80,000	146 (25.1)	171 (29.4)	133 (22.9)	121 (20.9)	
Missing	59 (10.2)	64 (11.0)	63 (10.8)	75 (12.9)	
SEIFA[a] (n %)					
Lowest quintile	159 (27.4)	148 (25.5)	152 (26.2)	140 (24.1)	0.33
Low quintile	134 (23.1)	148 (25.5)	132 (22.7)	153 (26.4)	
Middle quintile	140 (24.1)	113 (19.4)	127 (21.9)	118 (20.3)	
High quintile	103 (17.7)	136 (23.4)	133 (22.9)	123 (21.2)	
Highest quintile	37 (6.4)	32 (5.5)	34 (5.9)	41 (7.1)	
Missing	8 (1.4)	4 (0.7)	3 (0.5)	5 (0.9)	
Smoking status[a] (n %)					
Non-smoker	256 (44.1)	270 (46.5)	277 (47.7)	260 (44.8)	0.33
Ex-smoker	250 (43.0)	223 (38.4)	214 (36.8)	229 (39.5)	
Current smoker	68 (11.7)	82 (14.1)	87 (15.0)	86 (14.8)	
Missing	7 (1.2)	6 (1.0)	3 (0.5)	5 (0.9)	
Sleep quality[a] (n %)					
Very good	108 (18.6)	102 (17.6)	119 (20.5)	90 (15.5)	0.058
Fairly good	344 (59.2)	363 (62.5)	317 (54.6)	332 (57.2)	
Fairly bad	105 (18.1)	92 (15.8)	127 (21.9)	126 (21.7)	
Very bad	21 (3.6)	19 (3.3)	15 (2.6)	21 (3.6)	
Missing	3 (0.5)	5 (0.9)	3 (0.5)	11 (1.9)	
Alcohol risk[a] (n %)					
Non-drinkers, no risk	269 (46.3)	281 (48.4)	286 (49.2)	316 (54.5)	0.21
Low risk	230 (39.6)	217 (37.3)	212 (36.5)	191 (32.9)	
Intermediate to very high risk	25 (4.3)	24 (4.1)	30 (5.2)	27 (4.7)	
Missing	57 (9.8)	59 (10.2)	53 (9.1)	46 (7.9)	
PAL[a] (n %)					
No activity	104 (17.9)	122 (21.0)	106 (18.2)	93 (16.0)	0.51
Activity but not sufficient	248 (42.7)	230 (39.6)	241 (41.5)	239 (41.2)	
Sufficient activity	209 (36.0)	205 (35.3)	204 (35.1)	219 (37.8)	
Missing	20 (3.4)	24 (4.1)	30 (5.2)	29 (5.0)	
BMI[a] (n %)					
Normal_underweight	136 (23.4)	135 (23.2)	161 (27.7)	139 (24.0)	0.28
Overweight	240 (41.3)	216 (37.2)	218 (37.5)	237 (40.9)	
Obese	194 (33.4)	211 (36.3)	182 (31.3)	190 (32.8)	
Missing	11 (1.9)	19 (3.3)	20 (3.4)	14 (2.4)	
Bodily pain[a] (n %)					
No	294 (50.6)	271 (46.6)	268 (46.1)	281 (48.4)	0.41
Yes	287 (49.4)	310 (53.4)	313 (53.9)	299 (51.6)	

(table continues)

Supplementary Table 5.3 (table *continued*)

Characteristics of all study participants within each quartile of the animal-sourced nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	Q2 (*n*=581)	Q3 (*n*=581)	Q4 (*n*=580)	P-value
BP[a] (n %)					
High BP	148 (25.5)	141 (24.3)	165 (28.4)	155 (26.7)	0.3
No high BP	418 (71.9)	417 (71.8)	384 (66.1)	405 (69.8)	
Missing	15 (2.6)	23 (4.0)	32 (5.5)	20 (3.4)	
Diabetes[a] (n %)					
No diabetes	514 (88.5)	519 (89.3)	531 (91.4)	512 (88.3)	0.25
Diabetes	67 (11.5)	62 (10.7)	49 (8.4)	68 (11.7)	
Missing	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	
CVD[a] (n %)					
No CVD	514 (88.5)	509 (87.6)	508 (87.4)	495 (85.3)	0.68
CVD (inc TIA)	50 (8.6)	51 (8.8)	47 (8.1)	58 (10.0)	
Missing	17 (2.9)	21 (3.6)	26 (4.5)	27 (4.7)	
Depression (Stage 3)[a] (n %)					
No depressive symptoms	475 (81.8)	483 (83.1)	467 (80.4)	447 (77.1)	0.12
Depressive symptoms	92 (15.8)	89 (15.3)	108 (18.6)	114 (19.7)	
Missing	14 (2.4)	9 (1.5)	6 (1.0)	19 (3.3)	
Energy (kcal/day)[b]					
Mean (SD)	1782.45 (585.18)	1882.74 (468.46)	2090.86 (503.44)	2416.09 (544.26)	<0.001

[a]Pearson's chi-squared test ; [b]Two sample t-test

BMI - body mass index; BP: blood pressure; CVD - cardiovascular disease; PAL - physical activity level; SEIFA - socio-economic indexes for areas; TIA - transient ischaemic attack

Supplementary Table 5.4 Characteristics of all study participants within each quartile of the mixed-source nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	Q2 (*n*=581)	Q3 (*n*=581)	Q4 (*n*=580)	P-value
Age, Mean (SD)	58.6 (13.7)	56.7 (13.9)	58.1 (14.1)	56.4 (14.5)	0.015
Sex[a] (n %) Male	237 (40.8)	230 (39.6)	286 (49.2)	330 (56.9)	<0.001
Female	344 (59.2)	351 (60.4)	295 (50.8)	250 (43.1)	
Educational status[a] (n %)					
Did not complete school/ high school level	285 (49.1)	292 (50.3)	287 (49.4)	290 (50.0)	0.94
Trade/ certificate/ diploma	168 (28.9)	168 (28.9)	183 (31.5)	179 (30.9)	
Degree or higher	94 (16.2)	101 (17.4)	88 (15.1)	93 (16.0)	
Missing	34 (5.9)	20 (3.4)	23 (4.0)	18 (3.1)	
Marital status[a] (n %)					
Married or living with partner	346 (59.6)	386 (66.4)	397 (68.3)	389 (67.1)	0.009
Separated/divorced	100 (17.2)	71 (12.2)	67 (11.5)	72 (12.4)	
Widowed	54 (9.3)	51 (8.8)	63 (10.8)	45 (7.8)	
Never married	47 (8.1)	50 (8.6)	32 (5.5)	54 (9.3)	
Missing	34 (5.9)	23 (4.0)	22 (3.8)	20 (3.4)	
Work status[a] (n %)					
Employed	297 (51.1)	316 (54.4)	302 (52.0)	309 (53.3)	0.43
Unemployed	5 (0.9)	11 (1.9)	10 (1.7)	6 (1.0)	
Retired	202 (34.8)	186 (32.0)	195 (33.6)	183 (31.6)	
Other	43 (7.4)	48 (8.3)	51 (8.8)	63 (10.9)	
Missing	34 (5.9)	20 (3.4)	23 (4.0)	19 (3.3)	
Income per year[a] (n %)					
Up to $20,000	84 (14.5)	76 (13.1)	78 (13.4)	77 (13.3)	0.64
$20,001-$40,000	137 (23.6)	142 (24.4)	118 (20.3)	139 (24.0)	
$40,001-$60,000	76 (13.1)	94 (16.2)	86 (14.8)	95 (16.4)	
$60,001-$80,000	61 (10.5)	70 (12.0)	76 (13.1)	82 (14.1)	
More than $80,000	144 (24.8)	146 (25.1)	150 (25.8)	131 (22.6)	
Missing	79 (13.6)	53 (9.1)	73 (12.6)	56 (9.7)	
SEIFA[a] (n %)					
Lowest quintile	159 (27.4)	140 (24.1)	147 (25.3)	153 (26.4)	0.48
Low quintile	137 (23.6)	135 (23.2)	147 (25.3)	148 (25.5)	
Middle quintile	128 (22.0)	135 (23.2)	109 (18.8)	126 (21.7)	
High quintile	117 (20.1)	131 (22.5)	139 (23.9)	108 (18.6)	
Highest quintile	32 (5.5)	37 (6.4)	33 (5.7)	42 (7.2)	
Missing	8 (1.4)	3 (0.5)	6 (1.0)	3 (0.5)	
Smoking status[a] (n %)					
Non-smoker	277 (47.7)	266 (45.8)	268 (46.1)	252 (43.4)	0.29
Ex-smoker	229 (39.4)	234 (40.3)	230 (39.6)	223 (38.4)	
Current smoker	68 (11.7)	80 (13.8)	77 (13.3)	98 (16.9)	
Missing	7 (1.2)	1 (0.2)	6 (1.0)	7 (1.2)	
Sleep quality[a] (n %)					
Very good	114 (19.6)	95 (16.4)	105 (18.1)	105 (18.1)	0.59
Fairly good	342 (58.9)	341 (58.7)	330 (56.8)	343 (59.1)	
Fairly bad	97 (16.7)	117 (20.1)	121 (20.8)	115 (19.8)	
Very bad	21 (3.6)	23 (4.0)	18 (3.1)	14 (2.4)	
Missing	7 (1.2)	5 (0.9)	7 (1.2)	3 (0.5)	
Alcohol risk[a] (n %)					
Non drinkers, no risk	280 (48.2)	254 (43.7)	301 (51.8)	317 (54.7)	0.004
Low risk	203 (34.9)	249 (42.9)	212 (36.5)	186 (32.1)	
Intermediate to very high risk	30 (5.2)	25 (4.3)	21 (3.6)	30 (5.2)	
Missing	68 (11.7)	53 (9.1)	47 (8.1)	47 (8.1)	
PAL[a] (n %)					
No activity	108 (18.6)	109 (18.8)	109 (18.8)	99 (17.1)	0.84
Activity but not sufficient	231 (39.8)	235 (40.4)	234 (40.3)	258 (44.5)	
Sufficient activity	207 (35.6)	212 (36.5)	215 (37.0)	203 (35.0)	
Missing	35 (6.0)	25 (4.3)	23 (4.0)	20 (3.4)	
BMI[a] (n %)					
Normal_underweight	132 (22.7)	151 (26.0)	155 (26.7)	133 (22.9)	0.047
Overweight	253 (43.5)	212 (36.5)	208 (35.8)	238 (41.0)	
Obese	172 (29.6)	197 (33.9)	210 (36.1)	198 (34.1)	
Missing	24 (4.1)	21 (3.6)	8 (1.4)	11 (1.9)	
Bodily pain[a] (n %)					
No	258 (44.4)	286 (49.2)	275 (47.3)	295 (50.9)	0.15
Yes	323 (55.6)	295 (50.8)	306 (52.7)	285 (49.1)	

(table continues)

Supplementary Table 5.4 *(table continued)*

Characteristics of all study participants within each quartile of the mixed-source nutrient pattern, NWAHS Stage 3

	Q1 (*n*=581)	Q2 (*n*=581)	Q3 (*n*=581)	Q4 (*n*=580)	P-value
BP[a] (n %)					
High BP	155 (26.7)	159 (27.4)	134 (23.1)	161 (27.8)	0.19
No high BP	395 (68.0)	397 (68.3)	430 (74.0)	402 (69.3)	
Missing	31 (5.3)	25 (4.3)	17 (2.9)	17 (2.9)	
Diabetes[a] (n %)					
No diabetes	524 (90.2)	531 (91.4)	517 (89.0)	504 (86.9)	0.074
Diabetes	56 (9.6)	50 (8.6)	64 (11.0)	76 (13.1)	
Missing	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	
CVD[a] (n %)					
No CVD	490 (84.3)	520 (89.5)	509 (87.6)	507 (87.4)	0.24
CVD (inc TIA)	58 (10.0)	41 (7.1)	50 (8.6)	57 (9.8)	
Missing	33 (5.7)	20 (3.4)	22 (3.8)	16 (2.8)	
Depression (Stage 3)[a] (n %)					
No depressive symptoms	471 (81.1)	463 (79.7)	480 (82.6)	458 (79.0)	0.27
Depressive symptoms	95 (16.4)	107 (18.4)	89 (15.3)	112 (19.3)	
Missing	15 (2.6)	11 (1.9)	12 (2.1)	10 (1.7)	
Energy (kcal/day)[b]					
Mean (SD)	1541.76 (395.36)	1871.76 (355.93)	2121.30 (396.67)	2637.70 (515.30)	<0.001

[a]Pearson's chi-squared test ; [b]Two sample t-test

BMI - body mass index; BP: blood pressure; CVD - cardiovascular disease; PAL - physical activity level; SEIFA - socio-economic indexes for areas; TIA - transient ischaemic attack

Supplementary Table 5.5 Mean (SD) of nutrient intake across quartiles of plant-sourced nutrient pattern scores among Australian adults (NWAHS Stage 3, *n* = 1,743)

Factor	Total	Q1	Q2	Q3	Q4	*P*-value
	n = 1743	*n* = 436	*n* = 436	*n* = 436	*n* = 435	
	Mean (SD)					
Protein (g/d)	95.1 (28.1)	84.0 (25.6)	91.9 (29.2)	98.5 (25.0)	105.8 (27.7)	<0.001
Saturated fat (g/d)	28.8 (11.2)	29.4 (13.5)	28.3 (10.8)	28.7 (10.2)	28.7 (10.1)	0.48
Monounsaturated fat (g/d)	36.5 (12.5)	33.2 (11.0)	35.5 (12.1)	37.4 (12.3)	40.0 (13.4)	<0.001
Cholesterol (mg/d)	279.3 (106.3)	283.2 (108.0)	274.9 (113.2)	281.6 (99.5)	277.8 (104.3)	0.66
Starch and dextrin (g/d)	99.5 (44.3)	80.4 (31.0)	92.2 (32.1)	101.9 (33.1)	123.5 (61.4)	<0.001
Fibre (g/d)	27.2 (10.6)	17.8 (5.6)	23.3 (5.3)	28.8 (6.1)	38.9 (10.5)	<0.001
Riboflavin, B2 (mg/d)	2.4 (1.1)	2.1 (0.9)	2.3 (1.1)	2.4 (1.1)	2.8 (1.2)	<0.001
Pyridoxine, B6 (mg/d)	1.3 (1.6)	1.0 (0.8)	1.1 (0.7)	1.3 (1.6)	1.8 (2.4)	<0.001
Cobalamin, B12 (mcg/d)	3.4 (1.6)	3.7 (1.7)	3.4 (1.7)	3.2 (1.5)	3.1 (1.5)	<0.001
Vitamin C (mg/d)	135.3 (73.2)	75.3 (37.6)	108.9 (40.2)	148.3 (50.5)	208.7 (77.6)	<0.001
Thiamine, B1 (mg/d)	2.1 (1.3)	1.6 (1.0)	2.0 (1.2)	2.2 (1.2)	2.6 (1.5)	<0.001
Vitamin E (mg/d)	11.1 (4.0)	9.0 (3.1)	10.4 (3.5)	11.5 (3.6)	13.6 (4.2)	<0.001
Vitamin D (mcg/d)	3.5 (2.0)	3.9 (2.3)	3.3 (2.0)	3.3 (1.8)	3.3 (1.8)	<0.001
Calcium (mg/d)	868.5 (327.0)	791.4 (327.3)	837.9 (325.6)	882.8 (316.0)	962.2 (315.5)	<0.001
Magnesium (mg/d)	441.6 (156.6)	343.0 (127.9)	410.8 (130.4)	456.3 (127.5)	556.5 (156.5)	<0.001
Phosphorous (mg/d)	1598.7 (506.7)	1358.7 (402.3)	1504.6 (434.6)	1628.4 (407.6)	1903.9 (592.9)	<0.001
Potassium (mg/d)	3861.9 (1321.9)	2850.0 (839.7)	3495.6 (880.3)	3979.9 (835.0)	5124.9 (1433.6)	<0.001
Zinc (mg/d)	10.6 (3.7)	9.2 (3.4)	10.2 (3.7)	11.1 (3.2)	11.9 (3.7)	<0.001
Iron (mg/d)	12.7 (4.3)	9.8 (3.3)	11.7 (3.3)	13.5 (3.7)	15.9 (4.3)	<0.001
Folic acid in mg/d	0.5 (0.3)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.6 (0.4)	<0.001
Retinol (mcg/d)	325.4 (145.9)	365.7 (160.1)	316.6 (136.6)	313.1 (143.3)	306.2 (134.9)	<0.001
Beta carotene (mcg/d)	3310.0 (1800.1)	1717.5 (708.5)	2637.7 (956.6)	3548.4 (993.3)	5340.9 (1845.0)	<0.001
Alpha carotene (mcg/d)	756.0 (596.9)	341.2 (231.3)	559.9 (338.2)	819.5 (432.9)	1304.6 (746.3)	<0.001
Niacin, B3 (mg/d)	26.7 (12.9)	20.8 (8.3)	24.7 (10.6)	26.8 (10.4)	34.3 (16.9)	<0.001
Sodium (mg/d)	2414.9 (837.9)	2129.8 (752.8)	2312.4 (802.4)	2526.2 (807.6)	2691.9 (877.3)	<0.001
Iodine (mcg/d)	120.7 (49.7)	128.6 (57.5)	117.9 (49.8)	117.1 (48.0)	119.4 (41.6)	0.002
Lycopene (mcg/d)	10096.4 (9512.9)	5739.9 (4578.6)	8625.8 (7343.1)	11047.5 (8682.9)	14983.5 (12904.2)	<0.001
Palmitoleic acid (g/d)	1.3 (0.5)	1.3 (0.4)	1.3 (0.5)	1.4 (0.4)	1.4 (0.5)	<0.001
Omega-3 fatty acid (g/d)	3.6 (1.9)	3.3 (1.8)	3.6 (2.0)	3.7 (2.0)	3.8 (1.9)	<0.001
Lutein and zeaxanthin (mcg/d)	1541.7 (1277.3)	682.7 (493.8)	1167.5 (818.0)	1612.7 (826.6)	2706.8 (1643.4)	<0.001
Omega-6 fatty acid (g/d)	21.5 (11.0)	19.2 (10.3)	20.9 (10.5)	21.9 (10.6)	24.0 (11.9)	<0.001
Biotin, B7 (mcg/d)	34.4 (17.0)	27.2 (13.1)	29.8 (13.0)	34.1 (13.2)	46.4 (20.6)	<0.001
Energy (kcal/day)	2063.1 (577.0)	1812.3 (523.7)	1960.4 (525.3)	2109.4 (513.7)	2370.9 (591.1)	<0.001

Supplementary Table 5.6 Mean (SD) of nutrient intake across quartiles of animal-sourced nutrient pattern scores among Australian adults (NWAHS Stage 3, *n* = 1,743)

Factor	Total	Q1	Q2	Q3	Q4	*P*-value
	n=1743	*n*=436	*n*=436	*n*=436	*n*=435	
	Mean (SD)					
Protein (g/d)	95.1 (28.1)	83.8 (24.3)	89.9 (22.4)	96.7 (23.8)	110.0 (33.4)	<0.001
Saturated fat (g/d)	28.8 (11.2)	23.1 (8.2)	26.5 (8.8)	30.5 (10.4)	35.1 (13.1)	<0.001
Monounsaturated fat (g/d)	36.5 (12.5)	26.4 (7.9)	32.2 (7.9)	38.5 (8.9)	49.0 (11.8)	<0.001
Cholesterol (mg/d)	279.3 (106.3)	225.1 (76.1)	258.9 (79.4)	290.7 (91.3)	342.9 (131.7)	<0.001
Starch and dextrin (g/d)	99.5 (44.3)	102.8 (63.0)	91.4 (36.3)	98.1 (33.9)	105.6 (35.9)	<0.001
Fibre (g/d)	27.2 (10.6)	26.5 (12.9)	25.4 (9.2)	26.8 (9.5)	30.1 (9.8)	<0.001
Riboflavin, B2 (mg/d)	2.4 (1.1)	2.4 (1.2)	2.3 (1.0)	2.3 (1.0)	2.5 (1.1)	0.15
Pyridoxine, B6 (mg/d)	1.3 (1.6)	1.4 (2.2)	1.3 (1.9)	1.3 (0.9)	1.3 (0.8)	0.79
Cobalamin, B12 (mcg/d)	3.4 (1.6)	2.8 (1.4)	3.2 (1.4)	3.5 (1.5)	3.9 (1.8)	<0.001
Vitamin C (mg/d)	135.3 (73.2)	123.2 (69.6)	132.0 (68.2)	136.8 (73.6)	149.1 (78.8)	<0.001
Thiamine, B1 (mg/d)	2.1 (1.3)	2.1 (1.4)	2.0 (1.2)	2.0 (1.2)	2.2 (1.3)	0.18
Vitamin E (mg/d)	11.1 (4.0)	8.3 (3.0)	9.9 (2.7)	11.5 (3.0)	15.0 (3.8)	<0.001
Vitamin D (mcg/d)	3.5 (2.0)	2.5 (1.2)	3.1 (1.6)	3.7 (1.9)	4.5 (2.3)	<0.001
Calcium (mg/d)	868.5 (327.0)	846.9 (335.6)	832.9 (312.8)	865.1 (316.5)	929.4 (335.1)	<0.001
Magnesium (mg/d)	441.6 (156.6)	426.0 (173.2)	411.0 (143.3)	437.4 (143.2)	492.1 (152.9)	<0.001
Phosphorous (mg/d)	1598.7 (506.7)	1564.6 (646.7)	1497.9 (421.9)	1581.9 (413.9)	1750.9 (475.9)	<0.001
Potassium (mg/d)	3861.9 (1321.9)	3872.0 (1740.3)	3635.1 (1112.0)	3766.6 (1096.2)	4174.4 (1172.9)	<0.001
Zinc (mg/d)	10.6 (3.7)	9.9 (3.5)	10.2 (3.3)	10.5 (3.3)	11.7 (4.3)	<0.001
Iron (mg/d)	12.7 (4.3)	12.4 (4.7)	12.1 (4.1)	12.6 (3.9)	13.9 (4.3)	<0.001
Folic acid in mg/d	0.5 (0.3)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.6 (0.4)	<0.001
Retinol (mcg/d)	325.4 (145.9)	239.8 (111.0)	301.8 (123.6)	351.7 (137.6)	408.5 (152.3)	<0.001
Beta carotene (mcg/d)	3310.0 (1800.1)	3020.3 (1721.7)	3265.7 (1753.9)	3261.7 (1695.1)	3693.1 (1958.7)	<0.001
Alpha-carotene (mcg/d)	756.0 (596.9)	734.3 (547.2)	770.6 (620.5)	729.7 (594.6)	789.5 (622.3)	0.38
Niacin, B3 (mg/d)	26.7 (12.9)	29.1 (17.6)	25.4 (11.3)	25.2 (10.5)	27.0 (10.7)	<0.001
Sodium (mg/d)	2414.9 (837.9)	2042.9 (693.1)	2252.5 (704.8)	2490.1 (748.7)	2875.3 (945.2)	<0.001
Iodine (mcg/d)	120.7 (49.7)	114.0 (47.2)	115.3 (47.1)	122.6 (50.2)	131.2 (52.6)	<0.001
Lycopene (mcg/d)	10096.4 (9512.9)	7937.4 (7057.1)	9465.9 (8287.8)	9794.6 (7674.7)	13194.7 (13062.7)	<0.001
Palmitoleic acid (g/d)	1.3 (0.5)	1.1 (0.3)	1.2 (0.3)	1.4 (0.4)	1.6 (0.5)	<0.001
Omega-3 fatty acid (g/d)	3.6 (1.9)	1.9 (0.8)	2.8 (0.8)	3.8 (1.1)	5.8 (2.1)	<0.001
Lutein and zeaxanthin (mcg/d)	1541.7 (1277.3)	1375.8 (1110.7)	1472.4 (1245.9)	1536.9 (1215.5)	1782.4 (1478.1)	<0.001
Omega-6 fatty acid (g/d)	21.5 (11.0)	11.6 (4.4)	17.2 (5.2)	22.6 (6.5)	34.6 (10.2)	<0.001
Biotin, B7 (mcg/d)	34.4 (17.0)	31.3 (17.4)	31.1 (14.4)	35.0 (17.1)	40.1 (17.4)	<0.001
Energy (kcal/day)	2063.1 (577.0)	1817.7 (584.6)	1904.1 (470.1)	2105.4 (504.1)	2425.9 (545.7)	<0.001

