UTS UNIVERSITY OF TECHNOLOGY SYDNEY

The effects of a Mediterranean diet on symptoms of depression in young men

by Jessica Bayes

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy (Public Health)

under the supervision of
Prof David Sibbritt and Dr Janet Schloss

University of Technology Sydney
Faculty of Health

January 2023

CERTIFICATE OF ORIGINAL AUTHORSHIP

I, Jessica Bayes, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health, at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Signature: Production Note:
Signature removed prior to publication.

Date: 05/01/2023

STATEMENT OF AUTHOR CONTRIBUTIONS TO JOINTLY AUTHORED WORKS CONTAINED IN THIS THESIS

The structure of this thesis is by compilation. It comprises of a combination of both chapters and published articles. The published peer reviewed articles contained within this thesis are outlined below.

1) Bayes, J., Schloss, J., & Sibbritt, D. (2019). Effects of Polyphenols in a Mediterranean Diet on Symptoms of Depression: A Systematic Literature Review. *Advances in Nutrition*, 11 (3), 602-615. https://doi.org/10.1093/advances/nmz117

2) Bayes, J., Schloss, J., & Sibbritt, D. (2020). An Investigation into The Diets and Nutritional Knowledge of Young Men with Depression (The "MENDDS" study). *Nutrition*, 78, 110946. https://doi.org/10.1016/j.nut.2020.110946

Also presented via:

- Poster presentation at the 16th Word Congress on Public Health (Oct 2020)
- Oral Presentation at the Australasian Lifestyle Medicine Conference (Dec 2020)
- Video created via VideoScribe: https://sho.co/1DKPE

3) Bayes, J., Schloss, J., & Sibbritt, D. (2020). A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study): A study protocol. *British Journal of Nutrition*, 126 (5), 730-737. https://doi.org/10.1017/S0007114520004699

4) Bayes, J., Schloss, J., & Sibbritt, D. (2022). The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study): A Randomized Control Trial, *The American Journal of Clinical Nutrition*, https://doi.org/10.1093/ajcn/nqac106

Also presented via:

- Oral Presentation at the Australasian Lifestyle Medicine Conference (July 2022)
- Oral Presentation for the International Society of Nutritional Psychiatry Research (June 2022)

5) Bayes, J., Schloss, J., & Sibbritt, D. (2022). A Mediterranean diet intervention for young men with depression: patient experiences, challenges and benefits (the "AMMEND study") – A Cross-sectional Study, *Clinical Nutrition ESPEN.* https://doi.org/10.1016/j.clnesp.2022.12.016

Works currently under peer review:

6) Bayes, J., Schloss, J., & Sibbritt, D. The use of diet for treating depression in young men: Current evidence and existing challenges, *Nutritional Neuroscience.*

Authorship:

Conception and design of each article, data collection, data analysis and interpretation of the data was conducted by JB with supervision from JS and DS. JB wrote and drafted all of the articles with support and edits provided by JS and DS. All authors approved the final version of each manuscript prior to publication.

Jessica Bayes

Signature: Production Note: Signature removed prior to publication.

Date: 05/01/2023

Janet Schloss:

Signature: Production Note: Signature removed prior to publication.

Dates: 05/01/2023

David Sibbritt

Signature: Production Note: Signature removed prior to publication.

Date: 05/01/2023

Media Feature Articles and Interviews:

There are also a number of media publications associated with the research included in this thesis, including feature articles in several online and print magazines. These are outlined below:

1) *Medical News Today* - Mediterranean diet may improve depression symptoms in young men: https://www.medicalnewstoday.com/articles/327222#antidepressants

2) *VeryWell Mind* – Mediterranean Diet May Help Beat Depression in Young Men: https://www.verywellmind.com/mediterranean-diet-helps-beat-depression-in-young-men-5272383

3) *Inverse Magazine* – Best Diet to Boost Mood? A Study on Men And Depression: https://www.inverse.com/mind-body/what-diet-is-good-for-depression

4) *ZME Science* – A diet rich in fruits and vegetables can help tackle depression in young men https://www.zmescience.com/science/mediterranean-diet-depression-12052022/

5) *Fatherly Magazine* – Mediterranean Diet Reduces Depression In Young Men: https://www.fatherly.com/health/mediterranean-diet-reduces-depression-young-men-study

6) *Mediblurb* podcast (available on google, apple and Spotify) Mediterranean Diet Improves Depression in Young Men: https://mediblurb.com/podcast/mediterranean-diet-improves-depression-in-young-men/)

Media appearances associated with the research contained within this thesis:

1) Channel 9 News (11th May 2022) https://www.9news.com.au/national/sydney-study-find-mediterranean-diet-improves-depression-symptoms-in-young-men/611bc008-4e8e-4223-873f7277ce4e34a7?ocid=Social-9News

2) Channel 7 News (11th May 2022) https://www.youtube.com/watch?v=b1SI3FOoi7g

3) ABC Radio Sydney (3:45pm 10th May 2022)

4) Eastside FM (5:30pm 13th May 2022)

5) Joy Drive Radio (5:45pm 16th May 2022)

6) Medscape Interview (13th December 2022) https://www.medscape.com/viewarticle/983358?src=rss

ACKNOWLEDGEMENTS

I would like to acknowledge and thank several people and organisations, for making this thesis possible. I would like to thank UTS and Endeavour College for providing financial support and funding for the projects completed during my PhD. I would also like to thank the UTS Media outreach team, specifically Samantha Cook and Leilah Schubert, for their valuable assistance in promoting and disseminating these research projects to the public.

I am sincerely grateful to those who have encouraged and supported me during the process of completing this thesis. I would like to thank my supervisors Dr Janet Schloss and Professor David Sibbritt, whose guidance and support has given me the strength and confidence to complete this degree. I am so grateful to have been able to work alongside such incredible researchers. Their expert advice and encouragement helped me achieve milestones I never imagined possible.

Janet – you have been there since the very beginning of my research journey! I cannot thank you enough for your encouragement to pursue this PhD. You are a constant source of guidance and inspiration. David – I am so grateful for all the opportunities you have given me during my candidature. You have helped push me to grow and develop as a researcher and I am so thankful for your support and advice.

I would also like to thank my friends and family, for their unwavering encouragement during the past 3 and a half years. Particularly during the Covid-19 lockdowns and my own mental health struggles. Thank you for believing in me, and for knowing that I could make a difference. Special thanks to my fellow PhD student family, particularly Brad Leech and Carrie Thomson-Casey. Having such as strong support network around me has been vital to the successful completion of this thesis, and I am eternally grateful.

Finally, I would like to thank the young men who participated in the various projects included within this thesis. I am so grateful for their honesty, vulnerability, participation, insights and feedback. This thesis is dedicated to them, and to all young men suffering from depression.

TABLE OF CONTENTS PAGE

Certificate of Original Authorship..... ii

Published articles contained within thesis..... iii

Statement Of Author Contributions..... iv

Acknowledgments..... vi

List of Tables..... ix

List of Figures..... x

Definitions and Abbreviations..... xi

Abstract..... xiv

1. Chapter 1: Introduction 1

    1.1 Preface..... 1

    1.2 Introduction..... 1

    1.3 Depression Overview..... 2

    1.4 Depression in Men..... 11

    1.5 Depression in Young Adults..... 14

    1.6 Standard and Complementary Treatments..... 16

    1.7 Diet and Mental Health..... 20

    1.8 Diet & Food Mechanism of action 22

    1.9 Inflammation..... 23

    1.10 Microbiome..... 26

    1.11 Overview of diet and depression research..... 30

    1.12 Gaps in the research..... 37

    1.13 Chapter Summary..... 38

2. Chapter 2: Methods 39

    2.1 Preface..... 39

    2.2 Theoretical Framework..... 39

    2.3 Research Questions..... 43

    2.4 Aims & Objectives..... 44

    2.5 Methodological Overview..... 47

    2.6 Chapter Summary..... 48

3. Chapter 3: Literature Review 49

    3.1 Preface..... 49

3.2 Literature review article…… 50
3.3 Chapter Summary…….. 86
4. Chapter 4: The Men's Diet and Depression Survey (MENDDS) 87
4.1 Preface…… 87
4.2 MENDDS article…… 88
4.3 Translation & Dissemination…….. 103
4.4 Chapter Summary…….. 104
5. Chapter 5: A Mediterranean Diet for Men with Depression (AMMEND) Protocol 106
5.1 Preface…… 106
5.2 Protocol Article…… 107
5.3 Chapter Summary…….. 121
6. Chapter 6: A Mediterranean Diet for Men with Depression (AMMEND) Results 122
6.1 Preface…… 122
6.2 Results Article…… 123
6.3 Chapter Summary…….. 138
7. Chapter 7: A Mediterranean Diet for Men with Depression (AMMEND) follow up Survey 139
7.1 Preface…… 139
7.2 Results Article…… 139
7.3 Chapter Summary…… 151
8. Chapter 8: An Overview of Findings 152
8.1 Preface…….. 152
8.2 Article…….. 152
8.3 Chapter Summary…… 158
9. Chapter 9: Discussion 159
9.1 Preface…… 159
9.2 Discussion…….. 159
9.3 Chapter Summary…… 170
10. Chapter 10: Conclusion 172
10.1 Preface…….. 172
10.2 Research Questions Answered…… 172
10.3 Significance…… 173

10.4 Research Impact…… 174

10.5 Future Directions…….. 175

10.6 Final Statement…….. 176

Appendices:

Appendix 1: Literature Review Supplementary Material
Figure 1 – PRISMA-P Flow Chart…….. 177

Appendix 2: Literature Review Supplementary Material
Table 1 – Joanna Briggs Reviews Checklist for RCTs…….. 178

Appendix 3: Literature Review Supplementary Material
Table 2 – STOBE Checklist for Cohort, Case-control and Cross sectional…… 180

Appendix 4: Literature Review Supplementary Material
Table 3 – PRISMA Checklist…… 187

Appendix 5: Literature Review Supplementary Material
Table 4 – Literature Review Search Strategy Log Results…….. 190

Appendix 6: Literature Review Supplementary Material
ROB Interpretation…… 192

Appendix 7: Literature Review Supplementary Material
Narrative Synthesis Process…… 193

Appendix 8: MENDDS Article Supplementary Material
Figure 1 – Participant CONSORT Flowchart…… 194

Appendix 9: MENDDS article Supplementary Material
Table 1 – Diet History…….. 195

Appendix 10: MENDDS Questionnaire…… 197

Appendix 11: MENDDS article Poster Presentation for the 16th World
Congress on Public Health…….. 210

Appendix 12: AMMEND Protocol Consort Flow Chart…….. 211

Appendix 13: AMMEND Results Consort Flow Chart…… 212

Appendix 14: WHO QoL Domaine Results…… 213

Appendix 15: WHO QoL Total Results…… 215

Appendix 16: AMMEND Supplementary Material
Phone Screening Tool…… 216

Appendix 17: AMMEND Supplementary Material
Participant Information .and Consent Form…… 219

Appendix 18: AMMEND Supplementary Material

Case Report Form…….. 232
Appendix 19: AMMEND Supplementary Material
Participant Documents…….. 281
Appendix 20: AMMEND Supplementary Material
Adapted 15 item MEDAS…….. 305
Appendix 21: AMMEND Table 1 Baseline Characteristics with p-values……. 307
Bibliography…… 308

LIST OF TABLES

Chapter 3: Literature Review
Table 1: Data Summary of Experimental Trials Assessing Polyphenols in Depressed Participants…… 57
Table 2: Data Summary of Observational Trials Assessing Polyphenols on Depressive Symptoms. …… 67
Table 3: Characteristics of Included Articles…… 76
Table 4: Effects of Polyphenols on Symptoms of Depression…… 80
Chapter 4: The Men's Diet and Depression Survey (MENDDS) Article
Table 1: Demographic Characteristics of Study Participants…….. 92
Table 2: Nutrition Beliefs of Study Participants…… 94
Table 3: Associations Between Participants Beliefs of Diet Healthiness and Diet…… 95
Table 4: Associations Between Participants Beliefs of Diet Importance and Other Nutrition Beliefs…….. 96
Table 5: Participants food/symptoms observations…….. 98
Chapter 6: A Mediterranean Diet for Men with Depression (AMMEND) Results Article
Table 1: Demographic Characteristics of Study Participants…….. 136
Table 2: MEDAS Scores…… 137
Table 3: BDI-II Scores…… 137
Table 4: WHO QoL Scores…… 138

Chapter 7: A Mediterranean Diet for Men with Depression (AMMEND) Follow-Up Article

Table 1: Questionnaire Responses..... 149

LIST OF FIGURES

Figure 1: Factors Contributing to Depression..... 10

Figure 2: Characteristics of Male Depression..... 13

Figure 3: Mediterranean Diet Mechanisms..... 24

Figure 4: Theoretical Framework..... 48

DEFINITIONS & ABBRIVATIONS

Anhedonia	An inability to experience pleasure from activities usually found enjoyable.
ANZCTR	Australia and New Zealand Clinical Trials Registry
BDI-II	Beck Depression Inventory – version 2
BDNF	Brain Derived Neurotrophic Factor
Biomarkers	A naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified
CAM	Complementary and Alternative Medicine
CBT	Cognitive behaviour therapy (CBT) is a type of psychotherapy.
Co-morbidity	Comorbidity describes two or more disorders or illnesses occurring in the same person. They can occur at the same time or one after the other.
COAG	Council of Australian Governments
CONSORT	Consolidated Standards of Reporting Trials

CSIRO	Commonwealth Scientific and Industrial Research Organization
Dietary Patterns	A dietary pattern is defined as the quantity, variety, or combination of different foods and beverage in a diet and the frequency with which they are habitually consumed
DSM-VII	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition is the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders, the taxonomic and diagnostic tool published by the American Psychiatric Association
GBD	Global Burden of Disease
GIT	Gastrointestinal Tract
HPA axis	Hypothalamic-pituitary-adrenocortical axis
ICTRP	International Clinical Trials Registry Platform's
MEDAS	Mediterranean Diet Adherence Score
MDD	Major Depressive Disorder
Mediterranean Diet	The Mediterranean diet is a diet inspired by the eating habits of Spain, Italy and Greece in the 1960s
Mental Health	Mental health includes our emotional, psychological, and social well-being. It affects how we feel, act and think. It also determines how we handle stress, relate to others, and make choices.
MHCA	The Mental Health Council of Australia
Neurotransmitters	Neurotransmitters are chemical messengers that transmit a message from a nerve cell across the synapse to a target cell.
Microbiome	The microbiome is the genetic material of all the microbes - bacteria, fungi, protozoa and viruses - that live on and inside the human body
Monoamines	Monoamines refer to the particular neurotransmitter's dopamine, noradrenaline and serotonin.
Nutrition	Nutrition is the science that interprets the nutrients and other substances in food in relation to maintenance, growth, reproduction, health and disease of an organism. It includes

	ingestion, absorption, assimilation, biosynthesis, catabolism and excretion.
Nutritional Psychiatry	Mental Health Nutrition (Nutritional Psychiatry) is an emerging field of nutrition, dietetic and psychological sciences that explores the changes that nutritional interventions can make to one's mental health.
QOL	Quality of Life
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSRIs	Selective serotonin reuptake inhibitors
WHO	World Health Organisation
YLDs	Years lived with disability

ABSTRACT

***Background & Aims*:** The emerging field of nutritional psychiatry is a promising new area of research which examines the role of nutrition in mental health conditions. Yet despite the growing number of studies assessing the role of diet for depression, no research has explored the effect of diet in depressed young men (aged 18-25). This thesis addresses this research gap.