Supplementary Table 5.7 Mean (SD) of nutrient intake across quartiles of mixed-source nutrient pattern scores among Australian adults (NWAHS Stage 3, *n* = 1,743)

Factor	Total	Q1	Q2	Q3	Q4	P-value
	n=1743	n=436	n=436	n=436	n=435	
	Mean (SD)					
Protein (g/d)	95.1 (28.1)	69.7 (16.8)	87.3 (15.2)	99.7 (17.1)	123.6 (28.5)	<0.001
Saturated fat (g/d)	28.8 (11.2)	19.6 (5.8)	25.2 (5.9)	30.4 (7.5)	39.8 (12.6)	<0.001
Monounsaturated fat (g/d)	36.5 (12.5)	30.2 (11.2)	34.0 (10.2)	37.4 (11.3)	44.4 (12.5)	<0.001
Cholesterol (mg/d)	279.3 (106.3)	204.8 (69.1)	257.0 (75.7)	288.3 (75.9)	367.5 (122.9)	<0.001
Starch and dextrin (g/d)	99.5 (44.3)	70.1 (24.1)	90.0 (28.1)	102.4 (30.3)	135.4 (57.5)	<0.001
Fibre (g/d)	27.2 (10.6)	22.6 (8.7)	25.8 (8.9)	27.3 (8.8)	33.1 (12.7)	<0.001
Riboflavin, B2 (mg/d)	2.4 (1.1)	1.5 (0.5)	2.0 (0.7)	2.6 (0.7)	3.5 (1.1)	<0.001
Pyridoxine, B6 (mg/d)	1.3 (1.6)	1.0 (1.0)	1.2 (1.1)	1.4 (1.5)	1.8 (2.3)	<0.001
Cobalamin, B12 (mcg/d)	3.4 (1.6)	2.1 (0.8)	2.8 (1.0)	3.6 (1.2)	4.9 (1.7)	<0.001
Vitamin C (mg/d)	135.3 (73.2)	129.0 (78.0)	131.5 (69.9)	136.5 (71.3)	144.2 (72.6)	0.011
Thiamine, B1 (mg/d)	2.1 (1.3)	1.3 (0.6)	1.8 (0.9)	2.2 (1.1)	3.1 (1.5)	<0.001
Vitamin E (mg/d)	11.1 (4.0)	9.8 (3.9)	10.6 (3.6)	11.3 (3.7)	12.9 (4.2)	<0.001
Vitamin D (mcg/d)	3.5 (2.0)	2.2 (1.1)	3.0 (1.4)	3.7 (1.7)	5.0 (2.3)	<0.001
Calcium (mg/d)	868.5 (327.0)	590.0 (203.9)	770.3 (237.2)	941.3 (254.7)	1173.1 (283.1)	<0.001
Magnesium (mg/d)	441.6 (156.6)	342.2 (126.7)	424.0 (135.1)	451.8 (130.0)	548.6 (158.8)	<0.001
Phosphorous (mg/d)	1598.7 (506.7)	1126.9 (271.2)	1438.9 (255.1)	1669.5 (267.6)	2160.9 (498.9)	<0.001
Potassium (mg/d)	3861.9 (1321.9)	2970.4 (947.0)	3590.2 (959.0)	3931.7 (939.9)	4957.7 (1492.2)	<0.001
Zinc (mg/d)	10.6 (3.7)	7.4 (2.1)	9.5 (2.2)	11.2 (2.5)	14.2 (3.7)	<0.001
Iron (mg/d)	12.7 (4.3)	9.5 (3.0)	11.6 (3.1)	13.2 (3.4)	16.5 (4.2)	<0.001
Folic acid in mg/d	0.5 (0.3)	0.4 (0.2)	0.4 (0.3)	0.5 (0.3)	0.7 (0.4)	<0.001
Retinol (mcg/d)	325.4 (145.9)	212.7 (84.8)	283.9 (99.3)	345.8 (115.1)	459.6 (148.6)	<0.001
Beta carotene (mcg/d)	3310.0 (1800.1)	3174.5 (1903.8)	3303.7 (1888.7)	3281.9 (1694.6)	3480.2 (1694.4)	0.091
Alpha carotene (mcg/d)	756.0 (596.9)	749.5 (639.7)	754.2 (636.0)	751.9 (583.6)	768.5 (522.4)	0.97
Niacin, B3 (mg/d)	26.7 (12.9)	16.9 (5.1)	22.7 (6.8)	27.5 (8.4)	39.6 (15.7)	<0.001
Sodium (mg/d)	2414.9 (837.9)	1725.9 (497.6)	2213.4 (566.2)	2515.8 (645.3)	3206.6 (821.8)	<0.001
Iodine (mcg/d)	120.7 (49.7)	77.1 (23.9)	102.9 (28.9)	130.4 (37.7)	172.7 (45.3)	<0.001
Lycopene (mcg/d)	10096.4 (9512.9)	8115.1 (7599.1)	9638.0 (8025.6)	10190.4 (10103.4)	12447.4 (11347.8)	<0.001
Palmitoleic acid (g/d)	1.3 (0.5)	1.0 (0.3)	1.2 (0.3)	1.4 (0.3)	1.7 (0.5)	<0.001
Omega-3 fatty acid (g/d)	3.6 (1.9)	3.5 (2.1)	3.5 (1.8)	3.4 (1.7)	3.9 (2.1)	<0.001
Lutein and zeaxanthin (mcg/d)	1541.7 (1277.3)	1667.2 (1486.6)	1447.3 (1151.7)	1447.5 (1095.3)	1605.1 (1327.9)	0.018
Omega-6 fatty acid (g/d)	21.5 (11.0)	20.9 (11.1)	21.4 (10.3)	20.6 (10.3)	23.2 (11.9)	0.002
Biotin, B7 (mcg/d)	34.4 (17.0)	24.7 (11.1)	30.6 (12.3)	34.7 (13.7)	47.5 (20.4)	<0.001
Energy (kcal/day)	2063.1 (577.0)	1557.9 (370.9)	1890.1 (360.7)	2142.4 (391.8)	2663.3 (510.1)	<0.001

Supplementary Table 5.8 Pearson Correlation Coefficients between each nutrient pattern and the 39 food groups (NWAHS Stage 3, *n* = 1,743)

Food Group	Plant-sourced	Mixed source	Animal-sourced
Fruity vegetables	**0.69**	-	0.17
Root vegetables	**0.62**	-	-
Leafy vegetables	**0.53**	-	0.13
Cabbages	**0.52**	-	-
Other fruits	**0.50**	-	0.12
Stalk vegetables	**0.42**	-	0.13
Sugar	**0.37**	**0.52**	0.16
Tomato sauce	**0.32**	0.13	0.15
Nuts	**0.32**	-	0.21
Tea and water	**0.31**	0.40	-
Legumes	**0.30**	-	-
Potato without fat	**0.28**	-	-
Citrus fruit	**0.24**	-	-
High fibre bread	0.22	0.20	0.17
Jam and vegemite	0.21	**0.35**	-
Other cereals	0.20	0.21	-
Peanut butter	0.20	0.17	0.20
Juice	0.20	-	-
Fish	0.16	0.17	**0.27**
Medium fat dairy	0.16	0.23	-
Pasta and rice	0.11	0.14	-
High fibre cereals	-	-	-
Snacks	-	0.32	0.16
Potato with fat	-	-	-
Wine	-	-	-
Coffee	-	0.11	-
Poultry	-	0.20	-
Unsaturated spread	-	0.17	**0.30**
Red meat	-	**0.37**	0.20
Saturated spread	-	0.19	-
Eggs	-	0.21	**0.29**
Take away foods	-	0.30	0.23
Processed meat	-	**0.36**	**0.24**
Beer	-	0.11	-
Spirits	-	-	-
Flavoured milk	-	0.12	-
Soft drinks	-	-	-
White bread	-	0.13	0.13
High-fat dairy	-	**0.35**	0.14

Correlation coefficient higher than 0.23 ($p<0.001$) are typed in bold; correlation coefficient <0.1 are not reported

Supplementary Table 5.9 Pearson's correlation coefficients for MUFA, ω-3 PUFA, ω-6 PUFA, saturated fat, vitamin E with nutrients patterns (NWAHS Stage 3, *n* = 1,743)

	Plant-sourced NP	**Animal-sourced NP**	**Mixed-sourced NP**	**MUFA**	**ω-3 fatty acid**	**ω-6 fatty acid**
MUFA	0.2298* 0.0000	0.7329* 0.0000	0.4472* 0.0000			
ω-3 PUFA	0.1083* 0.0000	0.8238* 0.0000	0.0699* 0.0035	0.5906* 0.0000		
ω-6 PUFA	0.1764* 0.0000	0.8273* 0.0000	0.0714* 0.0029	0.6172* 0.0000	0.7573* 0.0000	
Saturated fat	-0.0135 0.5725	0.4253* 0.0000	0.7027* 0.0000	0.6721* 0.0000	0.2470* 0.0000	0.3080* 0.0000
Vitamin E	0.4648* 0.0000	0.6831* 0.0000	0.2969* 0.0000	0.8361* 0.0000	0.5788* 0.0000	0.6112* 0.0000

Supplementary Table 5.10 Association between CES-D factor structure and nutrient patterns at Stage 3 and NW15 in Australian adults (NWAHS Stage 3, *n* = 1525 and NW15, *n* = 891)

		OR (95% confidence interval)[a]											
		Stage 3						Stage NW15					
	(Ref) Q1	(Low intake) Q2	p-value	(Moderate intake) Q3	p-value	(Highest intake) Q4	p-value	(Low intake) Q2	p-value	(Moderate intake) Q3	p-value	(Highest intake) Q4	p-value
(Absence of) Positive affect													
Plant-sourced nutrient pattern													
Model 1	1	0.81(0.63-1.05)	0.118	0.72(0.56-0.93) **	0.014	0.63(0.48-0.83) ***	0.001	0.62(0.44-0.87) ***	0.006	0.65(0.46-0.91) **	0.014	0.54(0.37-0.78) ***	0.001
Model 2		0.96(0.73-1.25)	0.758	0.84(0.64-1.10)	0.212	0.75(0.56-1.00) *	0.056	0.71(0.50-1.01) *	0.058	0.81(0.57-1.16)	0.26	0.67(0.46-1.00) **	0.048
Animal-sourced nutrient pattern													
Model 1	1	0.94(0.73-1.21)	0.630	1.22(0.94-1.58)	0.128	1.04(0.79-1.37)	0.756	1.23(0.88-1.73)	0.212	0.72(0.51-1.02) *	0.068	1.00(0.70-1.44)	0.963
Model 2		0.97(0.75-1.26)	0.817	1.21(0.93-1.58)	0.149	1.02(0.77-1.35)	0.891	1.36(0.96-1.93)	0.080	0.77(0.54-1.10)	0.147	0.99(0.68-1.43)	0.960
Mixed-source nutrient pattern													
Model 1	1	0.97(0.74-1.26)	0.809	0.85(0.64-1.13)	0.264	1.00(0.70-1.43)	0.973	0.65(0.45-0.92) **	0.016	0.60(0.41-0.87) ***	0.007	0.72(0.45-1.14)	0.167
Model 2		0.96(0.73-1.26)	0.784	0.84(0.62-1.12)	0.242	0.91(0.63-1.32)	0.634	0.69(0.48-1.00) *	0.051	0.61(0.41-0.89) **	0.011	0.73(0.45-1.18)	0.205
Depressed affect													
Plant-sourced nutrient pattern													
Model 1	1	0.74(0.57-0.96) **	0.022	0.79(0.61-1.03)	0.085	0.60(0.46-0.80) ***	0.000	0.85(1.60-1.18)	0.343	0.78(0.55-1.09)	0.153	0.71(0.49-1.03) *	0.074
Model 2		0.87(0.65-1.14)	0.314	0.97(0.73-1.28)	0.822	0.74(0.55-1.00) *	0.054	0.88(0.62-1.26)	0.5	0.92(0.64-1.32)	0.671	0.85(0.57-1.26)	0.431
Animal-sourced nutrient pattern													
Model 1	1	0.97(0.75-1.25)	0.810	1.00(0.77-1.30)	0.977	1.18(0.90-1.57)	0.225	0.83(0.59-1.16)	0.293	0.82(0.58-1.15)	0.253	1.07(0.75-1.54)	0.692
Model 2		1.06(0.81-1.40)	0.634	1.00(0.76-1.33)	0.961	1.17(0.87-1.57)	0.283	0.87(0.61-1.23)	0.426	0.86(0.61-1.23)	0.437	1.02(0.70-1.49)	0.906
Mixed-source nutrient pattern													
Model 1	1	1.40(1.07-1.83) **	0.014	1.02(0.77-1.35)	0.898	1.22(0.86-1.74)	0.263	0.98(0.69-1.39)	0.919	1.23(0.84-1.78)	0.277	1.13(0.71-1.79)	0.591
Model 2		1.26(0.95-1.68)	0.107	0.90(0.67-1.22)	0.516	1.10(0.76-1.61)	0.598	0.89(0.61-1.28)	0.533	1.15(0.78-1.70)	0.460	1.10(0.68-1.79)	0.680

Model 1 was adjusted for sex, age and total energy intake

Model 2 was further adjusted for marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, physical activity and self-reported sleep quality, BMI, bodily pain, hypertension, diabetes and CVD

**** p<0.01, ** p<0.05, * p<0.1*

[a]*Ordinal logistic regression analysis; OR: Odds Ratio*

Chapter 6: Dietary inflammatory index and depressive symptoms

Dietary Inflammatory Index (DII®) and the risk of depression symptoms in adults

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6.1 PUBLICATION

This result chapter is reproduced in the exact form as it appears in the manuscript:

Shakya PR, Melaku YA, Shivappa N, Hébert JR, Adams RJ, Page AJ, Gill TK. Dietary Inflammatory Index (DII®) and the risk of depression symptoms in adults. Clin Nutr. 2020 (Submitted, Under review)

In keeping with the style of this thesis, the tables and figures have been re-numbered, the references reformatted and incorporated into the thesis master reference list, and the manuscript repaginated.

6.2 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Dietary inflammatory index™ (DII®) and the risk of depression symptoms in adults
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Submitted in 'Clinical Nutrition', the official journal of ESPEN, The European Society for Clinical Nutrition and Metabolism

Principal Author

Name of Principal Author (Candidate)	Prem Raj Shakya		
Contribution to the Paper	Conception and design, organization and interpretation of data, manuscript preparation, contribution to the materials/analysis tools and critical revision and editing of the manuscript		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	15/06/20

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	15/6/20

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Contribution to the Paper	Supervised the development of the work, conception and design, interpretation of results, critical manuscript evaluation and editing, contribution to the materials/analysis tools, and have given approval of the final version for publication		
Signature		Date	15/6/20

ABSTRACT

Background and aims

Findings from observational studies investigating the association between Dietary Inflammatory Index (DII®) scores and depression symptoms (DepS) are inconsistent. This study aims to assess the association between Energy-adjusted DII (E-DII™) and DepS using the North West Adelaide Health Study (NWAHS) cohort as well as update a previous meta-analysis.

Methods

A total of 1743 (mean ± SD age: 56.6 ± 13.6 years, 51% female) study participants from NWAHS were included in the cross-sectional study and 859 (mean ± SD age: 58.4 ± 12.1 years, 52.6% female) in the longitudinal analyses. The Center for Epidemiological Studies Depression Scale (CES-D) was used for the measurement of DepS. E-DII was calculated from the dietary data collected using validated FFQ. Data from two stages [Stage 3 (2008-10) and NW15 (2015)] were used. Log- and negative binomial regression were used to assess the association between quartiles of E-DII and DepS. A recent meta-analysis was updated by including 12 publications (six cross-sectional and six cohort studies) on the association between DII and DepS.

Results

In the cross-sectional analysis, a higher E-DII score (i.e. more pro-inflammatory diet) was associated with a 79% increase in odds of reporting DepS [$OR_{Quartile4vs1}$: 1.79; 95% CI: 1.14-2.81; $p = 0.012$; p for trend (p_{trend}) = 0.03]. Males with higher E-DII had a more than two-fold higher odds of DepS ($OR_{Quartile4vs1}$: 2.27; 95% CI: 1.02-5.06; $p = 0.045$; $p_{trend} = 0.09$). Females with higher E-DII had an 81% increase in odds of DepS

($OR_{Quartile4vs1}$: 1.81; 95% CI: 1.01-3.26; $p = 0.046$; $p_{trend} = 0.07$). These associations were consistent in the longitudinal analysis. Comparing highest to lowest quintiles of DII, the updated meta-analysis showed that a pro-inflammatory diet is associated with a 45% increase in odds of having DepS (OR: 1.45; 95% CI: 1.20-1.74; $p < 0.01$) with higher odds in females (OR: 1.53; 95% CI: 1.16-2.01; $p = 0.01$) compared to their male counterparts (OR: 1.29; 95% CI: 0.98-1.69; $p = 0.15$).

Conclusion

The data from the NWAHS and the updated meta-analysis of observational studies provide further evidence that a pro-inflammatory diet is positively associated with increased risk of DepS. These findings support the current recommendation on consuming a less inflammatory diet to improve DepS.

Keywords

Dietary inflammatory index, E-DII, Inflammation, CES-D, Depressive symptoms, Meta-analysis

INTRODUCTION

The World Health Organization (WHO) estimates that 322 million people live with depression globally [413]. In Australia, one in ten people (10.4%) had depression or feelings of depression in 2017-18 [115], representing a significant public health problem. Depression is a multifactorial disease with biological, psychological, social and behavioural determinants [146]. Of these factors, diet [449] and inflammation [450, 451] have been found to be important predictors of depression.

Increased levels of inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α), have been linked with depression [87, 452]. In a meta-analytic study of CRP levels, to determine the prevalence of low-grade inflammation among both sexes, nearly 1 in 4 patients with depression showed evidence of low-grade inflammation (CRP > 3 mg/L), and 58% exhibited mildly elevated CRP (>1mg/L) [453]. In addition to inflammatory biomarkers, food and nutrients have pro-/anti-inflammatory properties that may have an effect on depression [92].

Some studies have shown that the inflammatory property of diet was associated with an increased risk of DepS [88, 92, 93]. However, evidence from both cross-sectional [91, 94-101] and longitudinal studies [89, 102-108] have shown an inconsistent association between the inflammatory potential of diet and depression/DepS. In addition, many of these studies have limited generalizability as they used specific cohorts, such as middle-aged women [107], older adults (> 65 years) [108], female nurses [89], university graduates [105], primary care centres participants [97], health care centres participants [98] and office-based civil servants [104], rather than the general population. Further, these studies have not investigated the link between the Energy-adjusted Dietary Inflammatory Index (E-DII™) and specific components of the depression score such as depressed mood, feelings

of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance.

Therefore, this study aimed to explore the association between E-DII score and DepS in a representative sample of Australian adults, focussing on identifying specific DepS (from CES-D items) and updating the previous, most recent meta-analysis [109] by including the new data from the North West Adelaide Health Study (NWAHS) cohort.

METHODS

6.2.1 DATA SOURCE AND SUBJECTS

The data for this study were collected as part of the NWAHS, which is a longitudinal cohort study that recruited participants from the northern and western suburbs of Adelaide, South Australia. Three clinic-based stages of data collection had been conducted: 1999–2003, 2004–2006, and 2008–2010 [375]. In addition, a self-completed survey (postal or online) was conducted in 2015 (NW15). In the three clinic-based stages, in addition to the clinical assessments, data were collected using self-completed questionnaires and computer-assisted telephone interviews (CATI).

The details of this cohort have been published previously [375]. In brief, eligible study participants were adults aged 18 years and over when first recruited in Stage 1 from households with a landline which was randomly selected from the Electronic White Pages®. At the initial stage (Stage 1), a total of 4056 participants were enrolled. Data from Stage 3 (2008-2010, n = 2275) and NW15 (2015, n = 1300) were used in the current study. Dietary data were collected as part of Stage 3 (n = 2500) and 7.1% (n = 177) of participants were excluded because they did not have data on total energy intake or the energy intake was physiologically implausible (< 800 kcal for males, <600 kcal for

females and >4000 kcal for both sexes). Cross-sectional (n = 1743, 51% females) and longitudinal (n = 859, 52.6% females) analyses were conducted to determine the association between E-DII and DepS after further excluding 30.0% (n = 580) and 21.8% (n = 283) of participants respectively, due to at least one missing value of the covariates (*Figure 6.1*).

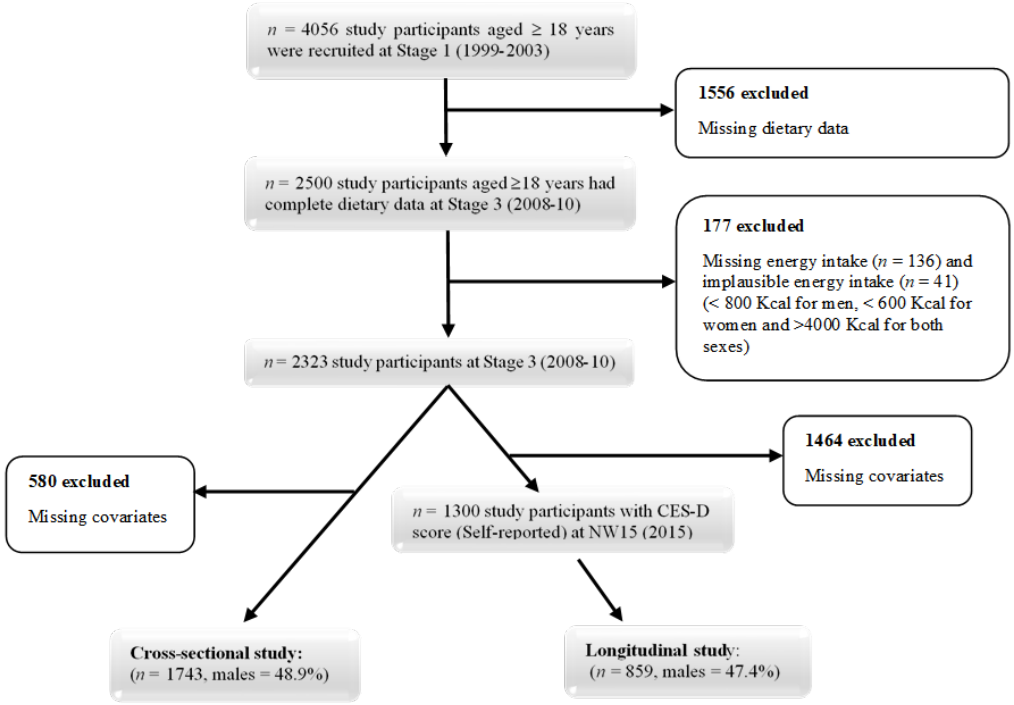


Figure 6.1 Flowchart of participants included in the study of association between E-DII™ and DepS from the NWAHS

CES-D - Centre for Epidemiological Studies Depression

6.2.2 ASSESSMENT OF DIETARY INTAKE AND COMPUTATION OF E-DII SCORES (EXPOSURE)

Dietary intake was assessed using the validated Dietary Questionnaire for Epidemiological Studies Version 3 (DQESV3), which is a revision of the food frequency questionnaire (FFQ) developed by Cancer Council Victoria [421]. DQESV3 is a well-

validated questionnaire specifically designed for Australian adults and has previously been used in many large-scale epidemiological studies in Australia, such as the Australian arm of the Breast Cancer Family Registry, Australian Prostate Cancer Family Study, and the Australian Longitudinal Study of Women's Health [376]. The details of the questionnaire have been published previously [422]. Briefly, the questionnaire consists of questions on consumption of different types of food and beverages, along with detailed information on alcoholic beverages. Photos illustrate three different serving sizes for foods such as potatoes, vegetables, and steak and the frequency of consumption of food items over the previous 12 months, with up to ten frequency options, ranging from never to three or more times per day, is determined. The completed questionnaires were sent to Cancer Council Victoria for analysis of total daily intake of food items and nutrients using software they developed, based upon the NUTTAB95 (Australian Government Publishing Service, Canberra) nutrient composition database [377].

We used the revised version of the DII calculation, developed by Shivappa *et al.* [83]. Briefly, the DII is a population-based index, based on a review of 1,943 peer-reviewed articles that evaluated the role of food parameters based on six inflammatory markers; either pro-inflammatory [(IL-1β, IL-6, TNF-α or C-reactive Protein (CRP)] or anti-inflammatory (IL-4 and IL-10) markers. In this extensive search, 45 food parameters were identified as being associated with the inflammatory markers. An individual score was assigned to each of the food parameters based on the weighted number of publications, the type of study, and whether the association between a food parameter and biological marker is pro- or anti-inflammatory. Eleven food consumption data sets, obtained from countries around the world, were used to compute an inflammatory effect score (Z = reported intake-world mean/world standard deviation) that was then converted to a proportion (values 0-1) and centred on zero by doubling and subtracting 1, as

described previously [83]. The centred proportion of each food variable, for each individual, was then multiplied by the respective effect score of the food variables (inflammatory potential for each food variable), which was derived from the literature review, to obtain a food variable–specific DII score for a subject. DII scores across food parameters were then summed to create an 'overall DII score' for each individual in the study. In the current study, we have used the E-DII, which is a logical extension of the original DII, but is calculated per 1000 calories of food consumed, and requires the use of the Energy-standardized version of the world database to control for the effect of total energy intake. The E-DII for this study was computed using data on 29 out of the 45 variables including pro-inflammatory components (carbohydrate, protein, fat, saturated fatty acids (SFA), iron, cholesterol, trans-fat, vitamin B12) and anti-inflammatory components (alcohol, fibre, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), ω-3, ω-6, niacin, thiamine, riboflavin, magnesium, zinc, vitamin A, vitamin C, vitamin E, vitamin D, vitamin B6, folic acid, β-carotene, tea, garlic and onions) (*Supplementary Figure 6.1*).

6.2.3 OUTCOME VARIABLE

DepS were measured using the Center for Epidemiological Studies Depression Scale (CES-D) [133], which assesses the frequency of DepS using 20 questions. Participants indicated how much of the time during the past week they experienced each symptom on a 4-point scale (rarely or none of the time, some or little of the time, occasionally or moderate amount of the time and most or all of the time) with a maximum score of 60 and a high score reflecting more significant DepS. Radloff *et al.* suggested a cut-off score of 16 across all items, was indicative of DepS [133]. It should be noted, however, that this scale is not generally used for diagnostic purposes [133]. In terms of reliability, the CES-D

has a high internal consistency; Cronbach's α ranges from 0.85 (general population) to 0.90 (psychiatric population) [132]. Incident depression was defined as a new onset of DepS between Stage 3 (2008-10) and NW15 (2015).

6.2.4 COVARIATES SELECTION

A DAG, created by a web-browser based software DAGitty [454], was used to determine the potential covariates of the association between E-DII and DepS scores. The selection of covariates was based on the literature indicating multiple potential confounding variables (*Supplementary Figure 6.2*). Covariates relevant to the current analysis included socio-demographic, behaviour and metabolic factors, as well as chronic conditions. The Index of Relative Social Disadvantage (IRSD) was used as the socioeconomic index for areas (SEIFA) index in this study and divided into quintiles, with the highest representing greatest advantage [387]. Marital status was categorized into married or living together with a partner (in a union), separated/divorced, widowed and never married. Annual household income was categorised as follows: up to A$20,000, A$20,001–A$40,000, A$40,001–A$60,000, A$60,001-A$80,000 and more than A$80,000.

Level of education was categorized into 'Did not complete school/high school level', 'Trade/certificate/diploma' and 'Degree/higher'. PAL was categorized into three categories: 'no activity', 'activity but not sufficient' and 'sufficient activity', with sufficient activity defined as the completion of at least 150 minutes of walking, moderate and vigorous activity (with vigorous activity time doubled to reflect its greater intensity) in the past week [455]. Sleep quality was assessed by a self-reported question and categorized as 'very good', 'fairly good', 'fairly bad' and 'very bad'. Smoking status was classified as non-smokers, ex-smokers and current smokers. 'Ex-smokers' were

those participants who did not currently smoke, but had regularly smoked daily, or had smoked at least 100 cigarettes, or smoked pipes, cigars, at least 20 times in their lifetime and 'current smokers' was those who reported at the time of interview that they regularly smoked one or more cigarettes, cigars or pipes [115]. Alcohol exposure was assessed using the frequency and number of standard drinks based on the 1989 National Heart Foundation Risk Factor Prevalence study classification [388] and was categorized as non-drinkers, low-risk, and intermediate to very-high-risk.

In this analysis, we included diabetes, hypertension and cardiovascular disease (CVD) as chronic conditions and body mass index (BMI), a measure of relative weight (i.e. weight(kg)/height(m)^2), as a metabolic factor. Standard protocols were used to measure height and weight which was converted into BMI, and further classified into underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese categories (> 30 kg/m^2) based on the WHO [389] guidelines on anthropometric measurement. Diabetes mellitus was diagnosed based on fasting plasma glucose (FPG ≥ 7.0 mmol/L) and/or self-reported doctor-diagnosed diabetes. Hypertension was diagnosed by considering both systolic (> 140 mmHg) and diastolic (> 90 mmHg) blood pressure. CVD was diagnosed based on clinically diagnosed self-reported data. Data for bodily pain were extracted from items 21 and 22 of the Short Form (SF) 36 questionnaire and categorized as 'Yes/No' based on a median cut-off score of 76 [391].

6.2.5 META-ANALYSIS ON DII AND DEPS

We updated a previous meta-analysis [109], which involved a search of the literature up to 3rd October 2018, to include the NWAHS findings. The meta-analysis techniques were undertaken using similar methods as those used previously by Tolkien *et al*. [109].

We then conducted literature searches in PubMed® and Scopus® from 4th October 2018 to 15th May 2020 based on the following search terms: 'inflammat*' AND 'diet' AND 'depress*'. Relevant articles were obtained and included in the meta-analysis if studies: i) measured DII/E-DII; ii) had depression or DepS as an outcome measure; iii) reported effect size and confidence intervals (CI) for the association between DII/E-DII and depression/DepS.

6.2.6 DATA SYNTHESIS AND STATISTICAL ANALYSIS

All searches, data abstraction, data verification and tabulation were completed independently by two independent reviewers (P.R.S and Y.A.M). Conflicts were discussed among all the authors and resolved. Newly identified observational studies from 4th October 2018 to 15th May 2020 were added to the preceding meta-analysis by Tolkien *et al.* [109] (Supplementary Table 6.1). Sex-specific effects were also extracted. All the reported effects, odds ratio (OR), the hazard ratio (HR) and relative risk (RR) effects, were pooled and presented as 'OR' representing the likelihood of depression or DepS in the highest category of DII/E-DII score, compared to the lowest category of DII/E-DII score.

6.2.7 QUALITY ASSESSMENT

To assess study quality and risk of bias in studies, the Newcastle-Ottawa Scale (NOS) for cohort studies was used [456] (*Supplementary Table 6.2*). This scale was modified to include cross-sectional studies to fit the analysis (Supplementary Table 6.3). A maximum score of 7 and 8 points was available for cross-sectional and longitudinal studies, respectively. Consistent with the previous study [109], these scores were converted

to percentages and scores of ≥75% were considered to be of high quality and those with <75% were classified as lower quality.

6.2.8 STATISTICAL ANALYSES

For the descriptive analysis, we used mean (±SD) (for continuous, normally distributed variables), medians and interquartile ranges (for continuous non-normally distributed variables) and proportions (for categorical variables). To compare the difference between categorical variables, the chi-square test was used, and continuous variables were tested using ANOVA. We used the Kruskal-Wallis test for continuous, but not normally distributed, data. DII scores and CES-D-scores were categorized into quartiles [Q1 (lowest intake), Q2, Q3 and Q4 (highest intake)].

Because an association between E-DII and DepS were observed using both cross-sectional and longitudinal analysis, three approaches were undertaken depending on the nature of the outcome variable data. Log-binomial regression was used in the model where DepS was used as a binary outcome variable. Negative binomial regression was used when DepS was a count variable. Ordinal logistic regression analysis was used to determine the association between quartiles of E-DII and each CES-D item. Results were reported as the odds ratio (OR) for log-binomial regression and ordinal regression analysis, whereas, for negative binomial regression, the prevalence ratio (PR) was reported.

Three models were generated for the analysis. The first model was adjusted for age and sex. The second model was further adjusted for educational status, marital status, employment status, annual income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality. The third model was additionally adjusted for BMI, bodily pain, antidepressant use, hypertension, diabetes and CVD. The trend of associations, as a

continuous parameter, was assessed across the quartiles of E-DII. Subgroup analyses for sex, educational status, work status, income status, PAL, smoking status, hypertension and CVD were performed using the fully adjusted log-binomial model to assess the association of the E-DII with DepS in various subgroups of the study participants.

The meta-analysis was performed using the '*meta*' and '*metafor*' package in R using a random effect model [457]. Heterogeneity between studies was assessed using the I^2 statistic that represents the percentage of variation across studies. Statistical analyses were performed using Stata version 15.1 (Stata Corporation, College Station, TX, USA) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

6.2.9 DESCRIPTIVE CHARACTERISTICS

The mean age (SD) of participants at Stage 3 was 56.6 (SD 13.6) years ranging from 24 - 94 years. The mean E-DII in this study was -1.30 (SD 1.35), and the scores ranged from -4.53 (most anti-inflammatory) to +3.79 (most pro-inflammatory). The anthropometric, socioeconomic and clinical characteristics of the participants stratified by quartiles of E-DII are illustrated in Table 6.1. As compared to subjects in the most anti-inflammatory E-DII category (Quartile 1), those in the most pro-inflammatory (Quartile 4) were significantly more likely to be younger [p for trend (p_{trend} < 0.001)], have a high school-level education (p_{trend} = 0.006), have never married (p_{trend} = 0.006), be current smokers (p_{trend} < 0.001) and be sedentary (p_{trend} < 0.001).

Table 6.1 Characteristics of study participants across quartiles of the E-DII score in adult Australians participating in the NWAHS, Stage 3 (2008-10; *n* = 1743)

	Total	Q1 (low-inflammatory diet)	Q2	Q3	Q4 (high-inflammatory diet)	P-value
	1743	436	436	436	435	
E-DII™ score[b]	-1.30 (1.35)	-2.89 (0.41)	-1.90 (0.26)	-0.95 (0.28)	0.54 (0.80)	<0.001
Age (years)[b]	56.6 (13.6)	58.4 (11.8)	57.1 (13.5)	56.9 (14.5)	53.9 (14.1)	<0.001
Sex[a]; n (%)						
Male	854 (49.0)	168 (38.5)	205 (47.0)	232 (53.2)	249 (57.2)	<0.001
Female	889 (51.0)	268 (61.5)	231 (53.0)	204 (46.8)	186 (42.8)	
Educational status[a]; n (%)						
Did not complete school/ high school level	870 (49.9)	203 (46.6)	208 (47.7)	227 (52.1)	232 (53.3)	0.006
Trade/ certificate/ diploma	554 (31.8)	140 (32.1)	132 (30.3)	133 (30.5)	149 (34.3)	
Degree or higher	319 (18.3)	93 (21.3)	96 (22.0)	76 (17.4)	54 (12.4)	
Marital status[a]; n (%)						
Married or living with partner	1,214 (69.7)	317 (72.7)	316 (72.5)	297 (68.1)	284 (65.3)	0.006
Separated/divorced	239 (13.7)	61 (14.0)	51 (11.7)	53 (12.2)	74 (17.0)	
Widowed	151 (8.7)	36 (8.3)	35 (8.0)	50 (11.5)	30 (6.9)	
Never married	139 (8.0)	22 (5.0)	34 (7.8)	36 (8.3)	47 (10.8)	
Work status[a]; n (%)						
Employed	1,003 (57.5)	235 (53.9)	245 (56.2)	254 (58.3)	269 (61.8)	0.14
Unemployed	23 (1.3)	7 (1.6)	7 (1.6)	2 (0.5)	7 (1.6)	
Retired	562 (32.2)	158 (36.2)	143 (32.8)	145 (33.3)	116 (26.7)	
Other	155 (8.9)	36 (8.3)	41 (9.4)	35 (8.0)	43 (9.9)	
Income per year[a]; n (%)						
Up to A$20,000	248 (14.2)	61 (14.0)	60 (13.8)	63 (14.4)	64 (14.7)	0.94
A$20,001-A$40,000	449 (25.8)	121 (27.8)	107 (24.5)	108 (24.8)	113 (26.0)	
A$40,001-A$60,000	303 (17.4)	72 (16.5)	85 (19.5)	75 (17.2)	71 (16.3)	
A$60,001-A$80,000	245 (14.1)	59 (13.5)	57 (13.1)	59 (13.5)	70 (16.1)	
More than A$80,000	498 (28.6)	123 (28.2)	127 (29.1)	131 (30.0)	117 (26.9)	
SEIFA[a]; n (%)						
Lowest quintile	443 (25.4)	101 (23.2)	104 (23.9)	114 (26.1)	124 (28.5)	0.022
Low quintile	430 (24.7)	122 (28.0)	86 (19.7)	102 (23.4)	120 (27.6)	
Middle quintile	378 (21.7)	95 (21.8)	106 (24.3)	91 (20.9)	86 (19.8)	
High quintile	383 (22.0)	92 (21.1)	113 (25.9)	92 (21.1)	86 (19.8)	
Highest quintile	109 (6.3)	26 (6.0)	27 (6.2)	37 (8.5)	19 (4.4)	
Smoking status[a]; n (%)						
Non-smoker	792 (45.4)	220 (50.5)	201 (46.1)	205 (47.0)	166 (38.2)	<0.001
Ex-smoker	705 (40.4)	170 (39.0)	191 (43.8)	165 (37.8)	179 (41.1)	
Current smoker	246 (14.1)	46 (10.6)	44 (10.1)	66 (15.1)	90 (20.7)	
Sleep quality[a]; n (%)						
Very good	319 (18.3)	93 (21.3)	73 (16.7)	73 (16.7)	80 (18.4)	0.51
Fairly good	1,023 (58.7)	258 (59.2)	254 (58.3)	263 (60.3)	248 (57.0)	
Fairly bad	347 (19.9)	72 (16.5)	93 (21.3)	87 (20.0)	95 (21.8)	
Very bad	54 (3.1)	13 (3.0)	16 (3.7)	13 (3.0)	12 (2.8)	
Alcohol risk[a]; n (%)						
Non-drinkers, no risk	933 (53.5)	212 (48.6)	227 (52.1)	252 (57.8)	242 (55.6)	0.003
Low risk	720 (41.3)	211 (48.4)	182 (41.7)	164 (37.6)	163 (37.5)	
Intermediate to very high risk	90 (5.2)	13 (3.0)	27 (6.2)	20 (4.6)	30 (6.9)	
PAL[a]; n (%)						
No activity	306 (17.6)	59 (13.5)	78 (17.9)	66 (15.1)	103 (23.7)	<0.001
Activity but not sufficient	752 (43.1)	168 (38.5)	181 (41.5)	199 (45.6)	204 (46.9)	
Sufficient activity	685 (39.3)	209 (47.9)	177 (40.6)	171 (39.2)	128 (29.4)	
BMI category[a]; n (%)						
Underweight	13 (0.7)	4 (0.9)	2 (0.5)	3 (0.7)	4 (0.9)	0.93
Normal weight	430 (24.7)	100 (22.9)	109 (25.0)	116 (26.6)	105 (24.1)	
Overweight	702 (40.3)	184 (42.2)	178 (40.8)	172 (39.4)	168 (38.6)	
Obese	598 (34.3)	148 (33.9)	147 (33.7)	145 (33.3)	158 (36.3)	
Antidepressant Use[a] (Stage 3); n (%)						
No	1,433 (82.2)	363 (83.3)	365 (83.7)	360 (82.6)	345 (79.3)	0.32
Yes	310 (17.8)	73 (16.7)	71 (16.3)	76 (17.4)	90 (20.7)	
Bodily pain[a]; n (%)						
No	837 (48.0)	193 (44.3)	207 (47.5)	211 (48.4)	226 (52.0)	0.16
Yes	906 (52.0)	243 (55.7)	229 (52.5)	225 (51.6)	209 (48.0)	

(table continues)

Table 6.1 *(table continued)*

Characteristics of study participants across quartiles of the E-DII score in adult Australians participating in the NWAHS, Stage 3 (2008-10; *n* = 1743)

	Total	Q1 (low-inflammatory diet)	Q2	Q3	Q4 (high-inflammatory diet)	P-value
BP[a]; n (%)						
Hypertension	469 (26.9)	126 (28.9)	106 (24.3)	126 (28.9)	111 (25.5)	0.3
No Hypertension	1,274 (73.1)	310 (71.1)	330 (75.7)	310 (71.1)	324 (74.5)	
Diabetes[a]; n (%)						
No diabetes	1,568 (90.0)	385 (88.3)	398 (91.3)	388 (89.0)	397 (91.3)	0.33
Diabetes (diagnosed and undiagnosed)	175 (10.0)	51 (11.7)	38 (8.7)	48 (11.0)	38 (8.7)	
CVD[a]; n (%)						
No CVD	1,590 (91.2)	390 (89.4)	396 (90.8)	406 (93.1)	398 (91.5)	0.28
CVD (inc TIA)	153 (8.8)	46 (10.6)	40 (9.2)	30 (6.9)	37 (8.5)	
Energy[b] (kcal/day)	2063 (577)	2034 (530)	2033 (556)	2109 (570)	2076 (644)	0.15
Depression (Stage 3)[a]; n (%)						
No depressive symptoms	1,448 (83.1)	384 (88.1)	364 (83.5)	365 (83.7)	335 (77.0)	<0.001
Depressive symptoms	295 (16.9)	52 (11.9)	72 (16.5)	71 (16.3)	100 (23.0)	

BMI - body mass index; *BP*: blood pressure; *CVD* - cardiovascular disease; *PAL* - physical activity level; *SEIFA* - socio-economic index for areas; TIA - transient ischaemic attack

[a]Pearson's Chi-squared test

[b]Two-sample *t* test

Table 6.2 shows the distribution of food and nutrient groups across quartiles of E-DII. Participants in the fourth quartile had lower consumption of anti-inflammatory foods and nutrients, such as β-carotene, garlic, onion, tea, PUFA and all vitamins and minerals, compared to participants in the first quartile. In contrast, the consumption of pro-inflammatory food and nutrients, such as alcohol, carbohydrates cholesterol, SFA and total fat, was found to be increased in the fourth quartile.