Methods: This thesis includes four main research projects. First, a systematic literature review assessing the role of polyphenols on depression. Secondly, a cross-sectional online questionnaire which assessed the diets and nutritional knowledge of 384 young men with depression via the Men's Diet and Depression Survey (the MENDDS study). Thirdly, a randomised control trial (RCT) which assessed a dietary intervention on the symptoms of depression in young men with moderate to severe clinical depression. A Mediterranean Diet for Men with Depression (the AMMEND study) assessed the effect of a 12-week Mediterranean diet verses a befriending control group. Lastly, a follow-up cross-sectional survey examining the experiences of the participants who completed the MD arm of the AMMEND study.

Results: The results from the literature review reveals that the polyphenols found within a MD appear beneficial for depression. The MENDDS study found that the current dietary patterns of young men with depression are poor. Their diets are high in processed foods and low in vegetables and wholegrains. They believe their diet has an impact on their mental health and would be willing to change it to help improve their depressive symptoms. The AMMEND study found that young men with depression and poor diets are capable of significantly improving their diets over 12 weeks under the guidance of a clinical nutritionist. These diet changes led to improvements in depressive symptoms and quality of life. The AMMEND end-of-trial evaluation found the main challenges to include increased cost and time commitment, and the negative attitudes of friends/family to the diet.

Conclusions: It is evident that diet appears to play a significant role in the mental health of young men. Based on these results, implementing a MD should be considered in the treatment of depression in young men, and referrals to nutritionists or dietitians should become routine. Additionally, by understanding the diet quality, nutrition knowledge, and barriers faced by young men, clinicians can tailor their dietary advice resulting in better outcomes. Further research is needed to determine the long-term effects of a MD in this demographic.

1. CHAPTER 1: INTRODUCTION

1.1 PREFACE

This thesis critically evaluates the role of a Mediterranean diet (MD) on the symptoms of depression in young men. Chapter 1 introduces several topics including an introduction to depression, it's history, symptoms and prevalence in Australia. Next, the role of gender in depression is examined and an overview into the unique experiences of men's depression provided. Further, a discussion on age, with a particular focus on young adults is included. Next, the standard medical treatments for depression are outlined and complementary medicine treatments are introduced. The field of nutritional psychiatry is then discussed and the potential role of diet in depression explored. Finally, a comprehensive overview of the potential dietary mechanisms influencing mental health are discussed, including the role of inflammation and the gastrointestinal microbiome. A brief overview of the literature investigating diet and mental health is provided and gaps in the literature are discussed at the conclusion of this chapter.

1.2 INTRODUCTION

There are several types of depressive disorders including major depressive disorder, bi-polar disorder, post-partum depression, premenstrual dysphoric disorder, seasonal affective disorder and atypical depression. When referring to depression throughout this thesis, it is in reference to major depressive disorder (MDD), also known as uni-polar depression, unless specified otherwise. Additionally, when referring to a "diet", such as the Mediterranean diet or Western diet, it is reference to overall dietary patterns and the kinds of food that a person or community habitually eats. The term "diet" is not used to refer to the activity by which a person restricts specific foods or calorie intake in order to lose weight, unless specified otherwise.

When referring to "men" throughout this thesis it is mostly referring to the social construct of *gender*, rather than the biological distinction of sex, unless specified otherwise. The majority of the research on men included within this thesis uses the term "man" or "male"

to refer to people who were assigned male at birth, and, who still identify as male – cisgender men. There is an unfortunate under-representation of those who identify as trans-men, gender fluid, non-binary and agender within the current published literature. We have made every effort to make this thesis inclusive to all. The main research project included within this thesis, the AMMEND randomised control trial, includes individuals who identify as male, including transgender men.

Note that the global COVID-19 pandemic which occurred during 2020 greatly influenced this thesis and the data collection process for the AMMEND RCT. This is outlined in more detail in Chapter 5.

1.3 DEPRESSION OVERVIEW

1.3.1 Disability and Cost

The World Health Organisation (WHO) has categorised depression as one of the most disabling clinical diagnoses in the world[1]. It is a common mental health disorder affecting approximately 350 million people worldwide[2]. In Australia, it's estimated that 45% of people will experience a mental health condition in their lifetime[3] and around 1 million Australian adults have depression in any given year[3]. The latest Global Burden of Disease (GBD) survey (2010) reported that depressive disorders were the second leading cause of years lived with disability (YLDs) worldwide[4] and the Burden of Disease and Injury in Australia report stated that depression is responsible for 6.2% of YLD in Australian men[5]. In health terms, mental illnesses are different to most other illnesses. The overwhelming burden of mental illnesses affects young people, while most other conditions are more likely to affect older adults[6]. Most mental illness is not fatal, however, the early onset of many mental illnesses can mean that sufferers can face varying degrees of disability for many years of their lives[6].

Depression also presents a significant financial burden on the economy with it costing an estimated $AUD 8 billion in national employer costs annually due to loss of productivity and sick leave[7]. A recent report suggests that even sub-clinical levels of depression represent a significant burden to the economy[7]. In addition, broken work patterns or less time working mean that people with mental ill-health have fewer opportunities to save for retirement through the superannuation system, and therefore, are more often substantially dependent

on the age pension[8]. The recent 2020 Mental Health Productivity Commission Inquiry Report found that the direct economic costs of mental ill-health and suicide in Australia are estimated at $AUD 43–70 billion in 2018-19[8]. These estimates include 1) the direct expenditure on healthcare and other supports and services ($AUD 16 billion), 2) the lower economic participation and loss of productivity ($AUD 12–39 billion), 3) the informal care provided by family and friends ($AUD 15 billion). It is also estimated that the cost of disability and premature death due to mental ill-health, suicide and self-inflicted injury equals approximately $AUD 151 billion per year[8].

The Australian Government funds primary care and out of hospital specialised care through the Medicare Benefits Schedule (MBS)[9] and medications through the Pharmaceutical Benefits Scheme (PBS)[10]. It also funds multiple different services for individuals living with mental health challenges which are monitored and coordinated via various initiatives[9]. The National Mental Health Strategy includes five 5-year National Mental Health Plans which cover the period 1993 to 2022, with the Council of Australian Governments (COAG) National Action Plan on Mental Health overlapping between 2006 and 2011[9]. In August 2017, the Fifth National Mental Health and Suicide Prevention Plan was agreed by Health Ministers and in the 2019 Federal budget, the Australian Government announced that $736.6 million would be provided for mental health and suicide prevention initiatives over seven years[9]. This includes $373 million for additional services through *Headspace*, a National Youth Mental Health Foundation, and $5.2 million over 4 years for measures in relation to Aboriginal and Torres Strait Islander suicide[9].

However, the burden of mental illness and associated disability within the community is not matched by the funding assigned to prevent, alleviate and rehabilitate individuals experiencing mental health illness[11]. Much criticism over this lack of funding has been made, with a call for more funding made by several groups including The Mental Health Council of Australia (MHCA), Victorian Mental Illness Awareness Council, the Mental Illness Fellowship Australia, and The Royal Australian and New Zealand College of Psychiatrists (RANZCP)[11]. The RANZCP suggest that $AUD 1 billion dollars per year is required to reform existing mental health service systems, guarantee a sustainable workforce, focus on equity issues and ensure an agreed level of service delivery in all geographic areas[11].

Inequity in mental health care in Australia is an important issue worth noting. Some groups of people receive more mental health care than others. For example, the complex needs of asylum seekers, particularly if they are in immigration detention, are not adequately catered for[12]. The rate of mental illness amongst prison inmates is also unacceptably high[13]. Spending on mental health in children and youth is not proportional with the prevalence or opportunities for early intervention[14]. There is also a significant divide between rich and poor. Individuals with lower socioeconomic status or those who do not have private health insurance have fewer treatment options, and are unlikely to be able to afford ongoing treatment for depression[15]. Nowhere is this more evident than in Australia's Indigenous communities[16,17]. Additionally, there is an over-representation of mental illness among the homeless[18] of which Indigenous people comprise an especially high proportion[19].

In summary, it is clear that the burden of depression is vast. It effects all levels from the human costs in terms of time lost to disability or death, and the stress that mental illness places upon patients, carers, and the community generally. There are financial costs to the economy which results from the loss of productivity brought on by illness. There is also the expenditure by governments, health funds, and individuals associated with combating mental illness. There are also several particularly vulnerable populations who receive disproportionally less mental health care and treatment than others.

1.3.2. A brief history of Depression

While no single person can be credited with the discovery of depression, there have been many great scientists who have contributed to the understanding of this illness. While the scientific understanding of depression has come a long way, there are still many unanswered questions about the cause, treatment and prevention of depressive disorders.

The earliest accounts of depression come from Mesopotamian texts in the second millennium B.C.E. Depression, was thought to be caused by demonic possession and was treated by priests as a spiritual disorder[20]. Several other cultures believed that evil spirits caused depression including the ancient Greeks, Romans, Babylonians, Chinese and Egyptians[21] and treated those afflicted with physical restraint, beatings and starvation.

While the majority of people believed in the demonic cause of depression, a growing number of Greek and Roman doctors believed the depression was a disorder of the body and mind.

These doctors recommended treatment involving a combination of gymnastics, massage, specialised diets, music and baths[22]. The Greek physician Hippocrates suggested that depression, which he termed melancholia, was caused by an imbalance of the four humours; black bile, yellow bile, phlegm and blood[23]. The term "melancholia" is derived from two Greek words: "Melas" and "Chole" which mean "black" and "bile", respectively. He treated melancholia with bloodletting (withdrawal of blood), baths, exercise and diet[23]. The Roman philosopher, Cicero, rejected Hippocrates theory and instead argued that melancholia was caused by violent rage, fear or grief[23].

During the common ere, many primitive and often barbaric treatments continued to be the norm. However, a Persian doctor, Rhaze, viewed mental illness as arising from the brain rather than the humours and recommended baths and an early form of behavioural therapy which involved positive rewards[24]. After the fall of the Roman empire scientific thinking about mental illness took a step backwards. During the middle ages' religion, especially Christianity dominated European thinking on mental health[23]. The devil was seen as the cause of all ills with the humeral theory mostly rejected[23]. Mental disorders were equated with sin and melancholia was viewed as one of seven deadly sins – sloth. Called acedia (from the Greek word meaning lack of care), it was characterised by boredom, depression, obsessions, anxiety, and a variety of psychosomatic signs[21].

During the Renaissance, witch hunts and executions of the mentally ill were common[25]. However, some doctors were starting to re-visit the idea that depression might have a natural, rather than super-natural cause. In 1621 Robert Burton published "Anatomy of Melancholy" in which he describes the psychological and social causes of depression such as poverty, fear and loneliness[23]. His recommended treatments included diet, exercise, travel, purgatives (to clear toxins from the body), bloodletting, herbs and music therapy[26].

During the 17th and 18th centuries, melancholia came to be viewed as a weakness in temperament that was inherited and could not be changed[27]. Mental hospitals and asylums become notorious warehouses for the mentally ill, where their purpose was neither treatment nor cure, but rather the enforced segregation of patients from society[27]. Most inmates were institutionalised against their will, lived in unsanitary conditions, chained to walls, and were commonly exhibited to the public for a fee. While inhumane by today's

standards, the view of insanity at the time likened the mentally ill to animals who did not have the capacity to reason and could not control themselves[27].

During the 1900's psychodynamic theory was invented and in 1917 Sigmund Freud suggested that melancholia was a response to loss, either real or symbolic, and believed that a person's unconscious anger for their loss led to self-hatred and self-destructive behaviour[28]. Swiss psychiatrist Adolf Meyer suggested a mixed social and biological framework, emphasising that reactions occur in the context of an individual's life. He argued that the term "depression" should replace melancholia[29]. The first edition (1952) of the diagnostic manual of mental disorders (DSM-I) spoke of *depressive reaction* and the second edition, DSM-II (1968) spoke of *depressive neurosis*[27]. By the mid-20th century other psychodynamic theories of depression were proposed including existential and humanistic theories as well as Victor Frankls logotherapy[30].

In the 1960's Aaron Beck developed a theory that depression results from a 'cognitive triad' of negative thinking patterns or 'schemas'[31]. This cognitive model of depression played an important part in the development of Cognitive Behaviour Therapy (CBT) which is considered one of the gold standard treatments for depression today[32]. The other gold standard in depression treatment today is the use of anti-depressant medication. This was discovered by accident in the 1950's when doctors noticed that the tuberculosis medication *isoniazid* significantly improved their patient's mood[33]. Scientists observed that isoniazid, a monoamine-oxidase inhibitor, could alter monoamine neurotransmitter levels. Thus, the theory that depression is caused by a chemical imbalance of neurotransmitters in the brain took hold[34].

The medical model of depression soon emerged which suggests that mental disorders are primarily caused by biological factors such as genetics, brain chemistry, hormones and brain anatomy[35]. This view has played an important role in the development and increased use of newer anti-depressant drugs. The term major depressive disorder (MDD) was also first introduced in the 1970's and became part of the third edition of the DSM in 1980. The current edition of the manual is the DSM-IV and is the primary tool used in diagnosing depressive disorders[27]. At present, depression is thought to arise from a combination of biological, psychological and social factors. As depression is such a complex illness, a multi-faceted

approach including medications, psychotherapies and lifestyle modifications should be explored[36].

In summary, the long history of depression and its treatments showcase a number of factors. Firstly, the significant negative stigma surrounding depression is apparent. Whether it was the demonic possession or sin of the Middle Ages[20], the inherited "weakness" and asylums of the 18th century[27] or Freud's unconscious self-hatred[28], the stigma and shunning by society is evident. Secondly, the use of diet and exercise as treatments for depression was relatively common throughout history[23,26]. These therapies are often thought of as new, however there use vastly pre-dates our current depression treatments: anti-depressants medication and talking therapy. Thirdly, the divide between mind or body theories of depression was common. Depression was either viewed as being a completely mind-based illness or a body/physical-based illness depending on the scientific thinking of the time. Today, most health practitioners subscribe to the blended *biopsychosocial model* of depressive illness which encompasses biological, psychological and social factors[37].

1.3.3. Signs and Symptoms of Depression

Depression can present differently in each individual, however the main characteristics include anhedonia or lack of pleasure and a depressed mood and altered cognitive function[38]. The diagnostic criteria for assessing MDD is founded on a subjective evaluation of various symptoms[38]. The current classification via DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) states that at least five of nine specific symptoms must be present nearly every day for two weeks. The nine symptoms include: 1) depressed mood; 2) markedly diminished interest or pleasure; 3) increase or decrease in either weight or appetite; 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue or loss of energy; 7) feelings of worthlessness or inappropriate guilt; 8) diminished ability to think or concentrate, or indecisiveness; and 9) recurrent thoughts of death or recurrent suicidal ideation[39]. Additionally, depressed mood and/or loss of interest/pleasure must be present[40]. The validity of these symptoms has been difficult to achieve due to the MDD criteria encompassing a group of disorders that are heterogeneous with respect to pathophysiology and aetiology[41]. Environmental, biological, psychological and genetic factors all contribute to the multifactorial aetiology of MDD[42].

1.3.4. Biological Factors and Depression

Developments in molecular genetics including the human genome project and the growing availability of genetic markers point towards the involvement of genes in the susceptibility to mood disorders[41]. Several genetic markers of MDD have been proposed as biological endophenotypes of depression[41]. These include rapid eye movement (REM) sleep abnormalities, functional and structural brain abnormalities and dysfunctions in the serotonergic, catecholaminergic and hypothalamic-pituitary-adrenocortical (HPA) axis[41]. No genes have consistently been identified for MDD, however, quantitative biological markers, which are associated with MDD may help in the assessment and diagnosis of the disease[41].

Several biomarkers for depression have been proposed[38]. Biomarkers are measurable features which can indicate disease or treatment outcome[43]. There is mounting evidence for numerous dysregulated features in patients with MDD including pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interluukin-6 (IL-6) and growth factors such as insulin-like growth factor-1 (IGF-1)[38]. Oxidative and nitrosative stress has also been observed in patients with MDD[44]. The reduced plasma concentration of key antioxidants, such as vitamin C and the reduced antioxidant enzyme activity from glutathione peroxidase leads to damage by reactive oxygen species (ROS)[44]. This can cause damage to fatty acids, proteins and DNA and could be a contributing factor to the increased levels of inflammation seen in major depression[44]. Altered endocrine, thyroid and insulin functions have also been well documented in mood disorders[38]. Thus, the development of biomarker panels to profile a varied range of features may help to define the heterogeneity of MDD and assist in diagnosis and monitoring treatment response[38].

Depression has long been associated with neurotransmitter imbalances, specifically serotonin, dopamine, noradrenaline and glutamate[45]. Deficiencies in serotonin availability, serotonin receptor abnormalities[46] and an increase in monoamine oxidase which metabolises serotonin in the brain[47] all support the neurotransmitter imbalance hypothesis for MDD[48]. This theory is also the basis for pharmaceutical treatment of major depression. A common class of anti-depressants, selective serotonin reuptake inhibitors (SSRIs), are thought to work by increasing the availability of monoamines such as serotonin and noradrenaline[48]. Dysregulation of neurotransmitters, in addition to the other factors discussed, can all be influenced by environmental, social, psychological and genetic factors[49]. A bidirectional relationship is thought to exist between these aspects and the aetiology of MDD[48].

Complex overlapping symptoms are often present in MDD with physical complaints such as unexplained pain being reported frequently[50]. Co-morbidity is common and is associated with greater impairment and exacerbation of the disease[50]. A recent literature review found that on average 65% of patients with MDD experience one or more symptom of pain and that by reporting these symptoms the recognition and treatment of MDD is negatively affected[51]. The presence of comorbidity raises several important issues. Firstly, when depression precedes other illnesses depression may be viewed as a causative factor. In reverse, when the other illness precedes depression, that disorder may be viewed as a causative factor for depression. And finally, when depression and the other illness occur simultaneously, they may be considered attributable to a different causes[51]. A possible explanation for the high rates of comorbidity reported in MDD could include similar pathophysiology, particularly in regard to the presence of inflammatory biomarkers[52].

1.3.5 Evolutionary Theories of Depression

Due to the strong genetic component of depression, researchers have been looking for possible evolutionary answers to the origin of depression[53]. There are several different theories aiming to explain why the genetic alleles that are most frequently associated with depression are so common in the modern gene pool[53]. Some theories, such as the social-risk hypothesis, suggest that depression is an adaptive response that aims to reduce exclusion from social groups[54]. For example, depression reduces competitive behaviours which could put an individual at risk of conflict or exclusion from the group[54].

Other theories suggest that depression is an evolutionary adaptation to prevent infection both in the affected individual and their social group[55]. This is because depressive symptoms are very similar to sickness behaviour observed in animals, whereby an infected animal retreats from the social group to rest and recover[55]. It is thought that depressive symptoms such as anhedonia, lack of motivation and lethargy encourage the individual to conserve energy resources for fighting infection and wound healing[56]. Furthermore, the hypervigilance characteristics of anxiety disorders, commonly comorbid with depression, serves to protect individuals from attack and subsequent pathogen exposure[57]. Additionally, the reduced sexual drive and reduced appetite for food common with depression could prevent further infections[56]. The hypothesis suggests that inflammatory activation associated with depression promotes survival in highly pathogenic environments[58].

Until the 1700s approximately 50% of humans died from infectious causes before adulthood, thereby providing strong selective pressure for genetic alleles that enhance host defence[59]. There is also extensive data supporting the role of inflammation in depression with individuals with major depressive disorder exhibiting all of the cardinal features of an inflammatory response, including increased expression of pro-inflammatory cytokines and their receptors, increased levels of acute-phase reactants and chemokines in peripheral blood and cerebrospinal fluid (CSF)[58]. Inflammatory cytokines can lead to reduced synaptic availability of monoamines, which is believed to be a fundamental mechanism in the pathophysiology of depression[59]. While the effects of inflammation may have provided an evolutionary advantage in early humans, in modern times these adaptations may be responsible for the high levels of depression observed today[58].

Given the multifaceted and complex aetiology of MDD and its comorbidities, it is paramount that future research encompass a holistic approach to the treatment and management of the disease[36]. Although the exact cause of MDD is still not well-defined, recent research has highlighted a number of relevant biological pathways which, when considered holistically, may provide important insights and future research direction for the disease. Figure 1 displays these common contributing factors.

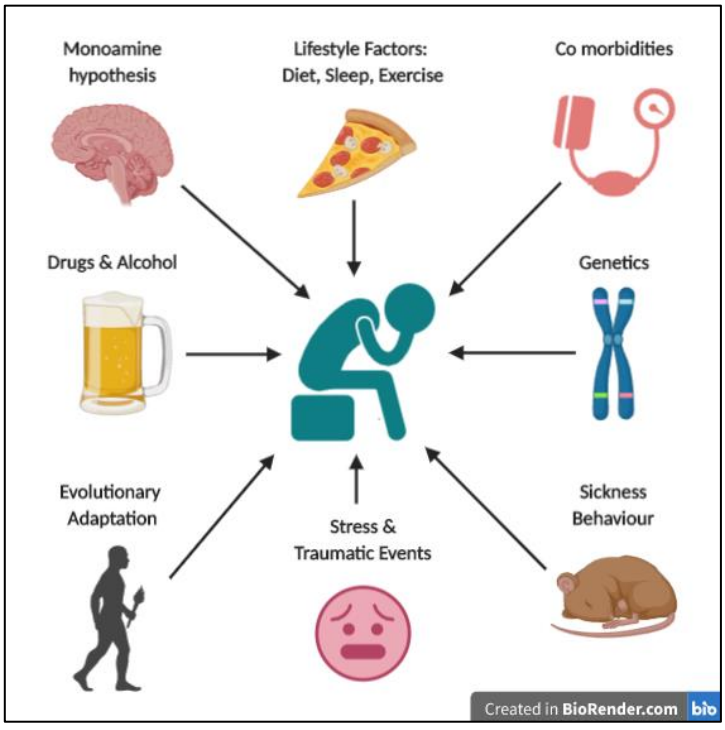


Figure 1. Factors contributing to depression

1.4 DEPRESSION IN MEN

Currently three million Australians are living with depression or anxiety[60] with around 1 in 6 women and 1 in 8 men being affected[60]. Although fewer men than women are diagnosed with depression each year, a reluctance in help seeking behaviour has been observed in men with only 1 in 4 men who experience depression accessing treatment[60]. Studies focusing on the role of gender in depression are relatively new. Many biological and sociological explanations have been theorised for these gender differences but very few have been adequately supported with empirical data[61]. This section aims to give an overview into the unique experiences of men's depression.

Recent research has suggested that gender differences in depression appear not in the experience of depression as such, but more in the expression of depression[62]. Features and behaviours associated with depression such as crying, mood amplification, emotionality, helplessness and passivity are more frequently reported in women and often fail to account for the expression of depression in men[63]. The current diagnostic criteria may be unrepresentative to the specific symptoms commonly displayed in men[64]. For example, depressive symptoms in men can often include anger, irritability and aggression[65] as well as emotional numbness and suicide[66]. Altered behaviour such as impulse control, substance abuse, increased risk taking and escaping behaviours are also commonly observed[67]. Given the differences in men's symptoms and behaviour, modifying the diagnostic criteria to better represent men's experiences with depression may assist in identifying the illness in clinical practise[64]. The recently developed Gotland Scale of Male Depression is a validated screening tool used to clinically assess male specific depression related behavoiurs[68] and is an important step forward in improving the recognition of major depression in males. It includes questions assessing externalising symptoms such as aggression/anger, irritability/frustration, overconsumption of alcohol or drugs and being hyperactive and needing to "blow off steam"[69].

Several cultural and societal pressures also contribute to the current male mental health crisis. The traditional masculine characteristics of dominance, self-reliance and stoicism expected of men can lead to health risk taking behaviours in order to conform with these apparent ideals of masculinity[64]. The male physical body is expected to be strong, independent and robust leading to many men denying or supressing illness in an attempt to

appear tough[64]. More research is beginning to explore the role of gender role conflict in men's depression with a recent study using a Gender Role Conflict Scale (GRCS) to assess the mental health consequences of adhering to traditional male ideals[70]. The results indicated that men who aligned the most strongly to traditional ideals of masculinity were more likely to experience depression and less likely to seek help[70].

Other studies are beginning to link depression-related behaviours and beliefs in men to dominant ideals of masculinity[71]. That is, men who sought help for depression were likely to engage in self-blame and held a fear of being seen as weak, thus causing many to hide their illness in order to minimise damage to their masculine self-image[71]. This can lead to self-medicating and other negative coping mechanisms which further impact health and quality of life. Commonly reported coping mechanisms in men include consumption of alcohol and escaping behaviours such as overinvolvement in work and sports[72]. Alcohol abuse can act as a catalyst for emotional disinhibition, facilitating impulsive behaviour and suicide[73].

Depression is known to be a high risk factor for suicide[60]. However, despite the lower incidences of reported depression in men, suicide rates are four times higher in men than in women[60]. In Australia, an average of 6 men take their lives every single day with suicide now the leading cause of death for men under the age of 54[74]. This gender paradox of high depression and low suicide in females, and lower depression rates but high suicide in men is a key challenge for researchers[73]. Several explanations have been postulated including cultural, psychosocial and economic approaches[73]. It has been suggested that males who behave according to traditional roles of masculinity commit suicide as a final act of taking back self-control[73]. Studies have shown that the attitudes of college students towards survivors of suicidal acts are distinctly more unsympathetic towards suicidal males[73]. Evidently, depression signifies vulnerability for many men and attracts significant stigma due to the contradiction of masculine ideals[75,76].

Despite emerging evidence outlining gender differences observed in depression, it still remains unclear if these differences affect treatment outcomes[77]. Studies of patients with depression often yield smaller numbers of men than women and gender differences in treatment response has not been well documented[77]. A recent drug trial looked at the gender differences in treatment response to a selective serotonin reuptake inhibitor (SSRI), and to a tricyclic antidepressant in chronic depression[78]. The study found that men and women

display different responsivity and tolerability to both SSRIs and tricyclic antidepressants suggesting biological factors may contribute to treatment outcomes[78]. More research investigating gender differences in treatment response is needed before conclusions can be drawn. Figure 2 displays the differences seen in male depression.

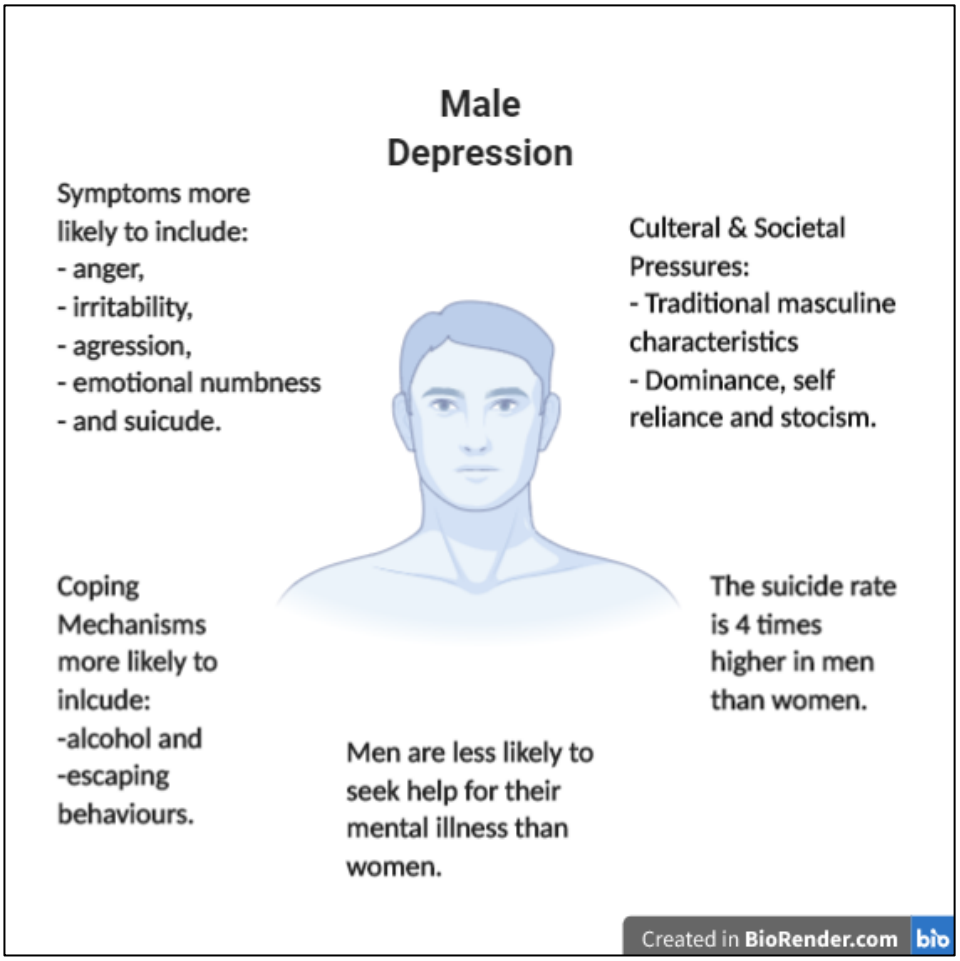


Figure 2. Characteristics of Male Depression

It is evident that the specific expression of depression in men can differ which may partially explain the lower reported depression rates in men. Adhering to beliefs of traditional male characteristics appears to be a major factor in help-seeking behaviour and coping mechanisms. Gender specific diagnostic and treatment approaches which focus on dismantling gender stereotypes could constitute the object of future studies. The possibility of different treatment approaches for men with depression warrants further investigation.

1.5 DEPREFSSION IN YOUNG ADULTS

The transition from childhood through to adolescence and adulthood comes with many challenges. From a developmental perspective, the ages 18–24 years old has been described as *emerging adulthood*, which is a transitional developmental stage between late adolescence and adulthood[79]. A sharp increase in depression rates are observed during this period with rates of mental illness peaking in young adulthood[80]. Several explanations have been postulated in regards to this issue which include increased sex hormones and inflammation[81], genetic influences, social isolation and loneliness[82], and more recently, social media use[83], internet[84] and smart phone addiction[85].