Table 6.2 Nutritional data of study participants across quartiles of the E-DII score in the Australian adults participating in NWAHS study, Stage 3 (2008-10; *n* = 1743)

	Total	Q1	Q2	Q3	Q4	P-value
n	1743	436	436	436	435	
Food and nutrients						
Alcohol (g/d)	3.4 (9.9)	2.3 (6.8)	2.7 (8.1)	3.4 (9.9)	5.1 (13.3)	<0.001
Beta carotene (mg/d)	3310 (1800)	4929 (1874)	3609 (1469)	2744 (1241)	1955 (946)	<0.001
Caffeine (mg/d)	351 (280)	381 (275)	348 (276)	378 (281)	296 (283)	<0.001
Carbohydrates (g/d)	209.6 (85.8)	201.3 (63.5)	204.6 (74.9)	214.3 (89.3)	218.5 (108.2)	0.009
Cholesterol (mg/d)	279 (106)	265 (100)	272 (100)	289 (108)	291 (114)	<0.001
Iron (mg/d)	12.71 (4.31)	13.65 (4.11)	12.95 (4.01)	12.79 (4.34)	11.45 (4.47)	<0.001
Fibre (g/d)	27.2 (10.6)	32.7 (10.0)	28.8 (9.2)	25.9 (9.5)	21.3 (10.3)	<0.001
Folic acid (mg/d)	173 (155)	196 (184)	165 (145)	170 (131)	160 (154)	0.029
Garlic (g/d)	0.5 (0.8)	0.8 (1.0)	0.6 (0.7)	0.4 (0.7)	0.3 (0.4)	<0.001
Tea (g/d)	306.9 (342.6)	317.3 (341.8)	354.9 (358.0)	306.2 (341.6)	249.0 (320.7)	<0.001
Magnesium (mg/d)	442 (157)	487 (146)	448 (149)	448 (153)	384 (161)	<0.001
Monounsaturated fat (g/d)	36.5 (12.5)	36.5 (11.7)	36.2 (12.1)	37.6 (12.2)	35.8 (13.7)	0.14
Omega-3 fatty acid (mg/d)	3595 (1945)	4013 (1930)	3638 (1939)	3735 (2023)	2994 (1737)	<0.001
Omega-6 fatty acid (mg/d)	21500 (10967)	23332 (10799)	21786 (10904)	22020 (10087)	18856 (11574)	<0.001
Niacin, B3 (mg/d)	27 (13)	28 (11)	26 (12)	27 (14)	25 (15)	0.015
Onion (g/d)	6.2 (6.2)	9.0 (7.7)	6.5 (6.1)	5.2 (5.3)	4.1 (4.4)	<0.001
Protein (g/d)	95.1 (28.1)	97.8 (27.6)	95.0 (26.3)	96.0 (27.6)	91.5 (30.4)	0.008
Polyunsaturated fat (g/d)	15.6 (6.3)	16.7 (5.9)	15.7 (6.6)	15.9 (5.9)	14.1 (6.5)	<0.001
Riboflavin combined (mg/d)	3.37 (1.85)	3.76 (2.10)	3.37 (1.75)	3.42 (1.67)	2.92 (1.77)	<0.001
Saturated fat (g/d)	28.8 (11.2)	24.8 (8.2)	27.1 (9.6)	30.4 (10.2)	32.8 (14.3)	<0.001
Thiamine (mg/d)	3.00 (2.00)	3.44 (2.31)	3.03 (1.85)	3.07 (1.79)	2.48 (1.89)	<0.001
Fat (g/d)	87.0 (27.6)	84.6 (25.1)	85.3 (27.3)	90.1 (26.9)	88.1 (30.7)	0.010
Retinol (mg/d)	325 (146)	287 (126)	308 (146)	351 (147)	355 (151)	<0.001
Vitamin B12 (mg/d)	3.4 (1.6)	3.1 (1.6)	3.2 (1.5)	3.5 (1.6)	3.5 (1.7)	<0.001
Vitamin B6 (mg/d)	1.32 (1.58)	1.56 (1.91)	1.50 (2.29)	1.16 (0.73)	1.05 (0.62)	<0.001
Vitamin C (mg/d)	135 (73)	188 (72)	149 (67)	119 (62)	85 (46)	<0.001
Vitamin D (mg/d)	3.5 (2.0)	3.4 (1.9)	3.4 (2.0)	3.6 (2.1)	3.4 (2.0)	0.15
Vitamin E (mg/d)	11.15 (4.00)	12.69 (3.99)	11.32 (3.72)	10.96 (3.77)	9.60 (3.93)	<0.001
Zinc (mg/d)	10.58 (3.67)	10.74 (3.51)	10.54 (3.49)	10.76 (3.54)	10.28 (4.10)	0.19
Energy (kcal/day)	2063 (577)	2034 (530)	2033 (556)	2109 (570)	2076 (644)	0.15

Values are expressed in Mean (SD)

6.2.10 E-DII AND PREVALENT DEPS

The overall prevalence of DepS was 16.9% (*n* = 295) with rates of 11.9% (*n* = 52), 16.5% (*n* = 52), 16.3% (*n* = 71) and 23.0% (*n* = 100) across E-DII quartiles. Log-binomial regression, after adjusting for 18 potential confounders at baseline (i.e., Model 3) and with the lowest E-DII as reference (Q1), showed that participants with a higher E-DII™ score (Q4) had a significantly higher level of prevalent DepS ($OR_{Quartile4vs1}$: 1.79; 95% CI: 1.14-2.81; $p = 0.012$; $p_{trend} = 0.026$). Stratification by sex revealed that men with higher E-DII scores had significantly higher odds of prevalent DepS ($OR_{Quartile4vs1}$: 2.27; 95% CI: 1.02-5.06; $p = 0.045$; $p_{trend} = 0.089$). A positive association was also observed between E-DII™ and DepS among female participants ($OR_{Quartile4vs1}$:

1.81; 95% CI: 1.01-3.26; p = 0.046; p_{trend} = 0.068). Negative binomial regression revealed similar findings, with a significant positive association between quartiles of E-DII score and CES-D score ($PR_{Quartile4vs1}$: 1.34; 95% CI: 1.15-1.56; $p < 0.001$; $p_{trend} <$ 0.001). This association remained in the stratified analysis by sex (Table 6.3).

After stratifying the subjects into two groups (<65 years, representing non-elderly adult population and ≥65 years, representing elderly population), we observed a significant positive association between E-DII score and DepS in the non-elderly adult population ($OR_{Quartile4vs1}$: 1.80; 95% CI: 1.05-3.07; $p < 0.05$; p_{trend} = 0.15). However, in the elderly population (≥65 years), we did not observe any significant association between E-DII and DepS. Using negative binomial regression, a significant association was observed between E-DII and DepS in both age groups (<65 years and ≥65 years) in the stratified cross-sectional analysis, while the association was not evident in the prospective analysis (Supplementary Table 6.4)

6.2.11 E-DII AND INCIDENT DEPS

The overall incidence of DepS, defined as new onset of DepS between Stage 3 (2008-10) and NW15 (2015), was found to be 12.6% (n = 108), with 9.3% (n = 20), 12.1% (n = 26), 14.0% (n = 30) and 15.0% (n = 32) across the E-DII quartiles from lowest to highest. Effect sizes and confidence intervals for the risk of DepS according to quartiles of E-DII are shown in Table 6.3. Results obtained from modelling DepS as a dichotomous variable suggested a positive association after adjustment of potential confounders ($OR_{Quartile4vs1}$: 1.44; 95% CI: 0.74-2.78; p = 0.28; p_{trend} = 0.27) which was more pronounced in males ($OR_{Quartile4vs1}$: 2.26; 95% CI: 0.63-8.17; p = 0.21; p_{trend} = 0.305) than in females ($OR_{Quartile4vs1}$: 1.22; 95% CI: 0.52-2.88; p = 0.65; p_{trend} = 0.64). When the analysis was undertaken with CES-D as a continuous score, after adjusting for

potential confounding variables, a positive trend was observed ($PR_{Quartile4vs1}$: 1.26; 95% CI: 1.01-1.58; $p = 0.047$; $p_{trend} = 0.02$) which was more pronounced in males than females (Table 6.3). The use of the continuous CES-D score may have contributed to a statistically significant result as dichotomising the variable may lead to some loss of information and overall reduced statistical power as outlined by Ragland *et al.*[448]. The significant results with continuous variable indicate that an association between a pro-inflammatory diet and an increasing number of DepS.

Table 6.3 Association between quartiles of E-DII score and prevalent DepS in Australian adults participating in the NWAHS, Cross-sectional analysis at Stage 3 (2008-10; *n* = 1,743) and Prospective analysis at NW15 (2015; *n* = 859)

	Q1 (Ref)	Q2	Q3	Q4	P for trend	Q2	Q3	Q4	P for trend
	Cross-sectional					Prospective			
[a]Log-binomial regression									
All participants									
Model 1	1.00	1.50 (1.02-2.21)*	1.51 (1.03-2.23)*	2.30 (1.58-3.35)***	0.000	1.35 (0.73-2.50)	1.64 (0.90-3.01)	1.74 (0.95-3.17)	0.057
Model 2	1.00	1.35 (0.88-2.09)	1.36 (0.87-2.11)	1.87 (1.22-2.86)***	0.005	1.21 (0.63-2.32)	1.52 (0.80-2.87)	1.45 (0.77-2.75)	0.199
Model 3	1.00	1.52 (0.96-2.39)	1.39 (0.87-2.21)	1.79 (1.14-2.81)**	0.026	1.26 (0.65-2.45)	1.43 (0.74-2.78)	1.44 (0.74-2.78)	0.267
Men									
Model 1	1.00	1.77 (0.92-3.41)	1.52 (0.79-2.93)	2.10 (1.13-3.93)***	0.042	1.79 (0.64-4.99)	1.87 (0.69-5.06)	1.73 (0.64-4.72)	0.357
Model 2	1.00	1.55 (0.75-3.21)	1.37 (0.66-2.87)	1.82 (0.89-3.75)	0.157	1.74 (0.56-5.48)	1.76 (0.57-5.45)	1.35 (0.43-4.20)	0.749
Model 3	1.00	1.94 (0.87-4.33)	1.79 (0.80-4.05)	2.27 (1.02-5.06)*	0.089	2.32 (0.64-8.40)	2.39 (0.67-8.51)	2.26 (0.63-8.17)	0.305
Women									
Model 1	1.00	1.34 (0.82-2.17)	1.51 (0.93-2.47)	2.55 (1.59-4.11)***	0.000	1.11 (0.50-2.45)	1.57 (0.72-3.44)	1.79 (0.84-3.82)	0.089
Model 2	1.00	1.28 (0.73-2.25)	1.42 (0.80-2.51)	2.20 (1.26-3.82)**	0.006	1.05 (0.46-2.42)	1.26 (0.54-2.91)	1.44 (0.63-3.27)	0.335
Model 3	1.00	1.41 (0.79-2.52)	1.30 (0.71-2.37)	1.81 (1.01-3.26)*	0.068	0.99 (0.42-2.32)	1.03 (0.43-2.46)	1.22 (0.52-2.88)	0.643
[b]Negative binomial regression									
All participants									
Model 1	1.00	1.27 (1.10-1.46)*	1.36 (1.18-1.57)**	1.54 (1.33-1.78)**	0.000	1.20 (0.97-1.48)	1.44(1.16-1.77)**	1.39 (1.12-1.72)**	0.001
Model 2	1.00	1.24 (1.07-1.44)*	1.35 (1.16-1.56)**	1.41 (1.22-1.64)**	0.000	1.19 (0.96-1.49)	1.45(1.16-1.80)**	1.29 (1.03-1.61)*	0.008
Model 3	1.00	1.23 (1.07-1.43)*	1.31 (1.13-1.52)**	1.34 (1.15-1.56)**	0.000	1.19 (0.95-1.48)	1.41(1.13-1.75)**	1.26 (1.01-1.58)*	0.017
Men									
Model 1	1.00	1.39 (1.11-1.73)*	1.40 (1.13-1.74)*	1.50 (1.21-1.86)**	0.001	1.35 (0.97-1.87)	1.26(0.92-1.74)	1.45 (1.06-1.99)	0.051
Model 2	1.00	1.39 (1.10-1.74)*	1.39 (1.11-1.74)*	1.42 (1.13-1.77)**	0.01	1.37 (0.96-1.95)	1.25(0.89-1.75)	1.30 (0.92-1.83)	0.274
Model 3	1.00	1.34 (1.07-1.69)*	1.36 (1.08-1.70)*	1.36 (1.08-1.70)*	0.026	1.37 (0.95-1.97)	1.27(0.90-1.80)	1.31 (0.92-1.86)	0.258
Women									
Model 1	1.00	1.18 (0.98-1.42)	1.33 (1.10-1.62)*	1.62 (1.32-1.98)**	0.000	1.09 (0.83-1.44)	1.62 (1.22-2.15)**	1.32 (0.99-1.76)	0.005
Model 2	1.00	1.18 (0.97-1.43)	1.33 (1.09-1.62)*	1.48 (1.20-1.83)*	0.000	1.09 (0.81-1.46)	1.60 (1.19-2.16)**	1.23 (0.91-1.66)	0.025
Model 3	1.00	1.22 (1.00-1.48)*	1.30 (1.06-1.59)*	1.37 (1.11-1.70)*	0.003	1.07 (0.80-1.44)	1.47 (1.08-2.00)**	1.09 (0.80-1.49)	0.216

[a]Values are expressed in ORs (95% CIs) [b]Values are expressed in IRRs (95% CIs)

Model 1 was adjusted for sex and age

Model 2 was additionally adjusted for marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, PAL and self-reported sleep quality

Model 3 was additionally adjusted for BMI, bodily pain, anti-depressant use, hypertension, T2DM and CVD

*p < 0.1, **p < 0.05, ***p < 0.01

6.2.12 E-DII AND SPECIFIC DEPS

Ordinal regression analysis (n = 1525) for the association between quartiles of E-DII and each CES-D item are illustrated in *Figure 6.2*. A significant positive association was observed with item 2 i.e. 'Appetite poor' ($OR_{Quartile4vs1}$: 1.99; 95% CI: 1.28-3.09; p = 0.002), item 8 i.e. 'Not hopeful about future', ($OR_{Quartile4vs1}$: 1.93, 95% CI: 1.42-2.63; $p < 0.001$), item 12 i.e. 'Did not feel happy' ($OR_{Quartile4vs1}$: 2.04; 95% CI: 1.45-2.88; $p < 0.001$), item 14 i.e. 'Felt lonely' ($OR_{Quartile4vs1}$: 1.99; 95% CI: 1.38-2.87; $p < 0.001$) and item 16 i.e. 'Did not enjoy life' ($OR_{Quartile4vs1}$: 2.05; 95% CI: 1.44-2.9; $p < 0.001$). Among these, items 8, 12 and 16 are the 'Positive affect' components of CES-D items. Further analysis with sex-specific models were also performed; *Supplementary Figure 6.3* and *Supplementary Figure 6.4* show females are generally, when comparing Q4 with Q1, more prone to DepS compared to males.

6.2.13 SUBGROUP ANALYSIS

Results of the subgroup analyses for E-DII with various covariates (sex, educational status, work status, income status, SEIFA, PAL, smoking status, hypertension and CVD) are presented in *Supplementary Figure 6.5*. We did not observe any significant interaction between E-DII and these parameters.

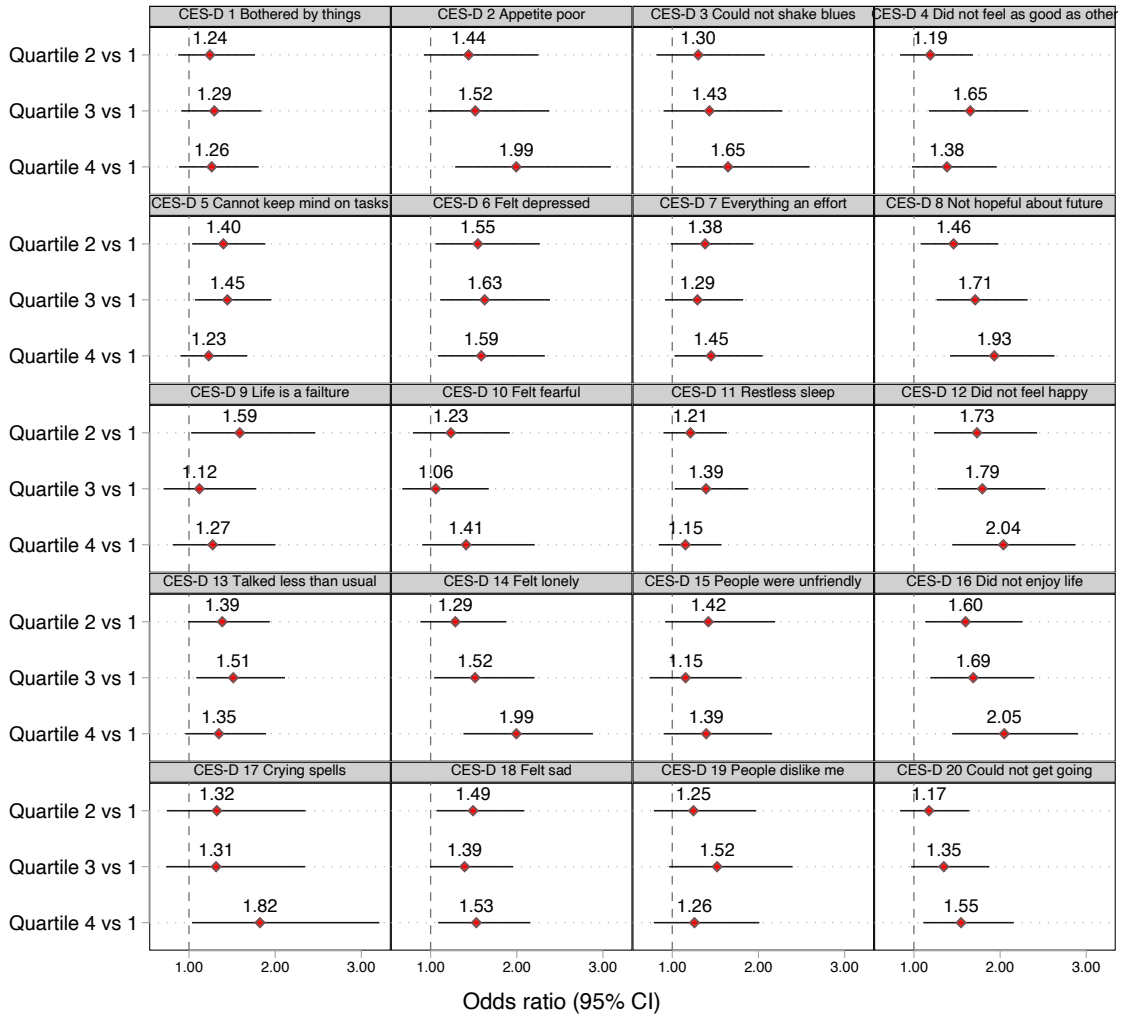


Figure 6.2 Association between a quartiles of E-DII and each CES-D items in NWAHS participants (n = 1525)

6.2.14 META-ANALYSIS

Our updated literature search (up to 15th May 2020) on PubMed® and Scopus® found four additional studies [94, 98, 99, 103]. Three met the inclusion criteria and were added to the studies included in the previous meta-analysis [109]. We excluded a study by Salari-Moghaddam *et al.* in which food-based DII (FDII) scores, from -14.67 to +8.29, was derived [99]. This study was excluded as the DII calculation was only based on food groups and cannot be compared with the original DII scores, and the low values were out of plausible range [83]. Therefore, a total of 12 studies (including the current NWAHS findings) were included in this meta-analysis on DII and DepS. The details of the study characteristics are in Supplementary Table 6.1. Briefly,

studies were included that assessed the inflammatory potential of diet specifically using the DII score [94, 97, 98, 100-107]. We excluded the studies that assessed the inflammatory potential of diet using reduced-rank regression methods via blood cytokine level measurements [89, 108], as the results are not comparable to those obtained using the DII and the idiosyncrasies of this regression approach may inflate measures of association when used in a study with similar population and measurement tools [458]. When a study utilized the same study populations, the study with the largest number of participants at baseline was selected for inclusion. This resulted in the inclusion of the study by Wirth *et al.* [101], as opposed to studies by Jorgensen *et al.* and Bergmans *et al.* [91, 96]. If the baseline populations also were similar, we selected the study which best described the exposure and outcome variable that was used in the current study. This resulted in the exclusion of the study by Shivappa *et al*. where the outcome variable was 'stress' [459] and the study by Haghighatdoost *et al.* where the outcome variable was 'highest tertile of mental health disorder profile' derived from factor analysis [95].

A total of 89,408 participants in twelve studies were included in the updated meta-analysis. Collectively, participants on the most pro-inflammatory diet had increased odds of being diagnosed with depression/DepS, compared to those who consume anti-inflammatory diets (Figure 6.3; $OR_{Quartile4vs1}$: 1.45; 95% CI: 1.20-1.74; $p < 0.01$). Effects were stronger in females ($OR_{Quartile4vs1}$: 1.53; 95% CI: 1.16-2.01, $p = 0.01$), compared to males (ORQuartile4vs1: 1.29; 95% CI: 0.98-1.69, $p = 0.15$). Models were unaffected by the type of study design [cross-sectional studies ($OR_{Quartile4vs1}$: 1.68; 95% CI: 0.98-1.69, $p = 0.06$); prospective studies ($OR_{Quartile4vs1}$: 1.29, 95% CI: 1.29-1.61, $p = 0.06$)], quality score [Higher quality ($OR_{Quartile4vs1}$: 1.44; 95% CI: 1.18-1.77, $p < 0.01$); lower quality ($OR_{Quartile4vs1}$: 1.50; 95% CI: 0.87-2.59, $p = 0.05$)]; effect measures [Hazard ratio (HR: 1.24; 95% CI: 1.07-1.43, $p = 0.31$); odds ratio (OR: 1.61; 95% CI: 1.23-2.10, $p < 0.01$); and relative risk (RR: 1.23; 95% CI: 1.04-1.45)] as shown by subgroup analysis Supplementary Figure 6.6 , 6.7 and 6.8.

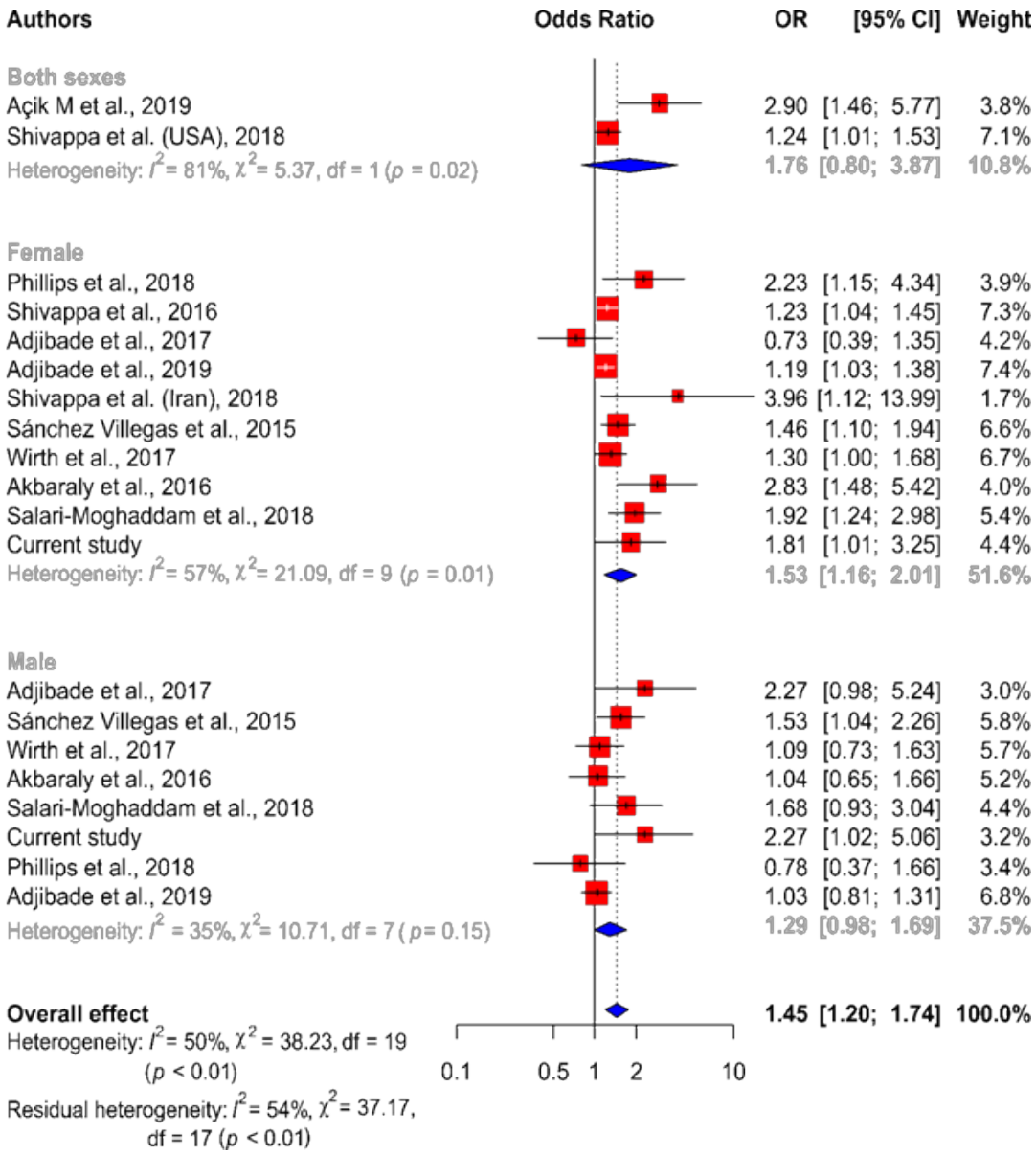


Figure 6.3 Random effect meta-analysis and forest plot for the association between a pro-inflammatory diet and depression or DepS. Results are also sub-grouped by sex-specific populations.

DISCUSSION

This study explored the association between E-DII and DepS using multiple approaches. First, we used a large community-based cohort to determine the cross-sectional and longitudinal association between E-DII and DepS. Second, we explored the association between E-DII scores and DepS by focussing on individual CES-D items to explore associations with specific DepS. Third, we updated the available data using meta-analytic techniques. To the best of our knowledge, no previous study has explored the association

between E-DII and DepS in such detail. In this cohort, the highest quartile of E-DII, (i.e., the most pro-inflammatory diet), was positively associated with increased risk of DepS compared to the lowest quartile; i.e., (the most anti-inflammatory diet).

6.2.15 COMPARISON WITH OTHER STUDIES

Our findings regarding the association between E-DII and DepS are consistent with some of the earlier cross-sectional studies, which reported higher odds of having depression/DepS with pro-inflammatory diets [94, 98, 100]. When stratified by sex, the association was found to be slightly stronger in males compared to females in the current study. This difference may be explained by sex-based differences in the choice of their foods. It has been reported that males are less likely than females to follow healthy eating recommendations [460-462]; however, at this stage, further studies are required to replicate these findings. Similar to the current study, in a prospective study in a French male population, found that a pro-inflammatory diet was associated with an over two-fold higher risk of having depression [102]. However, in the female population of the same study, no association was observed. In contrast, a cross-sectional study in an Irish population found that females with higher E-DII were at over two-fold higher risk of having depression, whereas a similar association was not observed in males [97].

Our meta-analysis findings are also in line with previously published meta-analyses [109, 164, 463]. We obtained ORs that were slightly higher than those reported by the previous meta-analyses [109, 164, 463], probably due to increased numbers as a result of the inclusion of more studies. In the updated meta-analysis, females were found to have higher odds of DepS with pro-inflammatory diet, while no association (although still a positive trend) was observed in the male population. This was in contrast to our cohort findings. In general, females have a higher prevalence of depression compared to males, probably due to hormonal fluctuations especially oestrogen, during puberty, prior to menstruation, following pregnancy and at

perimenopause [180]. Secondly, some CES-D items have been reported to have some gender bias, particularly item 17 (i.e., 'I had crying spells') which leads to inappropriate inflation of the CES-D score due to cultural norms regarding emotional expression, rather than an actual difference in DepS [420, 464]. Further research, to determine whether these gender differences in the diet-depression relationship are real or just attributable to methodological limitations in assessing male depression, is warranted.

6.2.16 POTENTIAL MECHANISM

The DII/ E-DII is a summary measure for assessing the inflammatory potential of the diet [83]. The construct validity of the DII and E-DII has been determined against inflammatory biomarkers in several different populations [465-470]. Overall, these validated results support the notion that diet plays an essential role in modifying inflammation. Diets can be either pro-inflammatory or anti-inflammatory, depending on the hormonal responses they generate [365]. A pro-inflammatory diet may increase the chronic, persistent activation of the immune system, which leads to low-grade inflammation. Activation of immune cells, especially polymorphonuclear leukocytes, leads to overproduction of ROS resulting in oxidative stress. It is not well understood how oxidative stress leads to the development of depression. However, the most likely hypothesis is that the brain neuronal cells are vulnerable to oxidative stress due to their requirement of higher oxygen consumption and consequent generation of ROS, as well as a relatively weak antioxidant defence [471, 472]. ROS activates inflammasomes such as NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3), a cytoplasmic protein complex that modulates innate immune function by activating caspase-1, which increases pro-inflammatory cytokines such as IL1β [473].

ROS also can regulate inflammatory processes by activation of transcription factors, including NF-κβ and activator protein-1 (AP-1), that lead to increased expression of pro-

inflammatory cytokines [473-475]. Conversely, these cytokines either: 1) stimulate indoleamine 2,3-dioxygenase (IDO) to convert tryptophan to kynurenine which is transformed into the neurotoxic quinolonic acid; or 2) exert an effect on the HPA axis which is linked to a reduction in hippocampal volumes, impaired neuronal plasticity, and decreased neurochemical functioning, resulting in DepS [476].

Another potential mechanism through which diet may influence DepS includes the brain-gut-microbiota axis, a bilateral communication network between the intestine and brain [477]. The intestinal microbiota and diet play an essential role in these gut-brain interactions and have been shown to be involved in the pathogenesis of psychiatric disorders, including depression [172, 478]. Depression is associated with an altered gut microbiota composition, richness and diversity [176]. First, the neurotransmitter 5HT may have antidepressant and anxiolytic effects [479]. Tryptophan, the main precursor of 5HT, is predominantly produced (>90%) by the gut microbiota [172]. It is evident that the consumption of probiotics, specifically, *Lactobacillus spp.* and *Bifidobacterium spp.*, affect mood by influencing 5HT level [480]. Second, in some preclinical studies in mice, consumption of a typical Western diet (high in animal protein and fat, low in fiber) led to a marked decrease in the numbers of total bacteria and proportional reduction of beneficial Bifidobacterium or Eubacterium species [481, 482] leading to diet-induced dysbiosis. This phenomenon results in increased permeability of the intestinal mucosa, also known as 'leaky gut', which may result in an increase in the immune response and chronic neuroinflammation [483]. This, in turn, stimulates pro-inflammatory cytokine production, which occurs when bacterial components such as lipopolysaccharides from the bacterial cell wall bind to circulating macrophages or monocytes [483, 484].

6.2.17 STRENGTH AND LIMITATIONS

The present study has several strengths. First, we used a large sample size that was equally represented by gender (51% female), had access to a wide range of confounding factors we could use in multiple statistical approaches and were able to update an existing meta-analysis. Second, we also examined the association between E-DII and the individual components of CES-D to find out the role of the inflammatory properties of the diet with specific DepS.

Despite the strengths of the current study, there are some limitations. First, dietary intake was estimated by FFQ, which has limitations in terms of recall bias and omission of food groups [230]. However, the FFQ used in this study is well validated and found to be reproducible in large cohorts. In addition, the FFQ has been widely used to assess major nutrient and food sources in the diet [421, 422]. Second, the non-availability of the information on the remaining 15 out of 45 food parameters for DII calculation may be a potential limitation. Third, although we used a DAG to map potential confounders, we cannot entirely rule out residual confounding. Fourth, the main results were presented from the cross-sectional analysis that precludes causal inferences based on temporality. However, we also used a longitudinal analysis, albeit with smaller sample size. One of the potential reasons behind not obtaining significant result with longitudinal analysis may be due to the smaller sample size at least with the log-binomial regression analysis. However, a positive trend was observed between E-DII and DepS in the longitudinal analysis using negative binomial regression analysis. It is possible that individuals with depression may increase their intake of pro-inflammatory foods such as sugary foods (high in refined carbohydrates). Fifth, the CES-D questionnaire was used as a measurement tool for DepS rather than another diagnostic tool for clinical depression. However, the CES-D is a widely used scale to measure DepS in population-based studies [133].

6.2.18 IMPLICATIONS

Although the definitive role of inflammation in depression has not been fully elucidated, the findings from this study suggest that promoting the consumption of anti-inflammatory foods and discouraging intake of pro-inflammatory foods could be a preventive strategy to combat inflammation-associated DepS at the population level. Future studies should examine the link between E-DII score and clinical outcomes of depression severity, to determine if an anti-inflammatory diet could reduce the incidence and the severity of depression, and consequently improve the treatment of depression.

CONCLUSIONS

In conclusion, data from this study support a positive association between a pro-inflammatory diet and increased risk of DepS. Our findings support the current recommendation of increasing the consumption of an anti-inflammatory diet and decreasing consumption of a pro-inflammatory diet to improve DepS. However, current evidence on the role of diet-induced inflammation in DepS should be reinforced using further longitudinal studies with extended follow up, larger sample sizes and repeated measures.

Author Contributions

All authors conceived the study; PRS drafted the manuscript; PRS and YAM analysed the data; NS and JRH designed the dietary inflammatory index; YAM, AJP and TKG commented on each draft of the paper. AJP, RJA and TKG provided critical revisions of the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript for publication. TKG has primary responsibility for final content.

Conflict of Interest

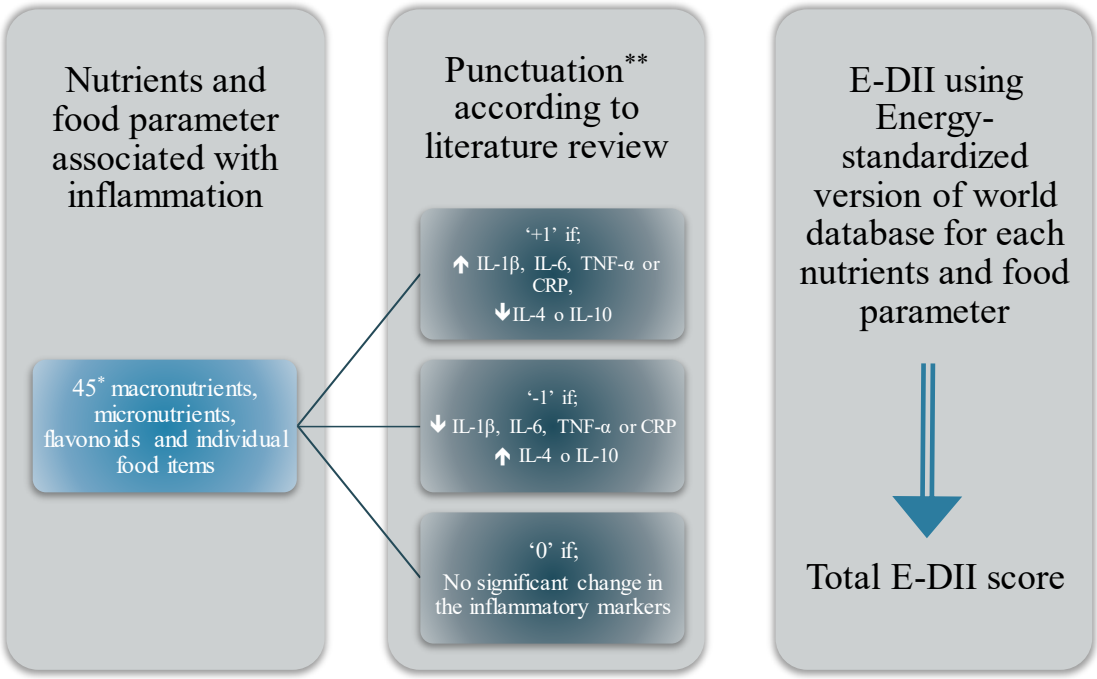
All authors declare no conflict of interest. Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his

invention of the dietary inflammatory index™ (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

Acknowledgments

We thank all of the participants from North West Adelaide Health Study (NWAHS) and all the members of the team comprising of research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants, and data entry staff, all of whom make the study possible. PRS was supported by Adelaide Scholarship International (ASI) scholarship provided by the University of Adelaide. The authors are also grateful to all of the providers of research funds for this project including the University of Adelaide, the South Australian Department of Health and Wellbeing, the Premier's Science and Research fund (SA Government) and The Hospital Research Foundation.

SUPPLEMENTARY MATERIALS FOR CHAPTER 6

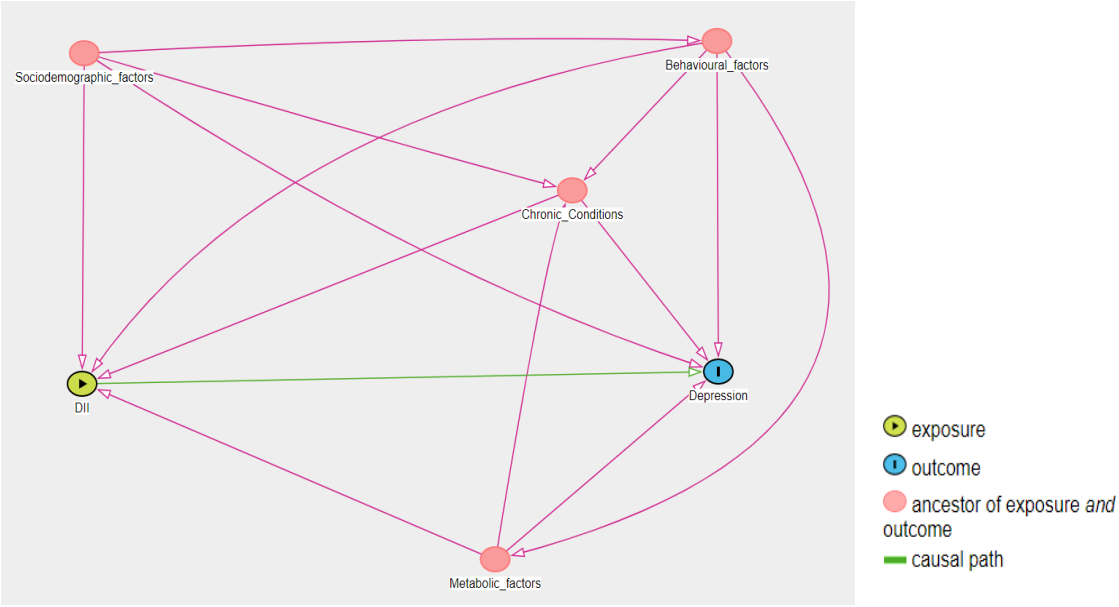


Supplementary Figure 6.1 Flow diagram of Energy adjusted Dietary Inflammatory Index (E-DII) calculation

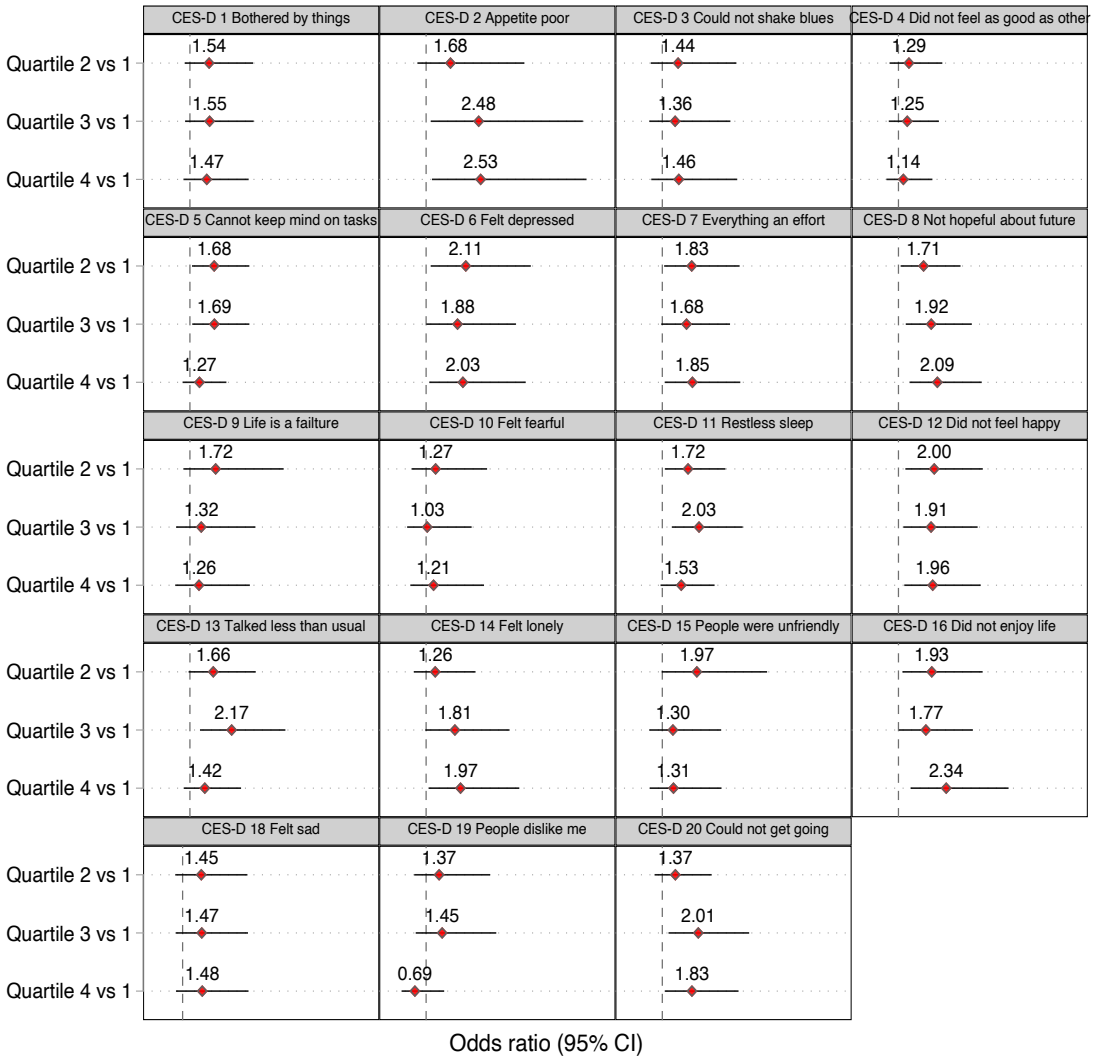
**Alcohol, Anthocyanidins[1], Beta Carotene, Caffeine, Carbohydrate, Cholesterol, Energy, Eugenol[1], Fat, Fibre, Flavan-3-ol[1], Flavones[1], Flavonols[1], Flavonones[1], Folic Acid, Garlic, Ginger[1], Iron, Isoflavones[1], Magnesium, MUFA, Niacin, Omega 3, Omega 6, Onion, Pepper[1], Protein, PUFA, Riboflavin, Rosemary[1], Saffron[1], Saturated Fat, Selenium[1], Tea, Thiamin, Thyme/Oregano[1], Trans Fat[1], Turmeric[1], Vitamin A, Vitamin B12, Vitamin B6, Vitamin C, Vitamin D, Vitamin E and Zinc.*

[1]Nutritional components not included (missing) in the E-DII score calculation in the NWAHS study

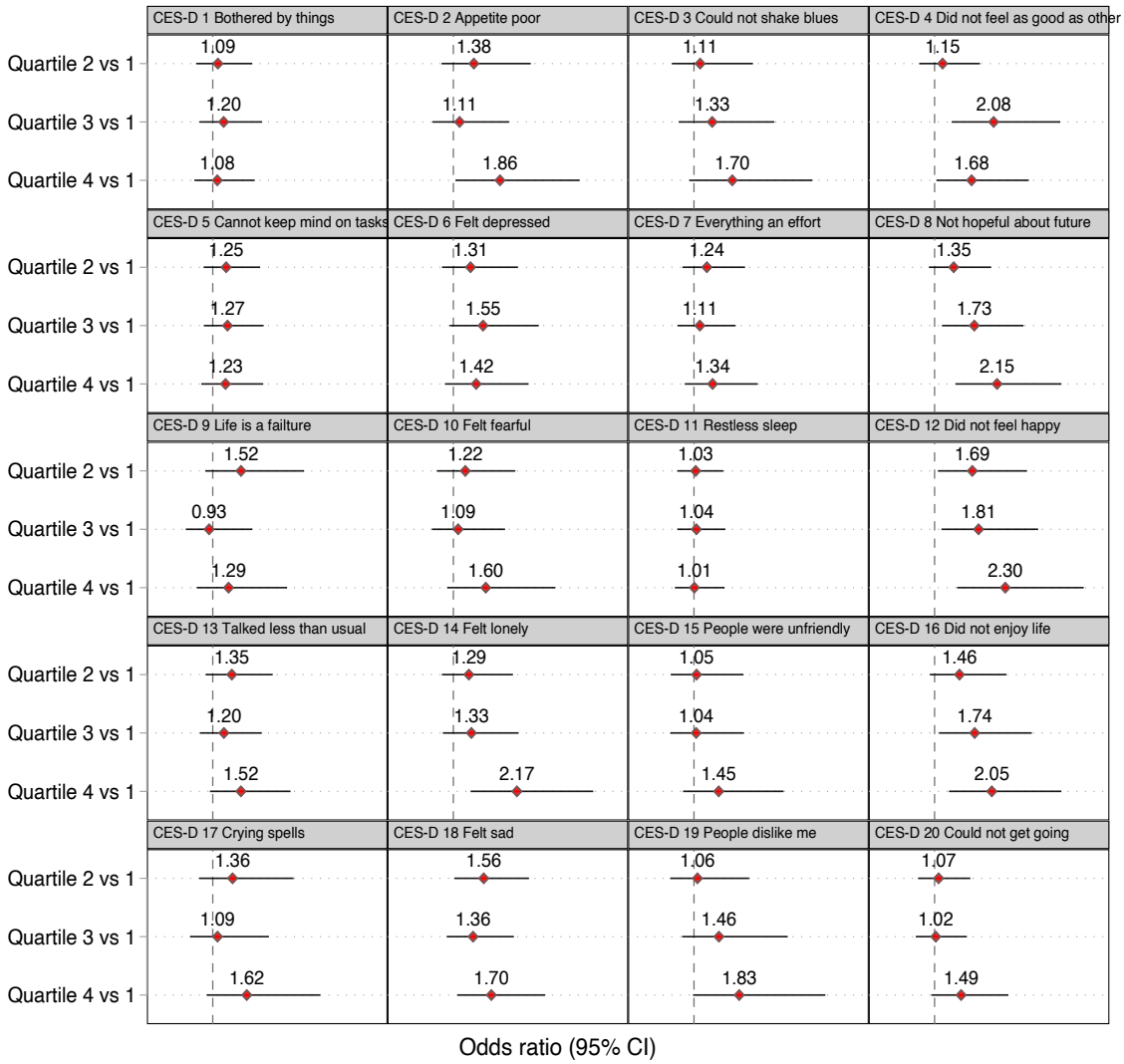
***The punctuation for each food parameter was weighted according to the study design. A global energy adjusted database was used to calculate z-scores and centered percentiles for each of the food parameters.*