Strong evidence links stressful life events with mental health outcomes, including depression onset[86]. Research which examined the life events and changes in the course of depression in 17-24 year old's found that a number of factors can influence the development of depression in young adults[86]. Factors such as lower social class, anxiety and negative and stressful life events increased the risk of new onset of depression[86]. Life events and changes which were viewed as negative and uncontrollable, particularly those involving school and education, family, work and living conditions, were significantly associated with increased odds for the onset of a major depressive episode[86].

Another significant factor effecting the mental health of young adults is the high use of social media platforms[87]. While online social connectedness may act as a positive social medium for support, a number of studies have found social media use to have a negative effect on mental health rather than a positive one[88]. A recent systematic review found that social media use was correlated with depression, anxiety and psychological distress[87]. The review also highlighted that certain social media behaviours, such as social comparison, can have a particularly negative impact on youth mental health[87]. Research has found evidence that both communication overload and reduced self-esteem are mechanisms by which social media interaction can influence psychological distress[89]. If left untreated, mental health disorders during this time can be particularly harmful as they can interfere with education, work and social interactions during a critical period of life where personal and social identity are formed[90].

Prompt treatment for mental health disorders should therefore be a high priority. However, several differences have been noted between the treatment preferences of mental health practitioners and young adults and their parents when it comes to selecting treatment options for depression. A 2007 study showed consensus among Australian general practitioners, psychiatrists, psychologist and mental health care nurses that antidepressant medications, Cognitive Behavioural Therapy (CBT), counselling and physical activity are the preferred treatment choices[91]. Another Australian study found similar findings and reports that specialist mental health clinicians believe that young people should be started on antidepressant medication immediately following diagnosis[92]. However, young adults and their parents show a preference for informal treatment methods such as utilising friends and family for support and have a preference for non-pharmaceutical treatments[93].

Additionally, a 2002 Australian survey found that a quarter of young people aged 18-25 years old believe that antidepressant medications are harmful[93]. This supports similar studies which also report a negative perception by the general public towards antidepressants, which are seen as potentially addictive and not solving the root cause of the problem[91]. The survey reported several interventions that are preferred by young adults and their parents but not by mental health clinicians. These include basic self-help techniques such as getting out of bed earlier, getting more sunlight, massages and self-help books[91]. This preference for non-pharmaceutical options and a mistrust of antidepressants by young people may explain the low levels of help seeking by this demographic for their depressive symptoms.

Stigma is another major barrier for young adults seeking help for their mental illness. A 2005 Australian survey assessed the stigmatising attitudes of young adults towards their peers with mental disorders[94]. The study looked at several different components of stigma which the authors labelled: social distance; dangerous/unpredictable; weak not sick; stigma perceived in others; and reluctance to disclose. The results indicate that exposure to mental disorders and personal help seeking can lower some stigma scores but not others. Additionally, most aspects of stigma were higher in male respondents than female, which is consistent with previous research[94].

Due to mental health awareness and anti-stigma campaigns in recent years, it has been hypothesised that young adults will hold less stigmatised attitudes than older adults[95]. A study published in 2020 explored this hypothesis[95]. However, the study findings did not

support this concept, instead, finding the opposite to be true. They found that the participants aged 40 years and over consistently reported lower levels of stigmatised attitudes towards mental health conditions compared with the 16–18-year-old age group[95]. The authors suggest that as individuals age, they become more informed about, and accepting of, those who differ to themselves[95]. Additionally, young people may present with more stigmatised views due to wanting to conform to social pressure coupled with an aversion of feeling "labelled"[95]. It is evident, that further work is still required to combat the stigma surrounding mental health in young people.

A recent review revealed that in addition to stigma, embarrassment, problems recognising symptoms and a preference for self-reliance are the major barriers to help seeking observed in young people[96]. A preference for self-reliance is of particular concern because depressed young adults can often utilise poor coping mechanisms. Research shows us that young people who misuse alcohol for example are much more likely to report higher rates of mental disorders and suicide[97]. A 2006 Australian survey examined the beliefs of young people aged 12-25 years old about the role of alcohol, tobacco and marijuana in the prevention and treatment of mental disorders[97]. Although 80% of participants agree that not using marijuana or consuming alcohol in excess would be helpful in preventing mental disorders, males were 2-3 times less likely to describe those substances as harmful compared with females. This same trend was also observed for the older participants aged 18-25 years and those participants with a higher level of psychological distress[97]. These findings that show males between 18-25 who have higher levels of mental distress are less likely to perceive alcohol, marijuana and tobacco as harmful and may explain why these substances are commonly used coping mechanisms among this demographic. These can be particularly harmful for young adults due to the various biological changes that occur during this period of life and the long-term consequences of their use.

1.6 MEDICAL AND COMPLEMENTARY TREATMENTS FOR DEPRESSION

In general, there are two models of treatment of mental illness: the medical model and the complementary medicine (CM) model. The medical model focuses on diagnosis, symptoms,

causation and remediation[98], while the CM model focuses on prevention, wellbeing and holistic care, which focuses on treating a human being as a whole person, rather than isolated symptoms[99]. Recently there has been increased interest in a third integrative model which combines the medical and CM model[100]. Integrative Medicine (IM) is patient-centred, holistic healthcare which embraces the body's self-healing capacity and emphasises the importance of lifestyle to enhance health[100]. IM is an evidence based, prevention focused, clinical approach that incorporates conventional medical treatments in combination with CM modalities[100].

1.6.1 Medical Treatments for depression

As the dominant paradigm governing the care and treatment of mental illness, the medical model emphasises pharmacological approaches that aim to cure mental disorders that find their genesis in bio-chemical disturbances. Less attention is given to the prevention of mental illness, to non-pharmacological treatments and to the psycho-social causes of mental health disorders. Despite the enormous worldwide prevalence of depression, the majority of affected individuals do not receive adequate treatment[101,102]. Repeated estimates show that 40%-80% do not seek help and of those who do, treatment is often inadequate or incomplete from a number of perspectives[1,101,102]. Several studies report rates of misdiagnosis to be as high at 50%[103,104] and a survey of patients with depression demonstrating that only 31% were prescribed a pharmaceutical medication for their illness and only 25% of those were an antidepressant medication[102]. It is noted that even in those who are treated with an antidepressant, reports of inadequate dosing and duration are still persistent problems[1]. However, the primary treatment option for depression continues to be antidepressant medications.

Several different pharmaceutical antidepressant medications are used to treat depression. These include selective serotonin reuptake inhibitors (SSRI's), serotonin and noradrenalin reuptake inhibitors (SNRIs), tri-cyclic antidepressants (TCAs), dopamine reuptake inhibitors (DRIs) and monoamine oxidase inhibitors (MAOIs)[105]. The aim of these antidepressant medications is to improve mood. The majority achieve this by altering the levels of certain neurotransmitters in the brain[106,107].

Neurotransmitters are chemical messengers which transmit signals across a chemical synapse from one neuron to another. Examples of neurotransmitters targeted by

antidepressant medications include the monoamines serotonin, dopamine and noradrenaline[108]. Each class of antidepressants achieve this via different mechanisms. For example, SSRIs block the reabsorption of serotonin into neurons resulting in more serotonin available to improve transmission of messages between neurons[109]. DRIs work by blocking the reabsorption of dopamine and TCAs work by blocking the reabsorption of serotonin and norepinephrine[109]. These medications are based on the monoamine hypothesis for the pathophysiology of depression, which postulated a deficit in serotonin and noradrenaline in key areas of the brain in affected patients[107].

The monoamine hypothesis has been the dominant hypothesis of depression over the last few decades. It states that depression is associated with reduced monoamine function. Hence drugs designed to increase monoamine transmission by inhibiting serotonin and noradrenalin reuptake has been central to depression research since the 1960s[109]. However, this hypothesis does not account for several factors including the effectiveness of antidepressants in the treatment of anxiety disorders. Nor does it explain why drugs such as tianeptine, which increase serotonin reuptake, are effective antidepressants[110]. A large meta-analysis of monoamine depletion studies concluded that monoamine depletion appears to decrease mood in subjects with a family history of depression and in drug-free patients whose depression is in remission[111]. However, monoamine depletion does not appear to decrease mood in healthy individuals and fails to demonstrate a causal relationship[111]. Perhaps this partially explains the large percentage of patients who are non-responders to anti-depressants.

Furthermore, an umbrella review published in 2022 assessed evidence on whether depression is associated with lowered serotonin concentration or activity reported[112]. The umbrella review included 17 studies which included several systematic reviews and meta-analyses, a genetic association study and an umbrella review[112]. The authors conclude that there is no consistent evidence supporting an association between serotonin and depression, and no support for the monoamine hypothesis or that depression is caused by lowered serotonin activity or concentrations[112].

Roughly 30% of patients with depression fail to respond to antidepressant medications and the rates of relapse are high[113]. This poor response rate may be due to the umbrella review findings mentioned above indicating that serotonin and monoamine may not be the cause of

the depression. Additionally, the therapeutic lag before medications become effective not only leave potentially suicidal patients vulnerable for several weeks, but can actually make them feel worse before any therapeutic effects are seen[114]. There are also several concerns with treating young people with anti-depressant medication. A large meta-analysis found that individuals under 25 years of age have a statistically significant higher risk of committing suicide when taking antidepressant medications in comparison to placebo, in contrast to older individuals where no difference was observed[115]. Other treatments, such as psychological talking therapies, may provide a safer alternative.

Each different school of psychology has their own approach to treating depression. However, the most common approaches are cognitive behavioural therapy (CBT), counselling, interpersonal therapy, psychoanalysis and problem solving therapy[116]. CBT is currently regarded as the gold standard in depression treatment[32] and has shown efficacy greater than or equal to that of medication in mild, moderate, and severe episodes of major depression[117]. Additionally, a recent meta-analysis found that CBT treatment alone for acute depression has a 61% chance of complete recovery relative to patients treated with medication alone, who have a 39% chance of complete recovery[118]. Core strategies of CBT are designed to encourage the patient strengths and capabilities and to teach new skills[119]. The therapeutic alliance is active and collaborative with the therapist acting as both a teacher and coach[119]. The therapist and patient work together to jointly set goals to accomplish in therapy. Goal setting is particularly important because it both increases motivation and helps patients to change behaviours that are likely to help their mood such as focusing on sleep, appetite and other activities[119].

Recently, internet-based CBT (ICBT) and other psychological treatments for depression are being explored[120]. Guided self-help is a format of treatment delivery that presents structured self-help materials via the internet coupled with therapist contact, usually by email[121]. The role of the therapist is to provide encouragement, support and occasionally direct various therapeutic activities[121]. Meta-analyses have found ICBT to be equal in efficacy to face-to-face therapy, although guided ICBT appears to be more effective than unguided ICBT[120]. Internet based therapies may be of particular interest to young adults and offers benefits such as convenience and low cost[122]

The current medical model of depression relies on anti-depressant medications and psychological talking therapies as the main treatments for depression. They are either used alone or in combination. However, several other treatment options are offered by other modalities which fall outside the mainstream medical model. These therapies, often called complementary or integrated medicine, include modalities such as naturopathy, traditional Chinese medicine (TCM), herbalism, aromatherapy, meditation and yoga.

1.6.2. Complementary Medicine treatments for depression

Complementary Medicine (CM) use is highly prevalent in Australia and represents one of the highest CM consumers in the developed world[123]. A recent cross-sectional online survey of Australian adults found that the prevalence of any CM use was 63.1%[124]. Depression has been identified as one of the most frequent indications for CM use, with a 2015 review finding a considerable level of CM use among both general and clinical populations of people suffering from depressive disorders[125]. A recent cross-sectional study which examined CM use among 300 patients with depression in Iran found that the most frequently used type of CM was herbal medicine[126]. The most widely used herbs among this population were borage (77%), chamomile (46.9%), and lavender (21.2%). Additionally, 62.8% of the patients reported that their main reason for using CM was its effectiveness and reported high levels of satisfaction with their CM use[126].

CM modalities are often preferred by patients with depression for a number of reasons[125]. A recent literature review found the primary motivating factor for CM use by patients with depression was symptom relief[125]. The participants viewed CM as being more effective than conventional medicine for alleviating depressive symptoms, in addition to associated symptoms of fatigue, poor memory, weight gain and low energy levels[125]. Another important motivation for CM use among patients with depression was a dissatisfaction with the health outcomes of conventional treatment, or the failure to prevent recurrent episodes[125]. Perceived safety was also an important motivator, with CM use deemed 'natural' with fewer adverse effects than conventional treatments amongst participants with depressive disorders[125].

In regards to CM therapies for treating depression, some treatments have been studied more than others[37]. Currently, the CM treatments showing the most efficacy for depression include certain herbs, nutrients, exercise and light therapy – specifically for seasonal affected

disorder (SAD), but new research is also showing promise for minor depression[37]. Of the herbs, St John's Wort (*Hypericum perforatum)* has been the most extensively studied. A meta-analysis which looked at five RCT's involving 2,231 patients with depression found St John's Wort to be just as effective as anti-depressant medications[127].

Other nutrients which have shown efficacy include omega-3 fatty acids which showed reduced depressive scores in a meta-analysis of 16 trials[128]. Oral S-adenosylmethionine (SAM-e) monotherapy also showed reduced depressive scores in 4 of 5 small randomized controlled trials[129]. Additionally, folate deficiency is associated with more severe depression, and supplementation reduced depressive scores in 2 of 3 randomized controlled trials[127]. There is also some preliminary research suggesting a therapeutic benefit of curcumin[130], saffron[131], 5-hydroxytryptophan (5-HTP)[132], vitamin D[133], yoga[134] and massage[135] for depression.

Recently, Haller et al. published an overview of systematic reviews investigating complementary therapies for clinical depression[136]. The authors aimed to systematically summarise the level 1 evidence on CM for patients with a clinical diagnosis of depression. They found that in patients with mild to moderate major depression, moderate quality evidence demonstrates the efficacy of St. John's wort compared to placebo[136]. For patients with recurrent major depression, the authors found moderate quality evidence demonstrating that mindfulness-based cognitive therapy was superior to standard antidepressant drug treatment for both prevention and relapse[136]. However, they argue that the quality of evidence for other CM therapies are low, due to methodological flaws in the study design and reporting[136].

Despite the promise many of these isolated nutrients are showing, many cannot be confidently recommended until further higher quality studies confirm their effectiveness and safety[136]. Recently, there has been a shift away from focusing on isolated nutrients and growing interest in whole dietary patterns as a therapeutic treatment for depression[137]. Particularly the Mediterranean diet which is high in many of the nutrients discussed above.

1.7 DIET AND MENTAL HEALTH

The field of *Nutritional Psychiatry* is a relatively new term and relates to the immerging field of research focusing on the role of diet and nutrition on mental health[137]. Recently the research focus has changed from individual dietary supplements in favour for a more wholistic dietary approach[138]. New investigations into the microbiome, immune and inflammation pathways demonstrate a powerful paradigm shift in the way we understand MDD[139]. Research into how diet and nutrition effects these pathways could yield valuable insights into potential treatment strategies for MDD. The Mediterranean diet (MD) has shown to be a promising treatment strategy and may help improve clinical outcomes in depression[140].