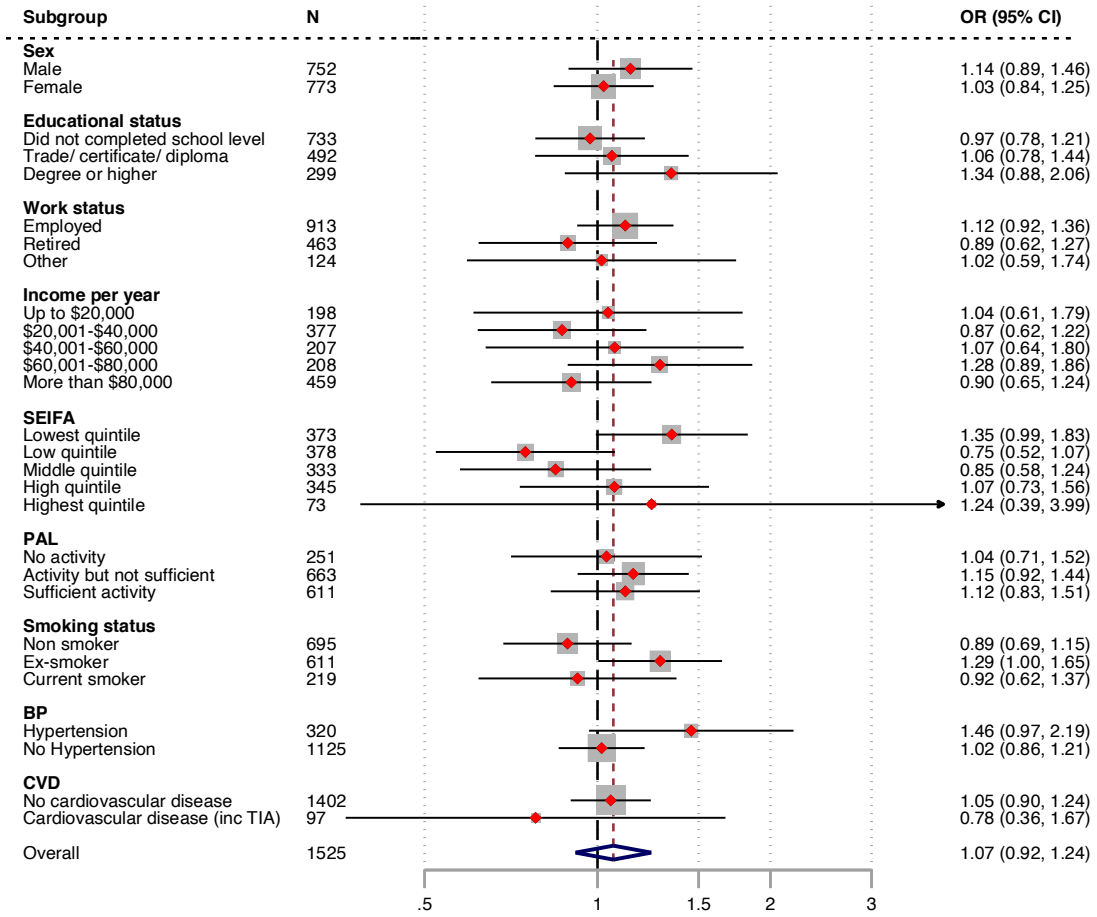
Supplementary Figure 6.2 Directed Acyclic Graph (DAG) for E-DII and DepS



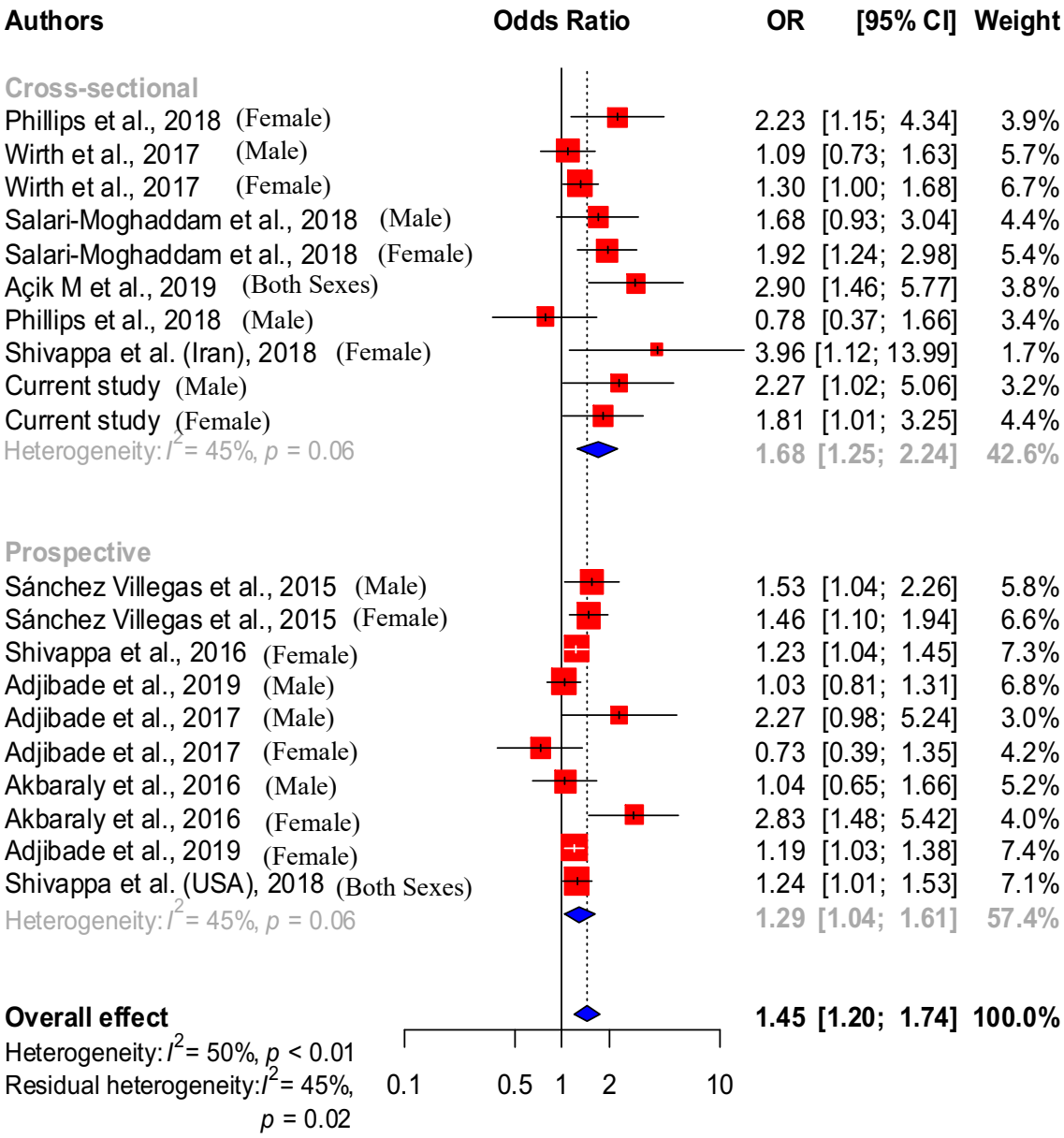
Supplementary Figure 6.3 Association between a quartiles of E-DII and each CES-D items in Male (n = 752) NWAHS participants; data analysis for CES-D item 17 'crying spells' for males could not be carried out as most of the participants chose 'rarely or none of the time' (n = 736) and only 16 participants rated the questionnaire as '1' (n =13) and '2' (n = 3).



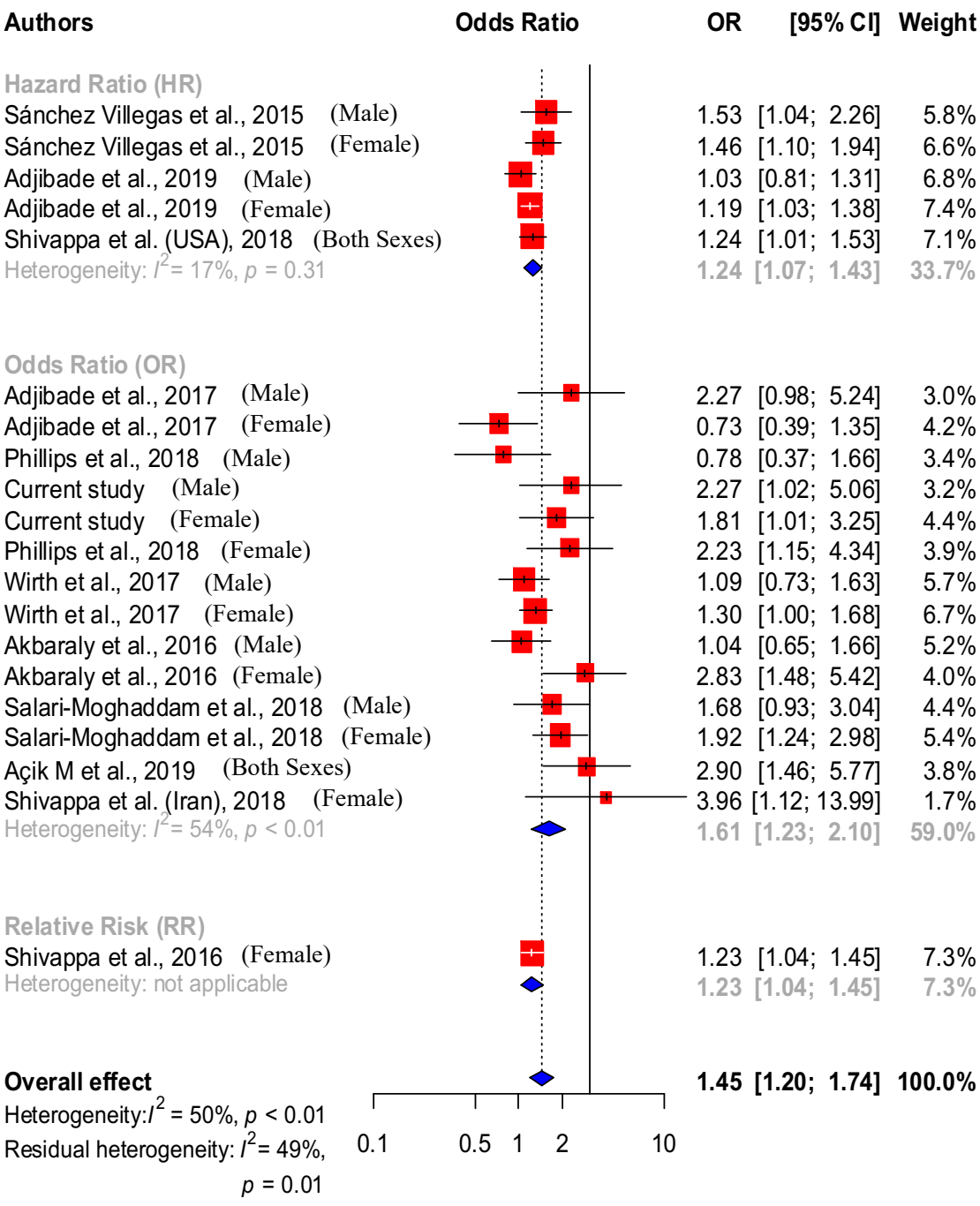
Supplementary Figure 6.4 Association between a quartile of E-DII and each CES-D items in Female (n = 773) NWAHS participants



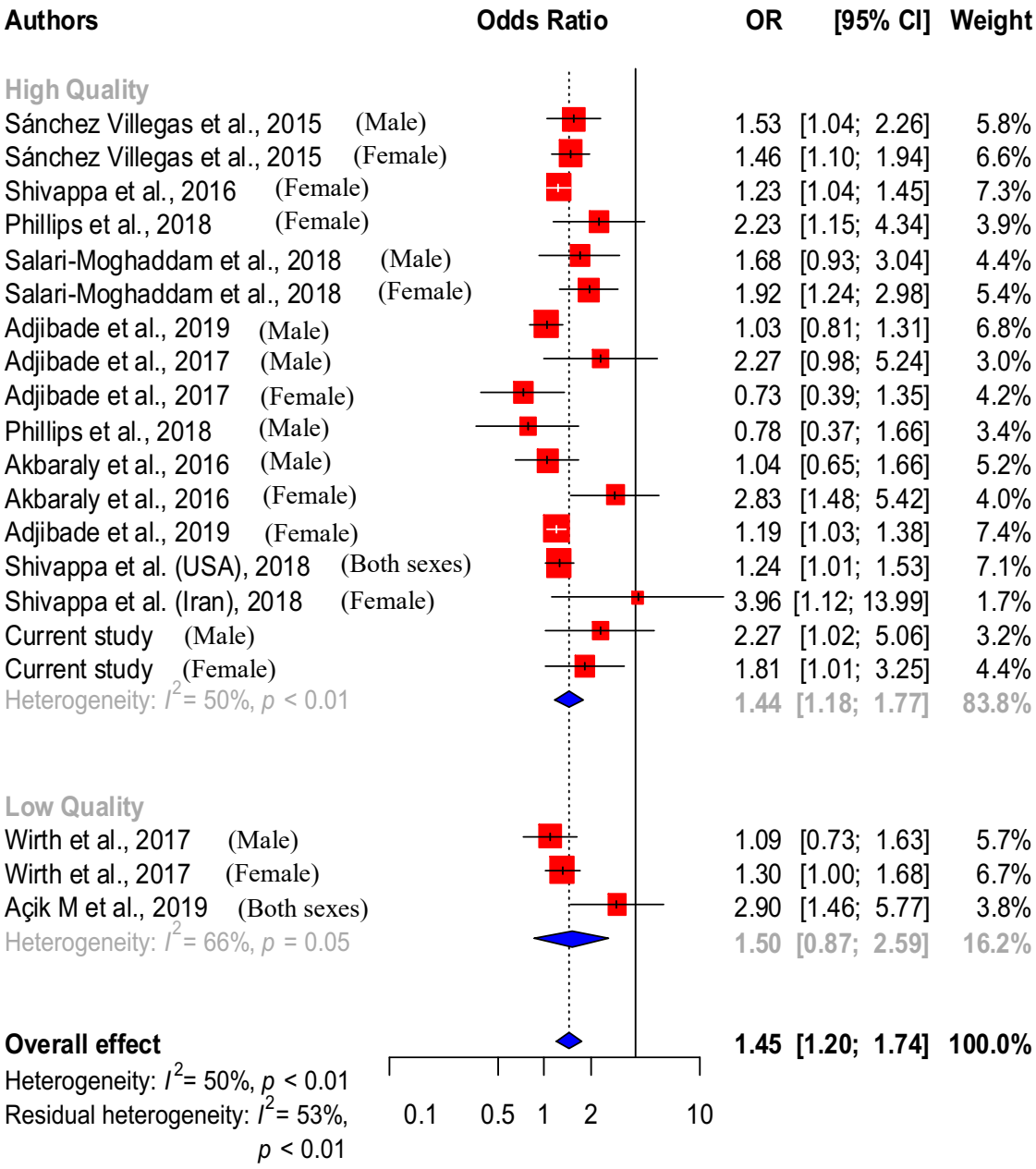
Supplementary Figure 6.5 Subgroup analysis of the association between fourth quartiles (highest intake) compared to first quartiles (lowest intake) of E-DII with depressive symptoms in fully adjusted model



Supplementary Figure 6.6 Random effect meta-analysis and forest plot for the association between a pro-inflammatory diet and depression or DepS. Results are also sub-grouped by study design



Supplementary Figure 6.7 Random effect meta-analysis and forest plot for the association between a pro-inflammatory diet and depression or DepS. Results are also sub-grouped by effect size



Supplementary Figure 6.8 Random effect meta-analysis and forest plot for the association between a pro-inflammatory diet and depression or DepS. Results are also sub-grouped by quality score

Supplementary Table 6.1 Study specific case definition with their criteria, inflammatory diet assessment method and effect size model adjustments

Study and Country	Design	Follow-up, years	Subjects at baseline, *n*	Females, %	Age at baseline	Case definition	Criteria for case	Exposure assessment	Food parameters derived	Covariate adjustments
NWAHS study (Current research); Australia	Cross-sectional	NA	1743	51	56.6 ± 13.6	DepS	CES-D ≥ 16	E-DII™	30	Age, sex, marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, PA, Sleep quality, BMI, bodily pain, hypertension, T2DM, cardiovascular disease and anti-depressant use
Açik M et al.; 2019, Turkey [94]	Cross-sectional	N/A	134	100		DepS	ZSRD ≥ 50	DII®	29	Age, energy intake, BMI, smoking, alcohol consumption, and PA
Adjibade et al.; 2019; France [103]	Longitudinal	5.4	26,730	76		DepS	CES-D (French) ≥17 for men and ≥23 for women	ADII	34	Age, sex, marital status, educational level, occupational categories, household income per consumption unit, residential area, energy intake without alcohol, number of 24-h-dietary records, alcohol intake, smoking status, PA, BMI, cancer, T2DM, and cardiovascular events
Salari-Moghaddam et al.; 2018; Iran [98]	Cross-sectional	N/A	3,363	58.3	36.3 ± 7.8	Depression	HADS ≥ 8	DII®	29	Age, sex, TEI, marital status, education, family size, home ownership, anti-depressant use, vitamin supplements use, smoking, PA, presence of chronic conditions and BMI

Abbr.: ADII: Alternate Dietary Inflammatory Index; BMI: Body mass index; CES-D: Centre for Epidemiologic Studies Depression Scale; DepS: depressive symptoms; DII: Dietary Inflammatory Index, E-DII™: Energy-adjusted Dietary Inflammatory Index; HADS: Hospital Anxiety and Depression Scale; HDL: High-density lipoprotein; PA: Physical activity; TEI: Total energy intake; T2DM: Type 2 diabetes mellitus; ZSRD: Zung Self-Rating Depression Scale

For other studies included in this study, refer to: Tolkien K et al., Clin Nutr. 2018. [109]

Supplementary Table 6.2 Newcastle - Ottawa Quality Assessment Scale cohort studies used for quality assessment on studies included in meta-analysis on the association between E-DII and depression

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed (pro-inflammatory diet) cohort
   a) truly representative of the average adult population in the community *
   b) somewhat representative of the average adult population in the community *
   c) selected group of users e.g. nurses, university students
   d) no description of the derivation of the cohort

2) Selection of the non-exposed (anti-inflammatory diet) cohort
   a) drawn from the same community as the exposed cohort. *
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure (diet)
   a) used a validated dietary assessment tool, such as the FFQ, to measure long-term dietary patterns *
   b) used a single 24-hour dietary recall
   c) written self-report
   d) no description

4) Ascertainment of the inflammatory potential of the diet
   a) used a validated inflammatory diet index, such as the DII *
   b) DII derived from other methods, such as FDII, ADII
   c) measured a blood cytokine panel such as IL-1, IL-6 and TNF-α
   d) self-reported
   e) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) statistical model controls for age, body mass index/waist circumference and smoking (all 3 are needed for 1 point) *
   b) statistical model controls for physical activity and energy intake (both are needed for 1 point) *

Outcome

1) Assessment of outcome (depression or DepS)
   a) depression diagnosed by a clinical professional *
   b) depressive symptoms measured using a validated scale, such as the CES-D *
   c) self-reported diagnosis
   d) no description

2) [Longitudinal studies only] Was follow-up long enough for depression or DepS to occur?
   a) yes (≥5 years) *
   b) no (< 5 years)

(Adapted from: *'The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.'* by Wells GA *et al.* The Ottawa Hospital Research Institute; 2019 (Canada)[456])

Supplementary Table 6.3 Quality assessment of included studies based on the modified Newcastle-Ottawa criteria

	Selection				Comparability		Outcome		
Study	1	2	3	4	1	2	1	2	Total
Sanchez-Villages et al., 2015 [105]		*	*	*	*	*	*	*	7 (88%)
Akbaraly et al., 2016 [104]		*	*	*		*	*	*	6 (75%)
Shivappa et al., 2016 [107]		*	*	*		*	*	*	6 (75%)
Wirth et al., 2017 [101]	*	*		*			*	N/A	4 (57%)
Adjibade et al., 2017 [102]	*	*	*	*	*	*	*	*	8 (100%)
Phillips et al., 2018 [97]	*	*	*	*	*		*	N/A	6 (86%)
Shivappa et al., 2018 (USA)		*	*	*	*		*	*	6 (75%)
Shivappa et al., 2018 (Iran) [100]		*	*	*	*	*	*	N/A	6 (86%)
Salari-Moghaddam et al., 2018 (DII) [98]		*	*	*	*	*	*	N/A	6 (86%)
Adjibade et al. , 2019 [103]	*	*			*	*	*	*	6 (75%)
Açik et al., 2019 [94]		*		*	*		*	N/A	4 (57%)
Current Study	*	*	*	*	*	*	*	NA	7 (100%)

Supplementary Table 6.4 Association between quartiles of DII score and prevalent depressive symptoms in Australian adults participating in the NWAHS by age groups, Cross-sectional analysis at Stage 3 (2008-10; *n* = 1,743) and Prospective analysis at NW15 (2015; *n* = 859)

	Q1 (Ref)	Q2	Q3	Q4	P for trend	Q2	Q3	Q4	P for trend
	Cross-sectional					Prospective			
[a]Log-binomial regression									
All participants (n = 1743)						**All participants (n = 859)**			
Model 1	1.00	1.50(1.02-2.21)**	1.51(1.03-2.23)**	2.30(1.58-3.35)***	<0.001	1.35(0.73-2.50)	1.64(0.90-3.01)	1.74(0.95-3.17)*	0.06
Model 2	1.00	1.35(0.88-2.09)	1.36(0.87-2.11)	1.87(1.22-2.86)***	0.005	1.21(0.63-2.32)	1.52(0.80-2.87)	1.45(0.77-2.75)	0.20
Model 3	1.00	1.52(0.96-2.39)	1.39(0.87-2.21)	1.79(1.14-2.81)**	0.03	1.26(0.65-2.45)	1.43(0.74-2.78)	1.44(0.74-2.78)	0.27
Age groups (< 65 years) (n = 1240)						**Age groups (≤ 65 years) (n = 583)**			
Model 1	1.00	1.87(1.19-2.95)***	1.68(1.06-2.67)**	2.54(1.63-3.96)***	<0.001	1.18(0.55-2.52)	1.69(0.81-3.53)	1.37(0.66-2.85)	0.29
Model 2	1.00	1.86(1.10-3.12)**	1.44(0.85-2.44)	2.06(1.24-3.43)***	0.02	1.00(0.45-2.26)	1.44(0.65-3.20)	1.10(0.50-2.42)	0.65
Model 3	1.00	1.94(1.13-3.34)**	1.35(0.77-2.36)	1.80(1.05-3.07)**	0.15	1.14(0.50-2.62)	1.47(0.64-3.37)	1.15(0.51-2.61)	0.66
Age group (≥ 65 years) (n = 503)						**Age group (> 65 years) (n = 276)**			
Model 1	1.00	0.82(0.38-1.78)	1.26(0.60-2.65)	2.07(1.00-4.29)*	0.03	1.38(0.46-4.16)	1.29(0.43-3.90)	2.39(0.80-7.14)	0.14
Model 2	1.00	0.47(0.18-1.21)	1.32(0.54-3.20)	2.05(0.82-5.12)	0.04	1.00(0.26-3.82)	1.47(0.40-5.40)	3.09(0.85-11.22)	0.07
Model 3	1.00	0.56(0.20-1.52)	1.55(0.59-4.04)	2.19(0.84-5.72)	0.03	1.17(0.25-5.58)	1.37(0.29-6.37)	4.84(0.95-24.64)*	0.07
[b]Negative binomial regression									
All participants									
Model 1	1.00	1.27(1.10-1.46)***	1.36(1.18-1.57)***	1.54(1.33-1.78)***	<0.001	1.20(0.97-1.48)*	1.44(1.16-1.77)***	1.39(1.12-1.72)***	0.001
Model 2	1.00	1.24(1.07-1.44)***	1.35(1.16-1.56)***	1.41(1.22-1.64)***	<0.001	1.19(0.96-1.49)	1.45(1.16-1.80)***	1.29(1.03-1.61)**	0.008
Model 3	1.00	1.23(1.07-1.43)***	1.31(1.13-1.52)***	1.34(1.15-1.56)***	<0.001	1.19(0.95-1.48)	1.41(1.13-1.75)***	1.26(1.01-1.58)**	0.02
Age groups (< 65 years) (n = 1240)						**Age groups (≤ 65 years) (n = 583)**			
Model 1	1.00	1.35(1.13-1.60)***	1.43(1.20-1.70)***	1.61(1.36-1.91)***	<0.001	1.09(0.84-1.41)	1.38(1.07-1.79)**	1.30(1.01-1.67)**	0.02
Model 2	1.00	1.31(1.10-1.57)***	1.34(1.12-1.60)***	1.45(1.21-1.73)***	<0.001	1.07(0.82-1.40)	1.33(1.02-1.74)**	1.16(0.89-1.52)	0.13
Model 3	1.00	1.27(1.06-1.51)***	1.24(1.04-1.49)**	1.32(1.10-1.59)***	0.007	1.07(0.81-1.40)	1.29(0.98-1.69)*	1.11(0.85-1.46)	0.28
Age group (≥ 65 years) (n = 503)						**Age group (> 65 years) (n = 276)**			
Model 1	1.00	1.10(0.85-1.42)	1.16(0.89-1.50)	1.37(1.04-1.81)**	0.03	1.39(0.95-2.02)*	1.42(0.98-2.05)	1.39(0.92-2.09)	0.12
Model 2	1.00	1.06(0.81-1.39)	1.28(0.97-1.69)*	1.43(1.07-1.92)**	0.008	1.29(0.84-1.99)	1.57(1.05-2.33)**	1.42(0.90-2.21)	0.06
Model 3	1.00	1.11(0.85-1.47)	1.32(1.00-1.74)*	1.39(1.03-1.87)**	0.02	1.25(0.81-1.94)	1.50(1.00-2.25)**	1.38(0.87-2.20)	0.08

[a]Values are expressed in Odds ratio (ORs) (95% CIs)

[b]Values are expressed in Prevalence ratio (PRs) (95% CIs)

Model 1 was adjusted for sex and age

Model 2 was additionally adjusted for marital status, educational status, employment status, income, Socio-Economic Indexes for Areas, alcohol risk, smoking status, physical activity and self-reported sleep quality

Model 3 was additionally adjusted for body mass index, bodily pain, hypertension, diabetes, cardiovascular disease and anti-depressant use

*p < 0.1, **p < 0.05, ***p < 0.01

Chapter 7: Discussion, future directions, and conclusions

This thesis reports the findings of three independent but related studies, investigating the association between nutrition and depressive symptoms (DepS). It comprises studies examining the association between i) dietary patterns (Chapter 4); ii) nutrient patterns (Chapter 5); ciii) dietary inflammatory index (Chapter 6) and DepS. These studies will contribute to the epidemiological literature by providing empirical support for the relationship between nutrition and DepS; with broader implications for future research that may impact clinical practice.

To meet the aims of these studies, various nutritional assessment tools and quantitative research methods were utilized. A detailed discussion of each study is provided in the preceding chapters and, therefore, only the key findings of the studies are summarised below, followed by discussion on methodology, challenges of dietary research and a discussion on the strengths and limitations of the studies contributing to this thesis. Finally, clinical and methodological implications with recommendations for future research are discussed.

7.1 SUMMARY OF FINDINGS

The first study (Chapter 4) was a prospectively designed observational cohort study using the North West Adelaide Health Study (NWAHS) data, aimed at investigating both cross-sectional and longitudinal associations between dietary patterns and DepS. This study used three different types of analytical methods [Principle Component Analysis (PCA) = 2; Reduced-Rank Regression (RRR) = 4 and Partial Least Squares (PLS) = 4 patterns) to determine the dietary patterns. The main findings on the

association between dietary patterns and DepS can be summarized in Figure 7.1. Briefly, the findings reveal that a 'prudent' (or healthy) dietary pattern, derived from PCA and RRR was inversely associated with DepS. In contrast, the 'western' (or unhealthy) pattern, derived from PCA and PLS was positively associated with higher DepS. Two more dietary patterns were derived from RRR and PLS compared to the PCA and named as 'typical Australian' pattern and 'modern pattern'. There was an inverse association between the 'typical Australian' pattern and DepS while the 'modern' dietary pattern did not show any significant association with DepS.

One of the plausible reasons for the inverse relationships between 'prudent' dietary pattern and DepS or 'western' dietary pattern and DepS could be the anti-inflammatory or pro-inflammatory properties of the foods associated with those patterns respectively [386, 392, 400, 401]. These may eventually either decrease (anti-inflammatory foods) or increase (pro-inflammatory foods), the oxidative stress in the body thus impacting DepS. Another reason for this association could be the effects of each food on neurotransmitters such as 5 hydroxy tryptamine (5-HT), for which the precursor is tryptophan which has a role in mood alleviation [485]. Most of food groups, that belongs to 'prudent' or 'typical Australian' dietary pattern, are good sources of tryptophan.

While, dietary patterns that are usually based upon food group, provide an enriched knowledge on diet and depression link, the underlying mechanisms are still difficult to establish using dietary patterns alone [63, 64]. In Chapter 5, Nutrient patterns (NPs), which are based upon the nutrients in food, were developed to determine the link between diet and DepS. To our knowledge, the association between NPs and DepS is limited to a single study [79], which failed to identify the specific DepS associated with NPs, by using factor-structure. In our study, we captured three NPs, 'plant-sourced', 'animal-sourced' and 'mixed-source'. The relative factor loadings for each pattern are summarized in

Figure 7.1. The 'animal-sourced' and 'mixed-source' NPs did not show any significant association with DepS. 'Plant-sourced' NPs, characterised by high consumption of β-carotene, fibre, vitamin C, potassium, α-carotene and lutein & zeaxanthin (LZ), were inversely associated with DepS. Nutrients that were highly loaded in 'plant-sourced' NPs have antioxidant properties and are anti-inflammatory in nature. In addition, the '(absence of) Positive affect' factor structure of Center for Epidemiological Studies-Depression (CES-D) was found to be associated with NPs.

	Dietary pattern										Nutrient pattern			
	PCA		RRR				PLS				PCA			
Food groups	**Prudent**	**Western**	**Prudent**	**Western**	**Modern**	**Typical Australian**	**Prudent**	**Western**	**Modern**	**Typical Australian**	**Nutrients**	**Plant-sourced**	**Animal-sourced**	**Mixed-source**
Fruity vegetables	0.76	0.02	0.12	0.14	0.13	0.12	0.29	-0.29	0.2	0.2	Beta carotene	0.82	0.04	0.12
Leafy vegetables	0.61	-0.06	0.12	0.08	0.15	0.09	0.22	-0.29	0.16	0.07	Fibre	0.81	0.39	0.08
Stalk vegetables	0.61	-0.12	0.15	0.06	0.1	0.04	0.2	-0.29	0.14	0.12	Vitamin C	0.71	0.09	0.12
Other fruits	0.57	0.06	0.02	-0.01	0.22	0.04	0.28	-0.16	0.2	-0.02	Potassium	0.69	0.61	0.04
Root vegetables	0.57	0.08	0.04	0.21	0.01	0.16	0.25	-0.14	0.17	0.35	Alpha-carotene	0.66	-0.01	0.00
Cabbages	0.54	0.03	0.09	0.21	0.01	0.09	0.2	-0.18	0.12	0.31	Lutein & zeaxanthin (LZ)	0.64	-0.04	0.12
Sugar	0.47	0.61	-0.17	-0.07	0.07	-0.06	0.22	0.07	0.31	0.12	Iron	0.57	0.64	0.11
Tea and water	0.43	0.4	0	0.17	0.14	-0.02	0.21	-0.07	0.14	0.13	Magnesium	0.53	0.53	0.12
Nuts	0.36	-0.11	0.08	0.12	0.02	-0.14	0.13	-0.16	0.01	0.05	Biotin (Vitamin B7)	0.49	0.53	0.17
Fish	0.34	-0.02	0.71	-0.29	0.28	0.1	-0.12	-0.45	0.26	-0.27	Niacin (Vitamin B3)	0.45	0.72	-0.10
Medium fat dairy	0.33	-0.02	0.05	0.21	0.08	0.01	0.18	-0.13	-0.01	0.14	Vitamin E	0.44	0.26	0.71
Legumes	0.32	-0.05	0.03	0.02	0.13	-0.02	0.15	-0.14	0.08	-0.09	Phosphorous	0.44	0.82	0.11
High fiber bread	0.31	0.11	-0.08	0.03	0.14	0.25	0.24	-0.02	0.19	0.06	Starch & dextrins	0.41	0.59	-0.02
Tomato sauce	0.31	0.22	0.03	0.03	0.04	0.14	0.09	-0.11	0.17	0.06	Lycopene	0.40	0.16	0.24
Potato without fat	0.31	0.09	-0.03	0.17	-0.07	0.12	0.15	-0.01	0.1	0.34	Thiamin (Vitamin B1)	0.35	0.57	0.00
Citrus fruit	0.29	-0.04	0.02	0.02	0.12	0.04	0.16	-0.09	0.09	-0.02	Zinc	0.31	0.74	0.18
Other cereal	0.2	0.16	0.02	0.16	-0.24	0.02	0.02	0.02	0.06	0.28	Protein	0.31	0.76	0.35
Jam and vegemite	0.19	0.37	-0.14	0.09	0.11	0.75	0.17	0.1	0.34	0.15	Folate	0.30	0.40	0.15
Juice	0.15	0.3	-0.03	-0.08	0.02	0.11	0.03	0.03	0.2	0.02	Sodium	0.30	0.69	0.36
Eggs	0.14	0.14	0.11	-0.15	0.04	0.03	-0.03	-0.1	0.16	-0.1	Riboflavin (Vitamin B2)	0.28	0.75	-0.01
Pasta and rice	0.13	0.11	0.01	-0.1	-0.1	-0.12	-0.05	-0.05	0.06	-0.01	Pyridoxine (Vitamin B6)	0.22	0.22	0.01
Poultry	0.12	0.17	0.2	0.02	-0.22	0.01	-0.22	-0.18	0.07	0.19	Monounsaturated fat	0.21	0.41	0.76
Peanut butter	0.12	0.19	-0.06	0.05	-0.03	0.07	0.05	0.03	0.09	0.11	Calcium	0.21	0.69	0.09
High fiber cereal	0.09	-0.03	0.07	0.12	0	-0.02	0.03	-0.08	-0.05	0.06	Omega-6 fatty acid	0.17	0.07	0.83
Red meat	0.06	0.33	0.3	0.17	-0.59	0.16	-0.32	-0.14	0.1	0.43	Omega-3 fatty acid	0.09	0.06	0.84
Snacks	0.05	0.5	-0.19	-0.2	-0.09	-0.06	-0.01	0.2	0.22	0.08	Saturated fat	-0.01	0.71	0.43
Saturated spread	0.05	0.15	-0.08	-0.07	-0.08	-0.05	0.02	0.07	0.05	0.06	Cholesterol	-0.03	0.61	0.44
Wine	0.04	-0.07	0.1	0.05	0	0.01	-0.04	-0.13	-0.02	0.03	Iodine	-0.07	0.75	0.14
Coffee	0.01	0.19	0.04	0.59	0.28	-0.19	0.16	-0.03	-0.27	0.14	Vitamin D	-0.11	0.56	0.40
Potato with fat	-0.02	0.24	-0.18	-0.01	-0.01	0.01	0.04	0.15	0.06	0.12	Retinol	-0.14	0.66	0.42
Unsaturated spread	-0.03	0.41	-0.19	-0.09	0.04	0.28	0.07	0.2	0.27	0.06	Cobalamine (Vitamin B12)	-0.16	0.69	0.29
Processed meat	-0.05	0.53	0.02	-0.04	-0.33	0.1	-0.23	0.06	0.19	0.26				
Flavoured milk	-0.06	0.19	-0.02	0.04	-0.11	-0.01	-0.06	0.07	-0.01	0.04				
Take away foods	-0.1	0.56	-0.03	-0.22	-0.13	0.06	-0.17	0.13	0.25	0.01				
Spirits	-0.13	0.13	-0.04	-0.01	0.02	0.08	-0.05	0.07	0.03	-0.02				
Beer	-0.14	0.29	-0.03	-0.07	-0.04	0.08	-0.11	0.07	0.1	0				
Soft drinks	-0.16	0.41	-0.15	-0.19	-0.09	-0.02	-0.1	0.19	0.09	-0.02				
High fat dairy	-0.18	0.22	-0.16	-0.11	0	-0.14	-0.04	0.18	-0.01	-0.06				
White bread	-0.28	0.39	-0.2	-0.18	-0.11	0.16	-0.12	0.25	0.14	0.02				
Study Outcome														
Depressive symptoms	-	+	+	Nu	Nu	-	Nu	+	Nu	Nu		+	Nu	Nu

Figure 7.1 Relative factor loadings of dietary and nutrient components of dietary patterns and NPs identified by PCA, RRR and PLS in NWAHS participants

[The different shades of colour gradient indicate the magnitude and direction of the correlation of the food groups and nutrients with their respective patterns. Higher factor loading means relatively higher correlation within the dietary patterns and NPs, represented in deep blue colour. Similarly, deep red colour denotes the relatively lower correlation or lower factor loadings of the food groups and nutrient within each pattern. '+' and '- 'sign denotes positive and negative association respectively. For the food groups or nutrients with no statistically significant, 'Nu' is indicated. NWAHS –North West Adelaide Health Study; PCA – principal component analysis; PLS – partial least-squares; RRR – reduced-rank regression]

The studies in Chapters 4 and 5 both indicate a linkage between inflammation and diet. To corroborate these results, the third study (Chapter 6) was undertaken to determine both cross-sectional and longitudinal associations between energy adjusted dietary inflammatory index (E-DII™) and DepS. In addition, the association between E-DII™ scores and specific DepS were explored. A higher pro-inflammatory diet was positively associated with increased risk of DepS, as defined by item 2 in the CES-D (i.e. 'Appetite poor'), item 6 (i.e. 'Felt depressed'), item 8 (i.e. 'Not hopeful about future'), item 12 (i.e. 'Did not feel happy'), item 14 (i.e. 'Felt lonely'), item 16 (i.e. 'Did not enjoy life'), item 18 (i.e. 'Felt sad') and item 20 (i.e. 'Could not get going'). This study also updated a previously published meta-analysis [109] and supported the findings of the previous meta-analysis studies that there was a higher odds of DepS associated with a pro-inflammatory diet [109, 164, 463].

7.2 DISCUSSION OF METHODOLOGY

7.2.1 GENERALIZABILITY OF THE RESULTS

The results of this thesis are based upon the data obtained from the NWAHS. Therefore, in terms of the population, the findings of the study are generalizable to individuals living in the Adelaide region only. Australia is a diverse and multi-ethnic country which is evident in the country's food, lifestyle, cultural practice and experiences. Therefore, when interpreting the findings of Chapters 4 and 6 in relation to other regions of Australia or other nations, caution should be applied. However, the findings of Chapter 5 can be more easily generalised to other populations because NPs are not affected by different social, cultural and geographical locations [64].

7.2.2 STUDY DESIGN

The main findings of this thesis are based upon a cross-sectional design [*n* = 1,743, Stage 3 (2008-10)] and, therefore, no causal inferences can be made between diet and DepS. Incident DepS (*n* = 859) and the association between dietary patterns and E-DII™ could be assessed as DepS data were available from both Stage 3 and NW15. However, dietary data were only available at Stage 3 thus limiting the longitudinal and potential casual associations.

7.2.3 SUBGROUP AND SENSITIVITY ANALYSIS

Subgroup analyses were performed in all three studies using various parameters, including sex, educational status, marital status, work status, income status, physical activity level (PAL), smoking status, hypertension, diabetes and cardiovascular disease (CVD). No significant interaction was observed among the selected covariates and the dietary patterns, NPs and E-DII™, indicating that primary findings on the association between diet and DepS were robust.

In Chapter 4, to determine if dietary patterns were affected by antidepressant medication and missing covariates, a sensitivity analysis was performed by including this information in the multivariable models. However, only minor changes in the estimates of associations between dietary pattern and DepS were observed. In Chapter 5, familial status (family with at least one child under 18 years old) was included as a covariate, as it could be a potential confounder in the diet-depression link, however, again, inclusion of this covariate had little impact on the demonstrated associations (Appendix D).

7.2.4 SELF-REPORTED DEPS

DepS was analysed as a binary outcome variable (using a validated cut-off score of ≥ 16) as well as using continuous scores (as an indicator of severity). There is the potential for a loss of information and reduced statistical power, when an outcome variable is dichotomised [448]. Therefore, in this thesis, factor analysis of the CES-D scale and the continuous score were used where possible, rather than the binary outcome variable. In Chapters 5 and 6, the CES-D scores were further analysed using the individual items. When the CES-D was first developed, Radloff *et al.* initially postulated a four-factor structure, i) depressed affect (DA; for example, feeling sad); ii) somatic/vegetative factors (SV; for example, feeling bothered, disturbed sleep, not feeling hungry); iii) interpersonal (IP; for example, feeling hated or isolated); and iv) 'positive affect; (PA; for example, feeling cheerful or optimistic) [133], however existing diagnostic criteria were not incorporated in the development of the CES-D [420]. Previous validation studies of the latent structure of the CES-D have captured one-, two-, and three-factor alternative structures [420]. In our data, we were only able to capture a two-factor structure, namely; i) 'depressed affect' and ii) '(absence of) positive affect'.

7.2.5 DIETARY PATTERN METHODS

In Chapter 4, three methods (PCA, RRR and PLS) were used to capture the dietary patterns. Each method has its own strengths and limitations as outlined in Chapters 2 and 3. Briefly, all three methods are identical in relation to their mathematical base and their process of acquiring factors. Every method derived coefficient vectors of the extracted linear functions which are eigenvectors of a covariance matrix [381]. The differences occur in where they obtain these coefficient vectors or covariance matrices from (PCA = predictors, RRR = response variables, PLS = between predictors and responses) [381].

To date, there have been inconsistent findings of the association between dietary patterns and DepS. Most of the studies have used the PCA approach or factor analysis method, however, more recently studies have used the RRR [57, 486, 487] approach while there was no study has undertaken a PLS approach in determining the relationship between dietary pattern and DepS. One of the probable reasons behind the inconsistent findings using these approaches is the differences in obtaining the coefficient vectors.

7.2.6 MEASUREMENT OF DIETARY INFLAMMATORY POTENTIAL BY E-DII™

The DII® without energy adjustment does not consider differences in total energy intake and, consequently, the E-DII™ has been developed to address this [458]. The E-DII™ uses a reference database of energy adjusted nutrient scores [458]. It was found that this E-DII™ improved prediction in diet-disease association, compared to unadjusted DII® scores [458]. Hence, we used E-DII™ to reduce any potential biases due to difference in energy intake.

7.3 CHALLENGES OF DIETARY RESEARCH

There are many challenges in conducting dietary research. First and foremost, most of the studies in this field are observational studies, based primarily on participant questionnaires. It is not always possible to capture every single covariate associated with the diet and disease [488] and, therefore, the data obtained can be incomplete and may miss a other crucial factors that might explain the link between diet and disease.

The second challenge lies in the causality, since many of the findings in this field of research come from cross-sectional studies i.e., data for both depression and diet are collected only at the same time. Longitudinal studies with data collected a several time points is thus required to clarify this issue [489].

The third challenge lies in the use of covariates (e.g. socioeconomic status, physical activity, smoking, sleep quality and chronic health conditions) associated with depression. There may be associations which occur in a bidirectional manner and, therefore, it is difficult to separate the relative contribution of each to the occurrent in depression. In this thesis, an epidemiological tool, the Directed Acyclic Graph (DAG), has been used to identify the potential confounders of diet-depression associations. Only the potential confounders with a possible link with both diet (predictive variable) and depression (outcome variable) have been included.

The fourth challenge is the measurement of diet, which is very prone to measurement errors (random or systematic) due to recall bias or other biases, as a result of using self-reported dietary assessment instruments [489, 490]. The most common error is under reporting of energy intake [491], possibly due to social desirability and social approval [491-493]. In order to limit the impact of this, a well validated questionnaire was used, specifically designed for Australian adults and which has previously been used in many large-scale epidemiological studies in Australia such as Australian arm of the Breast Cancer Family Registry, Australian Prostate Cancer Family Study, Australian Longitudinal Study of Women's Health [376].

The fifth challenge comes from the dietary or nutrient pattern analysis methods such as PCA which has some recognized limitations [494]. In the PCA approach, subjective and arbitrary decisions on how to interpret dietary or nutrient patterns are taken. The interpretability of the PCA approach depends upon the choice of variables to include in the analysis, whether to transform and or standardize the data, the number of components to retain and finally the threshold for factor loadings [64]. In addition, NPs identified by PCA, do not provide a true picture of exactly what is being consumed, as the same scores may be obtained with different combinations of nutrients or different amounts of foods,

which may be high or low in nutrient density. For example, the source of MUFAs could be from both animal origin such as red and processed meats, dairy products, butter and poultry or plant origin such as olive oil, nuts and salad dressings [495]. It is challenging to make food based dietary recommendation based upon the NPs analysis alone since many food sources have the same nutrient.

7.4 STRENGTHS AND LIMITATIONS

There are several strengths in the findings of this thesis. First, the studies used a large sample size that was equally represented by gender (51% female). Second, a wide range of confounding factors was also collected which addressed many of the factors associated with DepS and diet. Third, the results across all three studies demonstrated consistency in the relationship between diet and DepS, providing supporting evidence for an association between diet and DepS.

When interpreting the findings of this thesis, however, the following limitations should be considered. While detailed limitations for each study have been provided in Chapters 4 to 6, the major limitations are around the challenges of using food frequency questionnaires (FFQs), confounding issues and the self-reported CES-D questionnaire, as discussed above. DepS was assessed using questionnaires which would lead to some misclassification, which is particularly important for the prospective analysis. Some depression-related symptoms could have impacted on dietary habits. Since our study findings are mainly based upon cross-sectional data that prohibit causal inferences based on temporality. To overcome this limitation, we also assessed the association between incidence of DepS with dietary patterns and E-DII™, albeit with a smaller sample size (n = 859 compared to n =1,743 in cross-sectional analysis). Dietary data was available at Stage 3 only and, therefore limited the longitudinal and potential causal association.