Wholistic dietary approaches in nutrition research are starting to gain popularity. Previous research has focused heavily on the use of single-nutrient supplements in intervention trials[141]. This has recently been criticised as a flawed treatment strategy. Human digestion evolved to utilise a broad range of nutrients synergistically in the body[137]. Nutrients are never consumed in isolation in a natural diet and thus may not produce the desired or predicted effect in a clinical trial setting[141]. A 2012 literature review appraised the research on nutritional supplements for MDD and found only limited evidence to support individual nutrients as monotherapies in depression[142]. Whole diet interventions have produced more successful outcomes with a recent systematic review looking at the role of anti-inflammatory diets in depression[143]. The results suggest an association between pro-inflammatory diets and depression leading the authors to conclude that adopting an anti-inflammatory diet may be an effective strategy in reducing depression risk and symptoms[143]. Promising research has similarly been observed with the Mediterranean diet[144].

The term 'Mediterranean diet' reflects the diets of several countries in the Mediterranean Basin during the early 1960s[145]. It was noted that reduced mortality and morbidity from various diseases was associated with these countries[146]. One of the common linking factors was their shared dietary pattern which has since gained much attention, particularly for preventing coronary heart disease[147]. In 1993, the International Conference on the Diets of the Mediterranean defined the various components of the diet[145]. They conclude that it is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds and legumes.

The principle source of dietary lipids is in the form of olive oil. Red wine is consumed in moderate amounts generally with meals. It is low in processed foods and red meat. Dairy is consumed in low to moderate amounts and no more than 4 eggs are consumed per week[145]. It could be the combination of these various dietary components and overall eating pattern which result in favourable health outcomes, particularly in MDD.

1.8 DIET AND FOOD: MECHANISMS OF ACTION

Several biological mechanisms of actions for how certain foods and nutrients can affect mental health have been postulated[139]. These mechanisms include the role of inflammation and oxidative stress, mitochondrial dysfunction, hypothalamus-pituitary-adrenal (HPA) activation, neurogenesis and brain derived neurotrophic factor (BDNF), the GIT microbiome, tryptophan-kynurenine metabolism and methylation pathways[139]. Certain nutrients can positively affect these pathways and have been proposed to explain the benefits of a MD in depression. These nutrients include B vitamins, omega-3 polyunsaturated fatty acids (PUFAs)[144], monounsaturated fatty acids (MUFAs) and fiber[148]. The lipid profile of the MD, in particular the high consumption of PUFAs from fish and MUFAs from olive oil has been at the forefront of this research. Both lipids have highly anti-inflammatory properties and strong evidence in human studies show that adherence to a MD is associated with reduced inflammatory markers[48]. Thus, a MD may have a protective effect in depression due to its influence on inflammatory pathways[148]. Another major component of the MD includes the high consumption of plant-based foods and the effect on the microbiome[149]. The amount and type of fibre found in plant foods can dramatically alter the microbiome and exert positive effects in the body[149]. Researchers are starting to explore the role of the microbiome in the pathophysiology of MDD[150]. Promoting a healthy and diverse population of microbes via a high fibre diet may provide a protective effect against the symptoms of depression.

It is also important to note what a MD does *not* include as this could be an important contributor in the effectiveness of the diet for depression. The MD is low in highly processed and packaged food, red meat and sugar[151]. Dietary patterns high in these foods have constantly been linked with inflammation and poorer mental health outcomes, including depression[152]. Recent research has shown that a “Western diet” high in processed and fried foods is associated with a higher prevalence of mental health disorders and is not

confounded by age, socioeconomic status, education or other health behaviours[153]. When considering all the components of a MD, both what it does include and what it does not include, provides researchers new avenues for exploration in depression trials. Figure 3 depicts the components of the Mediterranean diet.

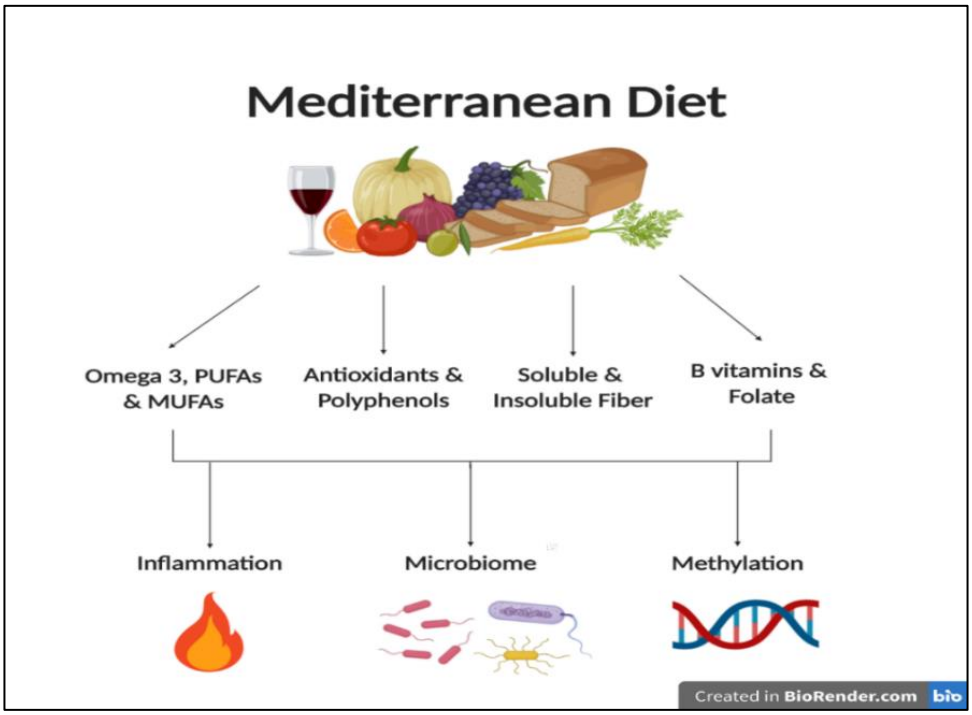


Figure 3. Mediterranean Diet Mechanisms

In summary, examining the role of diet and nutrition on mental health is a promising new area of research. Shifting the research focus from individual dietary supplements in favour for a more wholistic dietary approach may provide more a representative approach to diet and disease[138]. Exploring the microbiome, immune and inflammation pathways is changing the way we understand the pathophysiology of MDD[139]. Research into how diet can affect these pathways is starting to produce important insights into different treatment strategies for MDD[139]. The Mediterranean diet has shown to be a possible treatment approach for improving the clinical outcomes in depression[140].

1.9 INFLAMMATION AND DEPRESSION

Although the exact aetiology of MDD is still unknown, several similar disease mechanisms exist between MDD and inflammatory diseases such as cardiovascular disease (CVD), diabetes and cancer[154]. These mechanisms include insulin resistance, increased plasma homocysteine and endothelial dysfunction[155]. These traits are negatively influenced by proinflammatory cytokines and may be the linking factor between these diseases[156].

Inflammation is also increasingly being associated with depression, calling for a new paradigm shift in the approach to the disease[157]. It has been suggested that proinflammatory cytokines may contribute to the development of MDD via several pathophysiological mechanisms[158]. In particular, C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-1 (IL-1) have been associated with the prevalence and severity of MDD[155]. Three separate pathways have been hypothesised. First, that depression leads to increased inflammation. This occurs due to increased sympathetic and decreased parasympathetic nervous system activity affecting the release of IL-6 and CRP[159]. The second model proposes that inflammation leads to depression. Several animal studies demonstrate the development of sickness behaviour, which mimics the symptoms of depression, when administered inflammatory cytokines[160]. Prospective research in humans has revealed similar findings. Test subjects with higher circulating levels of CRP and IL-1 at baseline had increased depressive symptoms over a 5-year follow-up period[161]. These two concepts may actually suggest a third more complex bidirectional process[155].

High levels of circulating inflammatory cytokines can affect the brain in several ways. Neuroinflammation stimulates microglia which mediate the peripheral immune processes in the brain[162]. These cells play an important role in normal brain processes, including synaptic transmission and neural plasticity[163]. During pathological conditions, such as infection or injury, microglia modulate inflammatory, protective and toxic processes which affect neurons and other brain cells[164]. Microglia can alter glutamatergic neurotransmission[165] which may explain the changes in behaviour, cognition, and mood observed in MDD[164]. These observations highlight a link between inflammation, immunity and depression and may explain the high prevalence of depression in inflammatory based diseases, particularly those effecting the brain[164].

Increased inflammation can also affect responsiveness to antidepressants[166]. Inflammatory cytokines effect the function of monoamine reuptake inhibitor drugs used to treat MDD[167]. Cytokines can reduce monoamine precursors such as tryptophan, the primary precursor for serotonin, by activating enzymes which cause it to break down[168]. A number of other inflammatory biomarkers, including acute phase proteins, chemokines and adhesion molecules are also reliably elevated in patients with depression and are thought to also be involved in decreased drug response[158]. These factors could be responsible for the one-third of patients with depression who fail to respond to antidepressant medication[166]. Further research into the effects of inflammation on the efficacy of drug treatment is needed before any firm conclusions can be made as to the relationship between inflammation and MDD.

In addition to correlative data linking inflammation with depressive symptoms, research is now exploring the effect of inducing both chronic and acute inflammation in test subjects to measure outcomes in behaviour[158]. For example, when healthy volunteers were injected with the cytokine inducer lipopolysaccharide, an acute increase in depression and anxiety was observed[169]. Similar results were noted when healthy participants were administered a *Salmonella typhi* vaccine, with participants displaying fatigue, depressed mood and mental confusion[170]. Both studies demonstrated a correlation between symptom severity and blood cytokine concentrations[158] and confirm the consistent findings in animal studies of cytokine inducers causing depressive symptoms[171].

This inflammation model of depression allows for specific biomarkers to assist in diagnosis, monitoring and outcome predictions of patients with MDD. C-reactive protein (CRP) has a large body of evidence consistently linking it with depression[155,172] and is a widely available medical test. This high-sensitivity measurement does not fluctuate with time of day or proximity to meals[173] making it an convenient diagnostic tool. Other proposed biomarkers for depression include oxidative stress and antioxidant defence biomarkers such as malondialdehyde (MDA)[174] and superoxide dismutase (SOD)[175]. This area of research is still in its infancy and thus only a limited number of biomarkers have been studied[176]. Several others have been hypothesised including measurements of amino acid levels, which are the precursors to neurotransmitters; growth factors such as insulin-like growth factor-1; endocrine markers such as cortisol; and measures of individual antioxidant levels such as zinc, coenzyme Q10 and selenium[176]. Biomarkers have the potential to advance diagnosis and

treatment approach in patients with MDD, however considerably more research is needed before biomarkers can be routinely incorporated in clinical practice[176].

Alternative treatment options based on the inflammatory hypothesis of depression are starting to be investigated[157]. New therapeutic drug targets which focus on the inflammatory and neural-immune pathways could be promising research avenues[157]. In addition, the potential role of existing anti-inflammatory and anti-oxidative drugs and compounds should also be examined either as monotherapy or adjunctive therapy[177]. Furthermore, research focusing on the effect of various lifestyle modifications and dietary interventions for reducing inflammation also warrant further investigation.

Several randomised control trials have evaluated the effect of diet changes or single foods on inflammatory markers in defined populations[178]. Most studies have demonstrated a modest effect of diet on markers of inflammation[178]. The dietary factors which appear to have the greatest effect on markers of inflammation include glycaemic index (GI) and glycaemic load (GL)[179], fiber[180,181], fatty acids[182-184], magnesium[185], carotenoids[186], and flavonoids[187,188]. A traditional Mediterranean dietary pattern is typically high in all of these nutrients. The high levels of omega 3 fats, fruits, vegetables, legumes, and grains, has shown anti-inflammatory effects when compared with typical Western style dietary patterns in most observational and interventional studies[178]. This has led to the Mediterranean diet becoming the diet of choice for reducing chronic inflammation in clinical practice[178].

1.10 MICROBIOME AND MENTAL HEALTH

The human microbiome and its involvement in mental health is a rapidly expanding area of research. Progressively more studies are confirming a connection between the bacteria which colonise the digestive tract and activity in the central nervous system (CNS)[189]. The microbiome is being explored for its involvement in vagal nerve signalling, mediation of immune responses and inflammation, and its influence on neurotransmitters such as serotonin and GABA[190]. The composition of the microbiome can be influenced by a number of factors including medications, stress and diet. Modifying these factors could be an important step in improving the health of the microbiome and subsequently, mental health outcomes[191].

The digestive tract is home to nearly 100 trillion bacteria which are essential for good health[192] and collectively known as the microbiome. The influence of the microbiome affects multiple functions in the gastrointestinal tract (GIT) including regulation of GIT motility, maintenance and barrier function[193]. Researchers are now starting to look at the effects the microbiome has outside of digestive function. Growing numbers of observational studies have demonstrated an association between diet quality and prevalence risk of major depressive disorder (MDD)[194]. This has shifted the research focus to understanding the biological pathways which may mediate this association, primarily the microbiome[193].

The microbiome can signal the brain to alter physiological process via numerous mechanisms[195]. Microbes can influence the release of peptides from enteroendocrine cells, which activate cognate receptors of the immune system and vagus terminals[195]. Certain peptides, such as neuropeptide Y (NPY), can also be released by cytokines from immune activation[195]. These peptides then stimulate sensory neurons which relay information to the brain[196]. This cross talk between the immune system and brain neurocircuitry can drive the development of MDD[197]. Altered hypothalamus-pituitary-adrenal (HPA) function is frequently associated with MDD, with elevated plasma cortisol and corticotropin releasing factor often being observed[198]. Certain microbes can further affect HPA function by also altering levels of monoamines and their receptors involved in depression[198].

Monoamines frequently associated with MDD include serotonin, dopamine and noradrenaline[199]. The microbiome can alter levels of these substances by effecting production of their precursors[200]. For example, tryptophan, the precursor for serotonin, can be generated by microbes in the GIT and is capable of crossing the blood brain barrier (BBB) where it can synthesis serotonin[201]. Dopamine and GABA are other neurotransmitters associated with MDD which may be influenced by the microbiome[200]. Levels of these neurotransmitters, along with their precursors and metabolites, are reduced in the intestines of germ-free mice[202]. This suggests a link between the microbiome and the production of these neurotransmitters. However, the exact mechanism by which microbes alter these levels has not yet been determined[200]. It has been suggested that the microbiota directly signals to neurotransmitter-producing cells, such as enterochromaffin cells or alternatively to enteric neurons and glia, in order to regulate neurotransmitter production[200]. Neurotransmitter signalling is one of many pathways that demonstrate the microbiomes

influence on nervous system activity. Other pathways with growing data include the microbiome-inflammation-immune pathway.