In addition, there is also a possible loss to follow up which is also a recognized limitation in our study. In Chapter 4, in an attempt to address this, we have carried out sensitivity analyses by performing multiple imputation on the covariates with missing values using chained equations, however, there were minimal differences in the associations between dietary patterns and DepS, for both the cross-sectional and longitudinal analyses. Furthermore, there are other limitations which are common in dietary and nutrient pattern analysis methods, including subjective or arbitrary decisions in factor analysis, selection of precise response variables and non-availability of some of the food groups/nutrients in the dietary data including food group/nutrients required to calculate the E-DII™ as it was previously computed by Shivappa *et al.* [83]. A further limitation is that the nutrient pattern data was based on absolute amounts, without taking energy into account and, therefore, without accounting nutrient requirements, which is applicable for number of nutrients, particularly those used as cofactors for metabolism of energy.

7.5 IMPLICATIONS OF THE STUDY

The present findings contribute to the epidemiological literature by delivering empirical support for the relationship between dietary patterns, NPs and/or DII with DepS. In addition, all three studies have broader implications.

7.5.1 CLINICAL IMPLICATIONS

This research suggests a link between diet and DepS and, therefore, should stimulate future research to establish a definitive causal link between diet and DepS that can be used to promote healthy eating. Our results suggest that general physicians and psychiatrists should be encouraged to advocate the role of a healthy diet for patients who have DepS. Healthy diets such as the ‘prudent’, ‘plant sourced’ or ‘anti-inflammatory’ diets may confer benefits for those with DepS.

7.5.2 METHODOLOGICAL IMPLICATIONS

Some methodological implications can be drawn from this thesis. The methodological approaches used in this thesis have not been widely used previously [202, 239, 313, 487]. First, the outcome variable could be used not only as a binary variable but also as continuous score which assists in understanding disease severity. Second, exploration of components of DepS (as measured by specific questions) could be a focus for future research rather than only focussing on the overall depression score.

7.6 RECOMMENDATIONS FOR FUTURE RESEARCH

Our findings indicate that there is an association between the inflammatory potential of a diet and DepS. Chronic and acute inflammation may have a number of adverse effects on brain structure and function which, in turn, appear to have detrimental effects on cognitive function and subsequently the development of depression [496, 497]. However, future research using clinical or experimental studies, is required to examine the physiological impact of diet on biological inflammatory markers and investigate the complex association between nutrition and depression.

Lifestyle modalities, such as exercise [498-500] and sleep [501], also impact on brain function and, therefore, an integrated approach is needed to effectively treat or prevent depression using a large prospective longitudinal study.

Indices similar to DII® could be used for other lifestyle factors, such as physical activity, sleep, and stress and these indices could be integrated with DII®, which may then open up new avenues for nutritional epidemiological research [458].

Future studies may also consider incorporating dietary/nutrient patterns and the DII® simultaneously to determine their associations with depression. Using dietary patterns alone can compromise the understanding of the disease mechanisms that are

largely addressed by studies of nutrient action [502] and, therefore, combining these methods will provide additional insight on depression aetiology. When interpreting the factor analysis with the currently available dietary analysis tools, such as PCA, RRR and PLS, arbitrary decision have to be made in determining the number of factors and naming of the patterns, which is an acknowledged limitation in dietary/nutrient pattern analyses [410]. Newer techniques/methods are needed in the future to overcome these difficulties.

The use of a semi-quantitative FFQ, which does not accurately estimate the absolute intake of diet can limit the interpretability of results. Therefore, future studies should focus on developing new tools, including smartphone applications or artificial intelligence, for more accurate assessment of food intake.

In this research, we measured depression using a dimensional perspective [122] i.e. a symptoms-based approach represented as DepS using the CES-D questionnaire. However, in this approach, the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-V) or International Statistical Classification of Diseases version 10 (ICD-10) classifications were not met and, therefore, DepS cannot be claimed as 'clinical depression'. In a large epidemiological study such as this, it is difficult to recruit enough participants with diagnosis of clinical depression thus it is more pragmatic to use a symptoms-based approach. Nonetheless, it would be beneficial to recruit participants diagnosed with clinical depression, or at least recruitment based on history of, or current use of anti-depressant medications.

As diet-depression relations are bidirectional, causal inference could be inferred by performing either: i) long term prospective studies with repeated measures or ii) well designed randomized controlled trials (RCTs) with larger sample sizes. Therefore, future research should focus on this type of research to unravel the complex association between nutrition and depression.

7.7 CONCLUSION

The three independent studies detailed in this thesis support the hypothesis that a healthy diet, such as the 'prudent', 'typical Australian' or 'anti-inflammatory' diet, is associated with decreased odds of DepS, particularly in the adult population. A 'prudent' dietary pattern was characterised by fruit and vegetables, nuts, fish, medium fat milk products, legumes, and high fibre. The 'typical Australian' pattern was characterised by red meat, jam and vegemite, unsaturated spreads, bread, vegetables, tomato sauces, fruits, juice and fish. The NP analysis revealed a 'plant-sourced' pattern characterised by β-carotene, fibre, vitamin C, potassium, α-carotene, lutein and zeaxanthin, iron and magnesium was inversely associated with DepS. Conversely, a 'western' diet or 'pro-inflammatory diet', characterised by high intakes of processed foods, fast foods (snacks and takeaway foods), soft drinks, white bread and high-fat dairy products, was associated with an increased risk of DepS. Therefore, increased consumption of diet that are healthy and rich in foods and nutrients with anti-inflammatory properties, high in fruit and vegetables and rich in antioxidants, is inversely associated with DepS and may assist with the prevention of DepS.

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Appendices

APPENDIX A

Center for Epidemiologic Studies Depression Scale (CES-D)

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

		During the Past Week			
		Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1.	I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2.	I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3.	I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4.	I felt I was just as good as other people.	☐	☐	☐	☐
5.	I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6.	I felt depressed.	☐	☐	☐	☐
7.	I felt that everything I did was an effort.	☐	☐	☐	☐
8.	I felt hopeful about the future.	☐	☐	☐	☐
9.	I thought my life had been a failure.	☐	☐	☐	☐
10.	I felt fearful.	☐	☐	☐	☐
11.	My sleep was restless.	☐	☐	☐	☐
12.	I was happy.	☐	☐	☐	☐
13.	I talked less than usual.	☐	☐	☐	☐
14.	I felt lonely.	☐	☐	☐	☐
15.	People were unfriendly.	☐	☐	☐	☐
16.	I enjoyed life.	☐	☐	☐	☐
17.	I had crying spells.	☐	☐	☐	☐
18.	I felt sad.	☐	☐	☐	☐
19.	I felt that people dislike me.	☐	☐	☐	☐
20.	I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Adapted from 'The CES-D Scale: A Self-Report Depression Scale for Research in the General Population.' by Radloff et al. Appl Psychol Meas. 1977;1(3):385-401 [133]

APPENDIX B

Different variables collected during the NWAHS (1999-2010), South Australia

Phase	CATI	Questionnaire	Clinic
Stage 1 **(Ph1A 1999-2001) and Ph1B 2002/03)**	• **Chronic Health conditions** - doctor diagnosed diabetes, asthma, bronchitis, emphysema, heart attack, stroke, angina • **Smoking** - current and ever smoked regularly • **High cholesterol** *(Ph 1B only) - doctor diagnosis ever, current* • **High blood pressure** *(Ph 1B only) - doctor/nurse diagnosed ever, current* • **Height and weight** *(Ph 1B only)* • **Mental health conditions** (doctor diagnosed last 12 months) - anxiety, depression, stress-related, other; still current • **Demographics** - age, sex, work done for most of life, no of people 18+ in the household, no of children <18 in household	• **Short form survey (SF36)** (v1) • **Physical activity** (National Health Survey) • **Health care utilisation** (last year) • **Family history** - diabetes, heart disease, stroke • **Diabetes** - doctor diagnosed ever, gestational, high blood sugar ever and now, type; *Ph 1B only when first told* • **Asthma** • **Bronchitis** • **Emphysema** • **Lung function** - Chronic Lung Disease Index • **Alcohol** - frequency, amount • **Smoking** - current, amount, ever smoked regularly, cigs per day, age when last gave up smoking • **Demographics** -age when left school, trade or higher qualifications, annual gross household income, birth country, year of arrival in Australia, Aboriginal and Torres Strait islander status, marital status, work status, pension/benefit status, age, postcode	• **Appointment information** - date, time, date of birth, age, sex, location of clinic, location of blood sample, reimbursement status • **Clinic admin** - fasting, hospital patient, consent forms, GP and secondary contacts, Medicare consent • **Blood pressure** - systolic and diastolic, medication for hypertension; *Ph 1B only - currently on high blood pressure medication, taken in last 24 hours* • **Height and weight** • **Waist and hip circumference** • **Blood tests** - triglycerides, total cholesterol, HDL • cholesterol, LDL cholesterol, glucose, HbA_{1C}; *Ph 1B only - currently on cholesterol medication, taken in last 24 hours* • **Spirometry**

Ph: Phase, CATI: Computer Assisted Telephone Interview; SF-26: 36-Item Short Form Survey (SF-36)

Phase	CATI	Questionnaires	Clinic

Stage 2 2004-06	• **Chronic Health conditions-** doctor diagnosed ever) - heart attack, stroke, angina, Transient ischemic attack/ mini-stroke, osteoporosis, arthritis • **Health care utilisation** (last year) • **Low Back pain** • **Knees pain** • **Feet pain** • **Shoulders pain** • **Hands pain** • **Injury** - falls, fractures • **Menopause** - status, length of time • **Mental health conditions** (doctor diagnosed last 12 months) - anxiety, depression, stress-related, other **Depression** (CES-D)	• **Short form survey (SF36)** (v1) • **Physical activity** (National Health Survey) • **Family history** - diabetes, heart disease, stroke, osteoporosis • **Osteoporosis** • **Sunlight** • **Diabetes** - doctor diagnosis ever, gestational, type, vision affected, laser therapy on eyes, cataract surgery, tingling etc. of feet and toes • **Asthma** • **Bronchitis (chronic)** • **Emphysema** • **Lung function** • **Alcohol** - frequency, amount • **Smoking** - current, amount, ever smoked regularly, cigs per day, age when last gave up smoking and first started smoking • **Mental health and wellbeing** (GHQ12) • **Demographics** - family structure, highest educational qualification, annual gross household income, marital status, work status, pension/benefit status, age, postcode	• **Appointment information** - date, time, date of birth, age, sex, location of clinic, location of blood sample, reimbursement status • **Clinic admin** - fasting, urine sample, consent forms, GP and secondary contacts, Medicare consent • **Blood pressure** - systolic and diastolic • **Height and weight** • **Waist and hip circumference** • **Blood tests** - triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, glucose, HbA_{1C}, currently on cholesterol medication, taken in last 24 hours • **Arthritis** • **Spirometry** • **DEXA** (for those 50+ yrs.)

SF-36: 36-Item Short Form Survey (SF-36); GHQ12: 12-item General Health Questionnaire; GP: General physician; HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA_{1C}: Glycated haemoglobin; DEXA: Dual-energy X-ray absorptiometry

Phase	CATI	Questionnaires	Clinic
Stage 3 2008 – 2010	• **Chronic Health conditions-** doctor diagnosis ever - heart attack, stroke, angina, TIA/ mini-stroke, heart procedures (bypass, angiogram, stent), osteoporosis, gout, arthritis • **Mental health** (doctor diagnosed last 12 months) - anxiety, depression, stress-related, other • **Injury** - falls, fractures • **Shoulders** - pain, aching or chronic stiffness in last month, SPADI • **Health care utilisation** (last year) • **Physical activity** (Active Australia) • **Quality of life** (SF36 V2) • **Cardiovascular knowledge** • **Self-reported body measures** (height, weight, waist) • **Household food habits** • **Household environment** • **Household** - age, sex and relationship of household members • **Early learning** • **Demographics** - marital status, work, education, income, family structure, housing, pension, money situation	• **Short form survey (SF36)** (v2) • **Carers** – long term care, effect on health • **Family history** • **Asthma** • **Lung function** • **Alcohol** • **Smoking** • **Sleep** • **Depression** (CES-D) • **Mastery and control** • **Low Back pain** • **Hips pain** • **Feet pain** • **Knees pain** • **Hands pain** • **Major health event(s) in last 5 years** • **Feedback from participants** • **Cardiovascular knowledge** • **Food Frequency Questionnaire** (Cancer Council Victoria) (including alcoholic and non-alcoholic beverages)	• **Appointment information** - date, time, date of birth, age, sex, location of clinic, location of blood sample, reimbursement status • **Clinic administration** - fasting, consent forms, GP and secondary contacts, Medicare and DNA consents • **Blood pressure** - systolic and diastolic, medication for hypertension, currently on HBP medication, taken in last 24 hours • **Height and weight** • **Waist and hip circumference** • **Urine specimen** - sodium, potassium, creatinine, albumin, phosphate, micro-albuminuria, iodine and sodium • **Blood tests** - Multiple biochemical analysis 20 (MBA20) 20 different parameters in blood • **Complete blood count** • **Arthritis** • **Spirometry** • **Health Literacy**

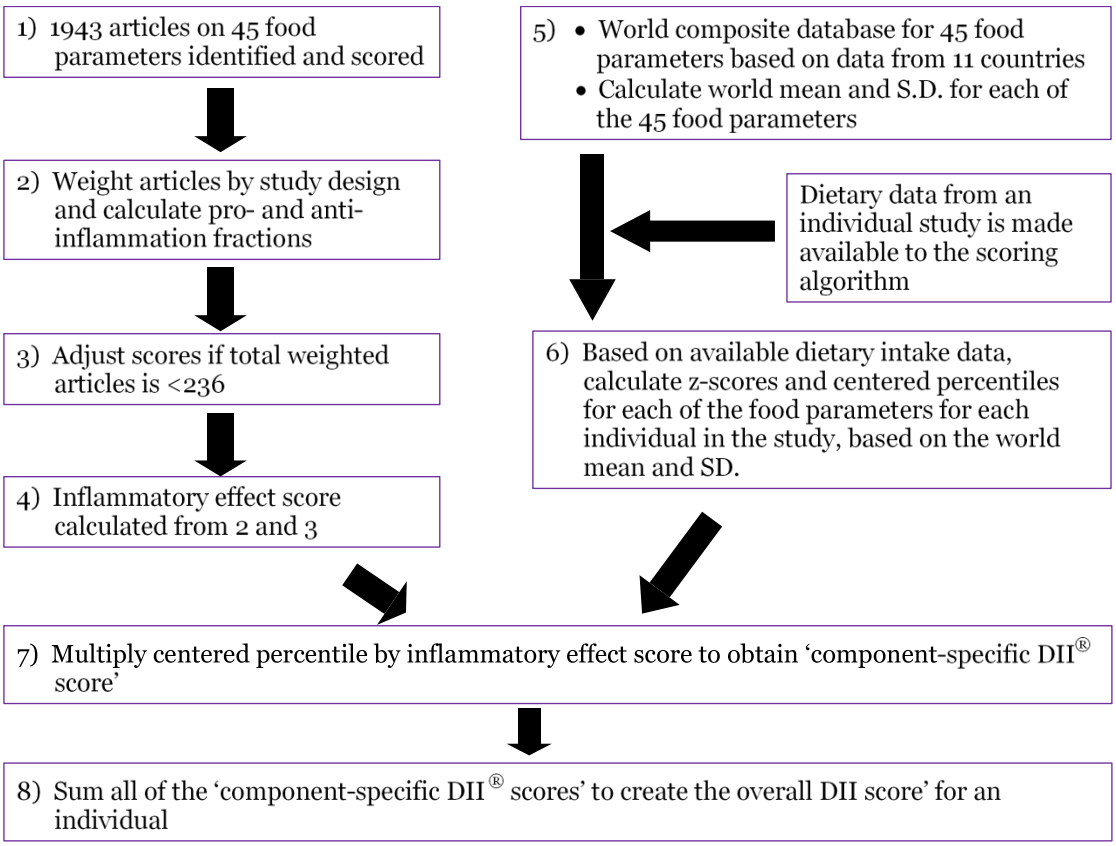
Adapted from: 'Cohort Profile: The North West Adelaide Health Study (NWAHS).' by Grant, J. F. et al (2008); International Journal of Epidemiology 38(6) [375]

Phase	Questionnaires
NW15 **(2015-16)**	• **Demographic factors** age when left school, trade or higher qualifications, annual gross household income, birth country, year of arrival in Australia, Aboriginal and Torres Strait islander status, marital status, work status, pension/benefit status, age, postcode • **Chronic conditions** • Doctor diagnosis ever - heart attack, stroke, angina, TIA/ mini-stroke, heart procedures (bypass, angiogram, stent), osteoporosis, gout, arthritis (including type); kidney disease, • Diabetes • Asthma, COPD • Mental health (doctor diagnosed last 12 months) - anxiety, depression, stress-related, other • Cancer • Nutrition water, soft drink, juice, sports drinks, processed food, eggs fruit and veg consumed • CES-D • Falls • General pain • Carers • Risk factors • Physical activity, smoking, alcohol, blood pressure, cholesterol • Mental Health • Health care utilization • HRQoL, SF36 • Work related musculoskeletal symptoms • Self-report height, weight, neck circumference • Sleep • Hip, knee, back, shoulder, hand, foot, neck pain • Self-reported medication use

COPD: Chronic Obstructive Pulmonary Disease; HRQoL: Health-related quality of life; TIA: Transient ischemic attack

APPENDIX C

DII® Calculation steps



Adapted from 'Designing and developing a literature-derived, population-based dietary inflammatory index' by Shivappa et al. Public Health Nutrition. 2014 Aug;17(8):1689-96. [83]

APPENDIX D

Associations of nutrient pattern with DepS at Stage 3 (2008-10; n = 1,743) and NW15 (2015; n = 1,015) in the Australian adults participating in the NWAHS after including familial status

	PR (95% confidence interval) [a]					OR (95% confidence interval) [b]			
	Q1 (Ref)	Q2	Q3	Q4 (Highest)	P for tren	Q2	Q3	Q4 (Highest)	P for trend
Stage 3[c]									
Plant-sourced nutrient pattern									
Model 2	1	0.88(0.76-1.02)	0.89(0.76-1.03)	0.78(0.66-0.92) **	0.005	0.86(0.57-1.30)	0.94(0.62-1.43)	0.76(0.48-1.20)	0.331
Animal-sourced nutrient pattern									
Model 2	1	0.98(0.84-1.13)	1.05(0.90-1.22)	1.05(0.89-1.23)	0.409	0.83(0.54-1.27)	1.16(0.77-1.76)	1.04(0.67-1.63)	0.542
Mixed-sourced nutrient pattern									
Model 2	1	1.09(0.94-1.26)	0.95(0.81-1.12)	1.04(0.85-1.28)	0.901	1.01(0.65-1.55)	0.71(0.44-1.14)	0.81(0.46-1.45)	0.245
Stage NW15[c]									
Plant-sourced nutrient pattern									
Model 2	1	0.96(0.79-1.16)	0.95(0.77-1.16)	0.89(0.72-1.11)	0.327	0.86(0.51-1.45)	0.97(0.56-1.68)	0.64(0.34-1.19)	0.254
Animal-sourced nutrient pattern									
Model 2	1	1.02(0.84-1.23)	0.86(0.71-1.05)	0.88(0.72-1.09)	0.112	1.22(0.72-2.09)	0.90(0.51-1.58)	0.81(0.44-1.50)	0.354
Mixed-sourced nutrient pattern									
Model 2	1	0.79(0.65-0.97)	0.90(0.73-1.12)	0.95(0.73-1.24)	0.944	0.46(0.26-0.82)	0.69(0.38-1.26)	0.52(0.25-1.09)	0.211

Model 2 was adjusted for sex, age, total energy intake, familial status, marital status, educational status, employment status, income, SEIFA, alcohol risk, smoking status, PAL, self-reported sleep quality, BMI, bodily pain, hypertension, diabetes and CVD

*** p<0.01, ** p<0.05, * p<0.1

[a]Negative binomial regression analysis; [b]Log-binomial regression analysis

[c]Sensitivity analysis including familiar status

APPENDIX E

Associations of nutrient pattern with prevalent depression at Stage 3 (2008-10; n=2,323)[a] and Stage NW15 (2015; n=1,300)[a] in the Australian adults participating in the NWAHS

	OR (95% confidence interval) [b]				
	Q1 (Reference)	**Q2**	**Q3**	**Q4**	**P for trend**
Stage 3					
Plant-sourced nutrient pattern					
Model 1	1.00	0.68(0.50-0.91) **	0.65(0.48-0.89) ***	0.53(0.38-0.73) ***	0.000
Model 2	1.00	0.89(0.63-1.27)	0.97(0.68-1.39)	0.80(0.54-1.18)	0.359
Animal-sourced nutrient pattern					
Model 1	1.00	0.95(0.69-1.31)	1.22(0.89-1.67)	1.36(0.98-1.89)	0.032
Model 2	1.00	0.92(0.64-1.33)	1.21(0.85-1.74)	1.18(0.80-1.73)	0.228
Mixed-source nutrient pattern					
Model 1	1.00	1.03(0.75-1.42)	0.83(0.59-1.18)	0.98(0.64-1.49)	0.605
Model 2	1.00	0.90(0.62-1.31)	0.72(0.48-1.07)	0.79(0.49-1.28)	0.209
Stage NW15					
Plant-sourced nutrient pattern					
Model 1	1.00	0.72(0.50-1.04) *	0.57(0.39-0.84) ***	0.47(0.31-0.71) ***	0.000
Model 2[c]	1.00	0.95(0.63-1.42)	0.85(0.55-1.30)	0.72(0.45-1.15)	0.156
Animal-sourced nutrient pattern					
Model 1	1.00	1.37(0.94-1.98)	1.07(0.72-1.59)	1.23(0.81-1.85)	0.576
Model 2[c]	1.00	1.46(0.96-2.22)	1.16(0.75-1.79)	1.03(0.65-1.64)	0.888
Mixed-sourced nutrient pattern					
Model 1	1.00	0.69(0.47-1.03)	0.82(0.54-1.23)	0.80(0.48-1.33)	0.515
Model 2[c]	1.00	0.60(0.39-0.92)	0.69(0.43-1.09)	0.65(0.37-1.13)	0.202

Model 1 was adjusted for sex, age and total energy intake

Model 2 was additionally adjusted for marital status, educational status, employment status, income, SEIFA alcohol risk, smoking status, PAL, self-reported sleep quality, BMI, bodily pain, hypertension, T2DM and CVD

*** p<0.01, ** p<0.05, * p<0.1

[a]Multiple imputation by chained equation method; [b]Log-binomial regression analysis; [c]Additionally adjusted with continuous depression score obtained from the Stage 3