Dysbiosis, or an imbalance of microbial species, can result in increased inflammatory responses which have been associated with MDD[203]. This occurs from potentially toxic gram-negative bacteria being present in the intestines which release the endotoxin lipopolysaccharide (LPS)[203]. LPS then activates nicotinamide adenine dinucleotide phosphate (NADPH) oxide, an enzyme complex, which is involved in the production of reactive oxygen species (ROS), leading to cell damage and increased inflammation[204]. Increased numbers of plasma immunoglobulins have also been observed in response to LPS which further indicates an increased immune response[204]. Recently, greater numbers of immunoglobulins have been identified in patients with depression[205]. These finding suggests a pathway by which dysbiosis can cause immune activation and further amplify inflammatory responses[203].

Bacterial translocation may also play a role in the inflammatory pathophysiology of MDD[204]. Increased permeability of the gut wall occurs as a result of the tight junctions between enterocytes loosening[204]. This results in gram negative bacteria, which are normally unable to cross this barrier, translocating into the mesenteric lymph nodes and systemic circulation[206]. From here the immune system can then mount a full attack, producing inflammatory cytokines and stimulating both oxidative and nitrosative stress pathways[207]. Thus, intestinal permeability and the resulting bacterial translocation can drive inflammation in the pathophysiology of MDD[207]. This raises important questions about what causes intestinal permeability and the role of the microbiome.

Several influences have been identified in the pathogenesis of intestinal permeability including lifestyle, stress and diet[208]. Diet greatly effects the composition of the microbiome and thus the integrity of the intestinal barrier with experiments showing that dietary alterations can induce large, temporary microbial shifts within 24 hours[209]. For example, numerous studies have shown differences in the microbiome of vegetarians verses meat eaters[210]. These differences appear to occur rapidly, but only last for as long as the diet is followed. Poor diets high in processed foods are consistently linked with unfavourable GIT microbe populations and subsequent intestinal permeability and depressive symptoms[211]. Furthermore, high fat diets are associated with a greater translocation of LPS across the gut

wall[212]. Moreover, meals rich in fibre have demonstrated the ability to reduce the effect of high fat intake on LPS translocation as well as reduce the inflammatory response[213].

Specific foods have also been researched for their ability to affect the microbiome. The relationship between fermented dairy products and the growth of beneficial microbes is well studied[214]. However, various other fermented foods and herbs can also have a positive effect on the intestinal microbiota. New research has demonstrated that when dietary polyphenols are fermented, the newly formed phytochemicals cause a beneficial shift in microbial growth[214]. For example, isomaltooligosaccharides which are found in honey, sake, miso, soy sauce and fermented cabbage (kimchi) can promote the growth of *Bifidobacteria* and *Lactobacillus* species[214,215]. These fermented foods are important, as their influence has demonstrated a longer-term effect on gut-brain communication[214].

Another dietary influence which is gaining much attention include probiotics and their role in modifying the microbiome and barrier function. Probiotics are defined as a live bacteria which when administered in adequate amounts confers a health benefit on the host[216]. Certain strains of bacteria have demonstrated beneficial effects on the microbiome composition and gut barrier integrity. For example, *Lactobacillus farciminis* is able to beneficially influence the mucus barrier[217] in addition to suppressing stress-induced changes in permeability, HPA axis activity, endotoxaemia, and neuroinflammation[218]. Certain probiotics can also decrease systemic cytokines, oxidative stress, and inflammatory markers as well as increasing microbial production of GABA and other neurotransmitters[219]. A recent systematic review and meta-analysis of randomised controlled trials found that probiotics were associated with a significant reduction in depression[220].The specific strains which currently show promise include *Lactobacillus helveticus R0052, Bifidobacterium longum and Bifidobacterium infantis*[220]. Probiotics which can modulate the brain-gut-microbiota axis for beneficial effects on mental health have been termed "*psychobiotics*"[221].

A recent 2020 meta-analysis explored the effect of probiotics on the symptoms of depression in participants with depression or under stress conditions[222]. The found that probiotics were effective in alleviating depressive symptoms and suggest that probiotics may be a useful adjunctive therapy for mood or emotional disorders[222]. However, the results from the literature review were limited by the small number of studies included and bias identified in many of the study designs. Additionally, the authors note that large variations in the criteria

for depression across the studies may impact the conclusions drawn[222]. More high-quality studies assessing probiotics in patients with depression are still needed.

Another important nutrient for maintaining the health of the GIT microbiome is prebiotics. Prebiotics are fibres metabolised and used for fuel by the microbiome, thus increasing levels of beneficial bacteria such as bifidobacteria[223]. Prebiotics are found in several vegetables such as celery, Jerusalem artichoke and garlic. When both pre- and probiotics are co-administered, which is becoming more common, the term *synbiotic* is used[224]. A number of small clinical trials have assessed the effect of certain prebiotics on psychological outcomes with promising results[223]. The Mediterranean diet not only includes these important prebiotics, but also includes fermented dairy products such as Greek yogurt and various polyphenols, all of which have a positive impact on the GIT microbiome[223]. Therefore, the Mediterranean diet may be effective for treating depression via its impact on GIT health.

In summary, the human microbiome and its involvement in metal health is a promising new area of research which requires further investigation. Several novel pathways connecting the microbiome, CNS and depression and are now starting to be explored[189]. The role it plays in vagal nerve signalling, immune responses, inflammation and the production of neurotransmitters all warrant further research[190]. Investigating how to influence these processes could yield valuable insights into the pathophysiology of MDD, and consequently, its treatment. Modifying the health of the microbiome through stress reduction and diet, particularly a MD, could therefore be a powerful tool in improving the symptoms of depression[191]. Previous research has demonstrated that following a MD leads to beneficial modulation of the gut microbiome[225]. However, these studies fail to determine the exact magnitude of these alterations, and the results may be impacted by numerus factors such as the study duration, patient age and lifestyle habits, and level of dietary adherence[225]. More research is needed to identify specific factors in the MD and how they affect the gut microbiome[225].

1.11 AN OVERVIEW OF DIET AND DEPRESSION RESEARCH

Several literature reviews have explored the relationship between diet and depression. Reviews of children[226], older adults[227] and pregnant women[228] all point towards diet having

an effect on mental health. In particular, reviews assessing specific dietary patterns consistently shows “Western” and “junk food” diets are linked with a greater risk of developing depression while traditional diets, such as the Mediterranean diet, are linked with reduced rates of depression[229]. All reviews call for more research, particularly experimental research to confirm a cause and effect relationship between diet and depression. There are several significant gaps in the research, particularly pertaining to experimental research designs and research on young adults and men.

A 2013 systematic review of observational studies by Quirk et al. assessed twenty-five studies from nine countries[230]. They assessed the association between diet quality and patterns and the likelihood of depression. They found evidence to support a negative association between traditional diets such as the Mediterranean and Norwegian diet and depression[230]. However, they reported conflicting evidence for associations between a traditional Japanese diet and depression, a “healthy” diet and depression and a Western diet and depression. They also found conflicting evidence for the suggestion that depressed individuals are more likely to eat a less healthy diet[230].

Several factors may explain these inconsistent findings. Firstly, the characteristics of the study populations were heterogeneous, with some studies using population-based cohorts, and others using participants who may have greater susceptibility to depression, such as those with pre-diabetes and cancer[230]. Integrating data derived from different study populations may increase the likelihood of bias, thus affecting the generalisability of the review’s findings. Furthermore, studies which include population groups with other physical illnesses may act as confounding factors affecting in the relationship between diet quality and depression[230]. Further studies are required to clarify whether a true causal association exists between these diets and depression.

A 2019 systematic review by Ljungberg et al. explored the importance of dietary habits on both depressive symptoms and clinical depression[231]. They found that higher adherence to healthy dietary recommendations resulted in less depression. These included avoiding processed foods, following an anti-inflammatory diet, consumption of magnesium, folic acid and various essential fatty acids, and fish consumption. A systematic review and meta-analysis by Lai et al. assessed dietary patterns and depression in community-dwelling adults

and found similar results. The authors report that high intakes of fruit, vegetables, fish, and whole grains may be negatively associated with a reduced risk of depression[232].

Another systematic literature by Opie et al. which assessed the impact of whole-of-diet interventions on depression and anxiety found some evidence supporting diet for depression[233]. The authors report that in the successful interventions, effect size for depression scores were between 0.19 and 2.02, which is a small to very large effect and is comparable to pharmacotherapy or psychotherapy. However, the evidence was not consistent, with just over half of studies revealing no effect of diet on mental health[233]. An important limitation of this review was that only one study included participants with a diagnosed depressive or anxiety disorders. Additionally, many of the studies specifically excluded those with pre-existing mental health symptoms or disorders. Thereby significantly limiting the ability to determine the effect of dietary interventions on mental health[233].

One review on the relationship between diet and depression in children and adolescence suggests that due to the development of the brain and the emergence of depression during this period, that the impact of diet on mental health could possibly be greater during this period than later in life[226]. Additionally, adolescents often become increasingly independent about the type and amount of food they consume. Particularly in regards to "junk" and "fast" foods[226]. Therefore, the relationship between diet and mental health in young people and children therefore warrants specific attention. The review found that overall, there was an association between healthy dietary patterns or consumption of a high-quality diet and lower levels of depression or better mental health[226]. Similarly, the authors observed a positive relationship between unhealthy diets and depression or poor mental health. However, the effect sizes of all the significant results were small[226].

Another systematic literature review examined the role of diet on depression during pregnancy and the post-partum period[228]. Perinatal depression, also referred to as maternal depression, is defined as depression during pregnancy and up to 1-year post-partum[228]. It is a common morbidity during pregnancy and lactation and can have severe and long-term consequences. During pregnancy and lactation, nutritional demands increase, and deficiencies thus arise more easily[228]. Various nutrients are needed for the synthesis of neurotransmitters and thus may be involved in mood regulation. It is therefore hypothesised that dietary intake could influences the risk of depression in the perinatal period[228]. The

review found that healthy dietary patterns, multivitamin supplementation, fish and polyunsaturated fatty acid (PUFA) intake, calcium, vitamin D, zinc and selenium demonstrated a protective effect against perinatal depression[228].

A recent 2019 systematic review and meta-analysis by Tolkien et al. assessed whether there is a link between the inflammatory potential of a diet and risk of depression or depressive symptoms[234]. Considerable evidence supports the role of inflammation in the pathophysiology of mental health disorders, including depression. Dietary patterns have demonstrated the ability to modulate inflammation, therefore highlighting their potential as a therapeutic tool in disorders with an inflammatory basis[234]. The review found a significant association between pro-inflammatory diets and an increased risk of a depression diagnosis or depressive symptoms. Those on an anti-inflammatory diet had less diagnosed depression and depressive symptoms thus making an anti-inflammatory diet a potentially effective intervention or preventative treatment[234].

A recent 2021 literature review by Patsalos et al. aimed to explore whether weight loss through dietary interventions has the additional effect of ameliorating depressive symptoms in patients with obesity[235]. They found that a calorie-restricted diet resulted in decreased depression scores, with effect sizes between 0.2 and 0.6. However, the small number of studies included in this review limits the generalisability these results[235]. Further RCTs are necessary to confirm the effect of calorie-restricted diets on depressive symptoms in patients with obesity.

The MD is well known for its anti-inflammatory effects. A recent literature review assessed the effect of the MD for depression and found that the majority (85%) of observational studies demonstrate that it reduces depressive incidence[236]. All the included intervention studies echoed these findings[236]. Very few experimental research designs have been used to assess the effect of diet on depression. One study looked at the effect of a MD on the level of serum micronutrients in patients with depression[237]. It found that following a MD did not affect serum selenium, zinc, iron, magnesium, vitamin B12 and folic acid levels[237]. Although participants in the MD did display slightly better depressive scores compared to the control group, these differences were not statistically significant[237].

However, this study has several limitations which may have affected the outcomes. The small sample size may explain the imbalances between baseline characteristics in the treatment group and the control group, specifically in regards to the male to female ratio, and number of participants diagnosed with MDD[237]. The intervention group had almost twice as many participants diagnosed with MDD which significantly affects any meaningful conclusions being drawn from this study. Furthermore, a validated dietary questionnaire was not performed at baseline and the dietary prescription instructions given to the participants did not adequately describe the MD in sufficient detail[237].

A recent randomized controlled cross-over design trial compared a MD with 3–4 daily serves of dairy food (the MedDairy group) to a low-fat (LF) diet (control group)[238]. Forty-one participants aged ≥45 years with systolic blood pressure ≥120 mm Hg and at least two other risk factors for cardiovascular disease completed each dietary intervention for 8 weeks, with an 8-week washout period separating interventions[238]. The trial assessed mood attention, processing speed, memory and planning[238]. Significant improvements were observed for processing speed, total mood disturbance, tension, depression, anger and confusion following the MedDairy intervention. The authors concluded that a MD supplemented with dairy foods may benefit cognitive function and psychological well-being in an ageing population at risk of dementia[238].

Another study by Sanchez-Villegas et al. assessed the effect of a MD on the prevalence of depression diagnosis over a three-year period[239]. The PREDIMED randomised trial assessed two different Mediterranean diets, one which included extra-virgin olive oil (EVOO) and the other which included mixed nuts. These were compared to a low-fat control diet. The study population was composed of men aged between 55 and 80 years and women aged between 60 and 80 years with no previously documented cardiovascular disease (CVD), but who were at high cardiovascular risk[239]. There was an inverse association with depression for participants assigned to a MD supplemented with nuts compared with participants assigned to the control group, although this was not statistically significant[239]. There was no significant decrease in depression risk among those assigned to MD supplemented with EVOO[239].

This lack of statistically significant findings could be explained by a number of factors. Firstly, the control group in the PREDIMED trial was assigned a healthy dietary pattern recommended by the American Heart Association to prevent CVD, and the baseline dietary

pattern that was similar to the MD[239]. This may partially explain the lack of significant findings when comparing the intervention groups to the control group. There may be a greater benefit of the MD if it were compared to a typical Western diet. Furthermore, the number of new depression cases reported during the three-year trial was low, which may have limited significant associations being found[239].

To date there has only been two randomised control trials assessing the effect of a MD on the symptoms of depression in patients with MDD. The first is the HELFIMED study by Parletta et al[240]. This RCT assessed the effect of a MD plus fish oil supplements in 152 adults with self-reported depression. A total of 85 participants completed the 6-month intervention. The average age of participants was 44 years old and 70% of participants were female. They found that Diet group reported statistically significantly greater improvement in their DASS depression score compared to the control group[240].

However, this study has several limitations. The depression diagnosis was via self-reporting, with only 37% of the participants indicating that they had a formal depression diagnosis[240]. Additionally, drop out levels were relatively high, particularly in the control group, where just over half withdrew before the end of the study[240]. The authors state that according to Cohen's power analyses, at least 60 participants were required in each group in order to detect a medium effect size[240]. Only 85 participants completed the study (47 in the intervention group and 38 in the control group), resulting in a lack of statistical power. These factors may limit the generalisability of the results[240].

The second study is the SMILES study by Jacka et al[140]. This 12-week randomised control trial assessed a modified Mediterranean diet (ModiMedDiet) in patients with major depressive disorder. The MD was based on the dietary guidelines of Greece, with the addition of lean red meats (to be consumed 3–4 per week)[140]. The addition of red meat was included in the SMILES study due to a previous cross-sectional study which reported that women who habitually consume less than the recommended intake of red meat were more likely to have a diagnosed depressive or anxiety disorder than those consuming the recommended amount[241]. The control group in the SMILES study received befriending's therapy, and the participants in both the intervention and control attended seven 60-minutes sessions over 12 weeks.

A total of 56 participants completed the trial. The average age of participants was 40 years old and 72% were female. The dietary group demonstrated statistically significantly greater improvement between baseline and 12 weeks on the Montgomery–Åsberg Depression Rating Scale (MADRS) than the control group[140]. However, the trial has several limitations which may have affected the results. The sample size calculation required 88 participants per group, however only 56 participants completed the trial (31 participants in the intervention group, and 25 in the control group), resulting in a lack of statistical power[140]. The small sample size may mean that sample was not representative and limit generalisability of the findings. The small sample size may also have inflated the effect sizes observed. Furthermore, the randomisation process utilized a block size of four, and while this is recommended for small sample sizes in order to avoid imbalances in allocation, this may have been insufficient to support allocation concealment and be a potential source of selection bias[140].

1.12 GAPS IN THE RESEARCH EXAMINING DIET AND DEPRESSION

Several significant gaps are evident in the research examining diet and depression. Firstly, the lack of experimental research designs assessing the effect of a Mediterranean diet for MDD. A growing body of evidence shows a link between diet and depression risk in observational studies however, the evidence from experimental studies is very limited. Randomised Control Trials (RCT's) are considered the gold standard of experimental research designs, yet only two studies have attempted to assess diet as an intervention for depressed individuals. This is important as the current observational evidence suggests diet and depression are correlated but cannot demonstrate causality. RCTs are able to determine the effectiveness of an intervention. The process of randomisation aims to reduce bias and so that any cause-and-effect relationships between the intervention and outcome can be explored[242]. Additionally, clinical practise guidelines often require high level evidence, guided by both observational and experimental research. Therefore, experimental research is needed to make clinical recommendations on the effectiveness of diet for treating and preventing depression.

The second significant research gap is the lack of evidence on dietary interventions in emerging adulthood and young adults as a distinct demographic. This is surprising because this age group is when the majority of mental illnesses first occur. In addition, this is when

dietary change could have the largest impact as young adults are starting to take charge of the foods they consume as they gain their independence. Coupled with the hesitancy of many young people to take anti-depressant medications, and the high rates of non-responders to these medications, diet could provide a low-risk, initial first step in treating depression in young adults. Additionally, early interventions could also make a significant impact on the number of prevalent years lived with disability (PYLD) and mortality rates caused by depression.

The third important gap is the lack of research on the effect of diet on depression in men. It is well established that men consume poorer quality diets compared to women so diet improvement could theoretically have a greater impact on the mental health of men. Additionally, despite ongoing efforts to reduce stigma and increase men's mental health literacy, men still access professional help for their depression infrequently[243]. Consistent findings of highly disproportionate incidence of men's suicide and substance overuse suggest that the prevalence rates of depression in men are under-reported[244]. Additionally, research shows that men prefer treatments structured around goals and progress, with a focus on "doing", rather than absolute talking therapies[245]. Therefore, diet therapy could potentially be seen as a more appealing option to men, as it involves action, goals and progress.

This thesis aims to address all three of these significant research gaps.

1.13 CHAPTER SUMMARY

This chapter has provided a detailed overview of depression, its history and conventional and complementary treatments. It has introduced the topic of nutritional psychiatry and appraised the current evidence on diet and depression, highlighting the limitations of the current research and outlining several important research gaps. The following chapter outlines the novel research questions this thesis aims to address along with the theoretical framework and chosen methodologies.

2. CHAPTER 2: METHODS

2.1 PREFACE

The previous chapter introduced the topic of depression, specifically in relation to men and young adults. Additionally, it provided an overview of the current research in nutritional psychiatry and several potential mechanisms of action. Specific gaps in the literature were also highlighted, which has led to the formulation of several novel research questions to be explored within this thesis. This chapter provides an overview of the theoretical framework and research paradigm which acts as the foundation of this research. Next, an overview of the research methodology is discussed with novel research questions, aims and objectives outlined.

2.2 THEORETICAL FRAMEWORK

Before selecting appropriate methodology and study design, several decisions pertaining to the theoretical framework and research paradigms were explored. A paradigm is a basic belief system and theoretical framework with assumptions about: 1) ontology, 2) epistemology, 3) methodology and 4) methods. When applied to health research this refers to the base assumptions from which new research is produced. The paradigmatic positioning in health care research influences both epistemology and ontology[246]. The epistemological standpoint refers to the researchers understanding of the nature of knowledge and the ontological standpoint is the understanding of reality. Together, all of these factors helped to shape the methodology and ultimately determine the specific methods used[246]. Thus, a research paradigm is a set of beliefs about how reality should be understood and studied. There are several research paradigms, however, the ones most relevant to this thesis include; positivism, pragmatism, and constructivist/interpretive theory.

2.2.1. Research Paradigms used in Research Exploring Diet and Depression

The most common paradigm used in research assessing the role of diet on depression is positivism. Positivism emphasises objectivity, knowability, and deductive logic and assumes

society can and should be studied empirically and scientifically[247]. The epistemological view claims that there is a fixed set of laws which empirical observations can determine via experimental means [248]. Positivism therefore includes quantitative research which measures dietary intake and depression outcomes. This includes both experimental and quantitative observational research designs where objective variables and numerical data can be measured and analysed.

The positivism paradigm sometimes contradicts that of qualitative research which follows a more interpretivist-constructionist paradigm. The interpretivist viewpoint argues that reality is constantly changing and evolving. Therefore the researchers aim is to interpret and understand different phenomena without directly intervening[248]. Limited research on diet and depression has been conducted using this framework. Examples include qualitative interviews and focus groups looking at topics such as dietary behaviours of those with depression and facilitators and barriers to healthy eating[249].

The third paradigm is pragmatism. Pragmatism approaches scientific questions by using the method which appears best suited to the research problem without being limited by philosophical debates[250]. Pragmatic research therefore uses any method, technique or procedure typically associated with quantitative or qualitative research. Mixed methods research therefore usually falls under this paradigm[250]. Being able to mix different approaches also has the advantages of enabling triangulation, which is a common feature of mixed methods studies[250]. Therefore, the theoretical framework and paradigmatic position chosen for this research is pragmatism.

2.2.2. Methodology

As mentioned above, each methodology fits within a different paradigm which ultimately guides the framework and methods used to answer each research question. This section explores the different methodologies in more detail and discusses the most appropriate options for our proposed projects.

When looking at different research methodologies there are three major design frameworks; qualitative, quantitative and mixed method research. Qualitative research aims to understand and interpret meanings and experiences whereas quantitative research focuses

on collecting data to establish relationships between variables. Mixed method research aims to encompass elements from both methodologies [251].

The majority of existing research assessing the role of diet on mental health is quantitative. It focuses on numerical data in the form of depression scales, food frequency questionnaires (FFQs) and other objective measurements. Strengths of quantitative research includes the relatively fast speed that data can be collected and the reliability of information gathered. However quantitative research can often be expensive and there is a limited ability to probe findings. In contrast, qualitative research in the form of surveys and focus groups are often used establish trends and themes in different groups. Strengths of qualitative research include increased flexibility in timing and location and the lower costs involved. Weaknesses include subjectivity and researcher bias. Increasingly, mixed method research is used, which combines elements from both methodologies. This requires greater preparation and additional costs but helps to gives a deeper understanding to a research question.

The majority of the projects within this thesis used quantitative methodology. With the exception of the MENDDS optional interview, which was used to assess young men's opinions and suggestions for the AMMEND study, which was more qualitative in design.

2.2.3. Research Design Frameworks

There are several different design frameworks within quantitative methodology which all emphasis the elements of objectivity, rationality, prediction and control[252]. Within quantitative research the three main types include descriptive, correlational and causal. Causal refers to an experimental research design which aims to establish a cause-and-effect relationship between two or more factors[252]. The researcher uses deductive reasoning to prove or falsify hypotheses. Experimental research designs include randomised control trials (RCTs) and quasi-experimental studies[253].

RCTs are often valued as the gold standard in experimental research designs due to their ability to obtain reliable information regarding intervention effect[253]. Participants are randomly allocated to receive either the treatment or be part of the control group[253]. There can be one or more treatments in a study and participants are usually blinded to which intervention they are receiving. The control group are also monitored throughout the study to provide a comparison. They may be given a placebo or no intervention at all[254]. RCTs are

often regarded as the best option in quantitative research due to a number of strengths within the framework.

The element of control is one of the major strengths that gives power to RCTs. Control can be applied in numerous ways including the use of a control group for comparison, random sampling, an inclusion and exclusion criteria, single or double blinding techniques, using accurate measuring tools and applying standardised statistical tests when analysing the final data[252]. All these factors add to the internal validity and rigor of the RCT so that findings can be reported with confidence. However, despite these strengths, there are several limitations within this framework which can affect the results and skew the data.

One of the greatest criticisms of the RCT is the reductionist nature of the framework. Despite the strict control and removal of interfering variables having a positive effect on reliability, it can also give an unrealistic representation of the population as a whole[252]. When the exclusion criteria are too great, the results from the study may no longer apply in a real-world setting and thus lack external validity. A reductionist approach often fails to address potential synergistic processes within whole systems[255].

Another weakness of this framework is based upon ethical issues. The control group will either receive no treatment or a placebo. In blinded interventions, the participants will not know which group they are in, and participants allocated to the control group could be subject to significant disadvantage. Therefore, RCTs require careful assessment of the risks and benefits that might be experienced. This information must be clearly articulated to potential participants during recruitment. The degree of risk should never exceed the potential benefits gained and is therefore not appropriate for all research questions. If this is the case, there are several other quantitative study design frameworks to choose from which will often omit a control group altogether. Examples incudes quasi-experimental study designs.

The main project included within this thesis, the AMMEND study, utilised a RCT design. Blinding participants to the intervention is particularly challenging in dietary trials. Therefore, the control group selection (befriending therapy), was presented as equal in it's possible treatment effect, in order to prevent expectancy bias.

2.2.4. Research Methods

Research methods refers to the data collection techniques used within a project to help answer the research question. These were very different for each project and are outlined in more detail in each chapter. Examples of methods included within this thesis include food frequency questionnaires (FFQs), depression scales and quality of life questionnaires.

2.2.5. Research Hypothesis

This thesis aimed to investigate the role of diet in depressed young men and had a number of research hypotheses; a primary overarching hypothesis and three secondary hypothesises.

Primary hypothesis:

1) *Dietary improvement can be achieved in individuals with major depressive disorder (MDD) who receive dietary counselling support from a nutritionist, and that their depressive symptoms will improve. The dietary intervention is modelled on the traditional Mediterranean diet.*

Secondary hypotheses:

1) *That polyphenols present in the Mediterranean Diet represent a potential therapeutic mechanism for its beneficial effect on depression.*
2) *That young men with depression display poor diet quality low in fruit and vegetables (which are high in polyphenols) which can affect their depressive symptoms.*
3) *That the diet quality of the control group participants will remain poor, and subsequently, that their depressive symptoms will not change.*

In order to test these hypotheses, the following research questions, aims and objectives were developed.

2.3 RESEARCH QUESTIONS

This thesis aimed to investigate the role of the Mediterranean diet on the symptoms of depression in young men and thus asked the following research questions:

1) *What is the effect of polyphenols found in a Mediterranean diet on the symptoms of depression?*

2) *What are the current dietary patterns of young men with depression?*
3) *What knowledge and attitudes do young men with depression have about nutrition?*
4) *Do young men with depression notice any associations between certain foods and the severity of their symptoms?*
5) *Does a Mediterranean diet effect the symptoms of depression in young men?*
6) *What attitudes do young men with depression have about following a Mediterranean diet?*

This thesis can be broken down into four projects: 1) a systematic literature review, 2) an online cross-sectional questionnaire, 3) a randomised control trial and 4) an end-of-trial evaluation questionnaire.

2.4 AIMS AND OBJECTIVES

Below are the main aims and objectives for all projects included in this thesis.

2.4.1 Project 1. Literature Review

A systematic literature review of evidence on the effect of all types and classes of polyphenols consumed as food or supplements for depression.

Aims and Objectives:

1. To examine the effects of polyphenols found in a Mediterranean diet on the symptoms of depression.
    a. By assessing both observational and experimental studies in humans exploring the effect of both dietary and supplemental polyphenols on the symptoms of depression.
    b. By provide a narrative synthesis of these findings.

This project addresses Research Question 1.

2.4.2 Project 2. Online Cross-sectional Questionnaire

An online cross-sectional questionnaire was used to survey young men with depression in order to investigate their diets and nutritional knowledge. This project can be divided into three parts and had the following aims and objectives

Aims and Objectives:

1. To examine the current diets of young men with depression.
    a) By assessing the types and quantities of foods consumed by young men with depression by using a food frequency questionnaire (FFQ).

2. To examine the nutrition knowledge of young men with depression.
    a) By exploring their understanding of a healthy diet
    b) By assessing their attitudes towards healthy eating

3. To examine any associations between certain foods or dietary patterns and severity of symptoms in young men with depression.
    a) By exploring any foods or dietary patterns associated with worsening of symptoms
    b) By exploring any foods or dietary patterns associated with improvement of symptoms
    c) By exploring any foods or dietary patterns associated with no change to symptoms

This project addresses Research Question 2, 3 and 4.

2.4.3. Project 3. Dietary Intervention via a Randomised Controlled Clinical Trial

A dietary intervention trial was conducted to determine if a Mediterranean diet effects the symptoms of depression in young men. The diet intervention was compared to a control group which received befriending therapy. This project had the following aims and objectives:

Aims and Objectives:

1. To determine if the diet quality of depressed young men could be improved via nutritional counselling.
    a) By measuring differences in the Mediterranean Diet Adherence Score before and after the intervention

2. To examine the effects of a Mediterranean diet on the symptoms of depression in young men.

a) By measuring differences in depression scores before and after the intervention using the Beck Depression Inventory (BDI-II).

3. To examine the effects of a Mediterranean diet on the quality of life in young men.
   a) By measuring differences in quality of life scores before and after the intervention using the World Health Organization Quality of Life Score (WHOQOL-BREF).

4. To determine if the effect of the Mediterranean diet differs significantly from that on the control group of befriending.
   a) By comparing the Becks Depression Inventory results and the quality of life score results between the intervention and control group.

This project addresses Research Question 5.

2.4.4. Project 4. End of Trial Evaluation Survey

A follow-up survey was conducted on the young men with depression who participated in the RCT, to understand their experience of following the Mediterranean diet. This project had the following aims and objectives:

Aims and Objectives:

1. To understand the experiences, perceived benefits and challenges of continuing to follow a Mediterranean diet by young men with depression
   a) By uncovering the perceived challenges to following a Mediterranean diet.
   b) By exploring which aspects of the Mediterranean diet participants found easy to follow.
   c) By assessing whether young men with depression would consider following a Mediterranean diet long term as part of an adjunctive treatment strategy.

This project addresses Research Question 6.

2.5 METHODOLOGICAL OVERVIEW

The theoretical framework and paradigmatic position chosen for this research is pragmatism. Pragmatism is based on the proposition that researchers should use the philosophical and/or

methodological approach that works best for the particular research problem that is being investigated. Due to the diverse nature of the research questions, mixed methodology has been used for this doctoral thesis. Firstly, a systematic literature review was conducted examining the effect of polyphenols on the symptoms of depression to verify this as a potential therapeutic mechanism for the Mediterranean diet.

Secondly, the target demographic, young men aged 18-25 with depression, was directly engaged via a self-administered online questionnaire. This survey was used to investigate their diets and nutritional knowledge and opinions. This involved 61 multiple choice questions which included the Center for Epidemiologic Studies Depression Scale Revised (CESD-R10) and the 26 item NIH Dietary Screener Questionnaire (DSQ). An optional qualitative email/zoom interview was also included in this project. This included 10 open-ended questions asking for opinions on the design of our next project. Data was gathered from 20 young men and their opinions on the methodology of our third research project helped shape the design of the trial.

The main research question was to examine the effect of a Mediterranean diet on the symptoms of depression in young men. In order to answer this research question, an experimental design was chosen. Participants were randomly allocated to either the diet group or a social support control group. The trial intervention was 12 weeks in duration and involved three appointments. Once at baseline, a follow up at week 6 and the final appointment at week 12. Data collection was via case report forms which measured several variables including potential confounding factors such as exercise, sleep quality, stress levels, time spent in nature, hobbies, vitamin or herbal supplements, medications, alcohol consumption and recreational drug use. Quality of life was also measured during the trial via the World Health Organisations (WHO) Quality of life (QOL) form. The main outcome measure was data collected from the Becks Depression Inventory.

Finally, a questionnaire was used to determine how appropriate recommending a Mediterranean diet is for this population group and determine its “real-world” application. The aim of this questionnaire was to understand the attitudes, perceived benefits and challenges of continuing to follow a Mediterranean diet by young men with depression and therefore created an end-of-trial evaluation questionnaire for the participants in the diet

group. This online questionnaire consisted of 16 multiple choice questions and 4 open-ended questions where participants were invited to elaborate on their experiences and opinions. Figure 4 outlines the theoretical framework and chosen paradigms underpinning this research, highlighting the pragmatic and mixed methods approach to answering these research questions.

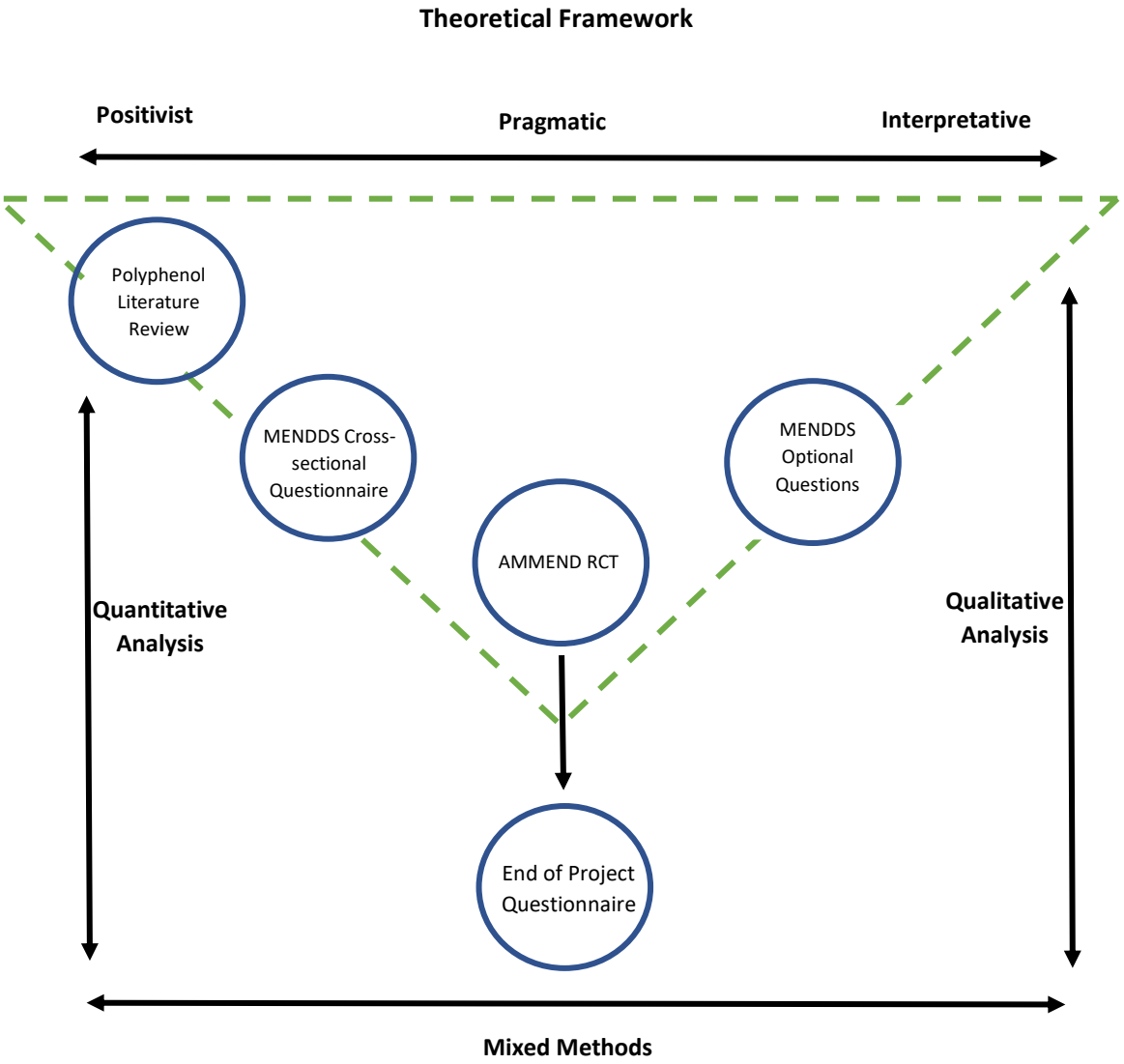


Figure 4. Theoretical Framework

2.6 CHAPTER SUMMARY

This chapter has provided a detailed overview of the theoretical framework and research paradigm used within this thesis. The research hypothesis, questions, aims and objectives were also outlined along with an overview of the selected research methods for each project.

3. CHAPTER 3: LITERATURE REVIEW

3.1 PREFACE

The previous chapter provided an overview of the research questions, aims and objectives as well as detailing the theoretical framework and chosen methodologies. The hypothesis that diet effects depression has been explored in Chapter 1 and several potential mechanisms were discussed.

As discussed in Chapter 1, a recent systematic review, which assessed the effect of a MD and risk of depression in observational studies found a significant relationship between the MD and odds of depression in cross-sectional studies[256]. A second systematic review, which also assessed the MD pattern and depression risk, found a similar results[236]. The findings from these reviews are promising, but more research is needed to determine the exact therapeutic components of the MD. One particular therapeutic component of interest are polyphenols in the Mediterranean diet.

Therefore, a systematic literature review was conducted in order to explore this potential therapeutic component further. The review assessed research on all forms and types of polyphenols, including both observational and experimental research designs and included polyphenols consumed as both foods and as nutraceutical supplements. This chapter includes the accepted manuscript which has been published in *Advances in Nutrition: An International Review Journal* (IF: 8.7) in November 2019. It is reproduced here with permission from Oxford University Press.

> Bayes, J., Schloss, J. and Sibbritt, D., 2019. Effects of Polyphenols in a Mediterranean Diet on Symptoms of Depression: A Systematic Literature Review. *Advances in Nutrition*. 11(3), 602-615.

3.2 LITERATURE REVIEW

Effects of polyphenols in a Mediterranean diet on symptoms of depression: A systematic literature review

This review is registered with PROSPERO: CRD42019125747

Supplementary Materials can be found in the Appendix:

- Figure 1 PRISMA-P flowchart - Appendix 1
- Table 1 The Joanna Briggs Institute Critical Appraisal tool for Systematic Reviews. Checklist for Randomized Controlled Trials - Appendix 2
- Table 2 Critical Appraisal for Observational studies STROBE Checklist for cohort, case-control, and cross-sectional studies - Appendix 3
- Table 3 PRISMA Checklist – Appendix 4
- Table 4 Literature Search Strategy Log Results – Appendix 5
- ROB interpretation – Appendix 6
- Narrative synthesis process – Appendix 7

ABSTRACT

Depression is a mood disorder which currently effects 350 million individuals worldwide. Recently, research has suggested a protective role of diet for depression. The Mediterranean style dietary pattern has been highlighted in several systematic reviews as a promising candidate for reducing depressive symptoms. It has been speculated that this could be due to the high polyphenol content of foods commonly found in the diet. Therefore, the aim of this review was to assess the effects of polyphenols found in a Mediterranean diet on the symptoms of depression. A systematic literature review was conducted of original research which assessed the role of polyphenols on the symptoms of depression in humans. The following databases were searched: PROQUEST, SCOPUS (Elsevier), MEDLINE (EBSCO), CINAHL, and EMBase up to the 18th February 2019. The inclusion criteria consisted of both observational and experimental research in adults aged 18-80 and assessed depression scores in relation to polyphenol intake. A total of 37 studies out of 12084 met the full

inclusion criteria. Of these, 17 were experimental studies and twenty were observational studies. Several different polyphenols were assessed including those from tea, coffee, citrus, nuts, soy, grapes, legumes and spices. Twenty-nine of the studies found a statistically significant effect of polyphenols for depression. This review has found both an association between polyphenol consumption and depression risk, as well as evidence suggesting polyphenols can effectively alleviate depressive symptoms. The review uncovered gaps in the literature regarding the role of polyphenols for depressive symptoms in both young adults and men.

Keywords: Polyphenols; phytochemicals; flavonoids; depression; major depressive disorder; mental health

INTRODUCTION & BACKGROUND

Depression is a mood disorder characterised by anhedonia or lack of pleasure, a depressed mood and altered cognitive function[38]. Currently, 350 million individuals suffer from depression globally[257] with the World Health Organisation (WHO) estimating that mental health conditions are now the leading cause of disability worldwide[258]. Although the exact aetiology of depression is still unknown, several similarities exist between depression and inflammatory diseases such as cardiovascular disease (CVD), diabetes and cancer which include reduced insulin sensitivity, endothelial dysfunction and increased production of proinflammatory cytokines[155].

The field of *Nutritional Psychiatry* is relatively new and relates to the emerging research focusing on the role of diet and nutrition on mental health[137]. New investigations into the microbiome, immune and inflammation pathways demonstrate a powerful paradigm shift in the way we understand depression[189]. Research into how diet and nutrition effects these pathways could yield valuable insights into potential treatment strategies for depression. A recent review examining the role of fruit and vegetable consumption and various health outcomes suggested several possible links between these foods and depression pathophysiology[259]. The free-radical scavenging and anti-inflammatory components found in fruits and vegetables, particularly the high content of carotenoids, vitamin C and polyphenols appear to play an important role[259]. Other possible therapeutic components include folate and the effects to methylation, homocysteine and vitamin B12 as well as the effect of fibre on gastric emptying and brain-derived neurotrophic factor (BDNF)[259].

Several traditional diets which are high in fruits and vegetables have been associated with a reduced risk of depression, including the traditional Japanese diet[260] and Norwegian diet[230]. Currently, the diet with the most evidence for protecting against depression risk is the Mediterranean diet (MD) which has recently been hypothesised as a promising treatment strategy for improving clinical outcomes in depression[148]. Several reviews on diet and depression have speculated that the efficacy of the Mediterranean diet for depression may be due to the high polyphenols content[148,261,262]. Therefore, conducting a systematic review to examine the research on these polyphenols may assist in verifying this potential mechanism of action.

The term *Mediterranean Diet* reflects the diets of several countries in the Mediterranean Basin during the early 1960s[145]. It was noted that the populations within these countries had reduced mortality and morbidity from various diseases[146]. One of the common linking factors was their shared dietary pattern which has since gained much attention, particularly for preventing coronary heart disease[147]. In 1993 the International Conference on the Diets of the Mediterranean defined the various components of the diet[145]. They conclude that it is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds and legumes. The principle source of dietary lipids is in the form of olive oil. Red wine is consumed in moderate amounts generally with meals[145]. All of these dietary components are rich in polyphenols which may explain the favourable health outcomes, particularly in depression.

Polyphenols are natural compounds found in a wide variety of foods and are particularly high in plant-based foods[263]. Polyphenols exert protective effects on mental health via upregulating the body's natural defence systems, stabilising free radicals, and reducing oxidative damage[264]. Additionally, neuroprotective properties have been observed, with polyphenols modulating specific cellular signalling pathways involved in cognitive processes [264]. The main classes of polyphenols are defined according to the nature of their carbon skeleton: phenolic acids, flavonoids and the less common stilbenes and lignans[265].

The aim of this literature review is to assess the effects of polyphenols on the symptoms of depression.

METHODOLOGY

A protocol was developed according to the Preferred Reporting Items For Systematic Reviews And Meta-Analysis Protocols (PRISMA-P) 2015 statement [266]. The review is registered with PROSPERO: CRD42019125747

Search Strategies and Inclusion Criteria

A literature search was conducted in the following databases: PROQUEST, SCOPUS (Elsevier), MEDLINE (EBSCO), CINAHL, and EMBase. Search terms were divided in two groups and combined within the search. Group 1: Polyphenols OR Phytochemicals OR flavonoids. Group 2: depression OR major depressive disorder OR major depression OR mental health. Initial investigations on search terms for group 1 included the search terms phenolic acids, ligands, stilbenes, and anthocyanins. These terms found no results and hence were excluded from the group.

Original research, published up to the 18th February 2019, which assessed the effect of polyphenols on the symptoms of depression were included in the review. All fruits, vegetables, nuts and seeds, wholegrains, beans and legumes, plant oils and common culinary herbs and spices were included. This is the first literature review to assess the role of polyphenols on depressive symptoms.

Articles were excluded from the review for the following reasons: articles which were not published in English; articles which were not related to the search terms such as those on Alzheimer's Disease or cognitive decline; not original research; articles which did not use a depression rating scale; studies which examined polyphenols not usually consumed as part the diet such as the medicinal herbs St. Johns wort, lavender and Ginkgo biloba.

Study Selection and Data Extraction

The initial search identified 12084 papers. After removal of 790 duplicates, articles were screened by title and by abstract. The remaining articles were then screened by full text resulting in 35 articles which met the full inclusion criteria. After hand-searching the references of the full text articles an additional 2 articles which used different key words were included. This resulted in 37 articles to be assessed in this review. Screening was performed by JB and citations were stored and filed in EndNote X7. The article selection process is outlined in Supplemental Figure 1.

Assessment of Risk of Bias and Data Summary Table:

Each paper was critically appraised for methodological consistency using critical appraisal tools. For the 17 experimental studies the Joanna Briggs Institute Critical Appraisal tool for Systematic Reviews Checklist for Randomized Control Trials was used[267]. For the 20 observational studies the STROBE checklist for cohort, case-control, and cross-sectional studies was used[268]. Overall, the appraisals found reliable methodology and no papers were excluded from the review. **Supplemental Table 1** displays the results for randomized control trials (RCTs) and **Supplemental Table 2** displays the results for the observational studies. During this process data was extracted from the final articles and summarised in **Tables 1** and **2**.

RESULTS

Study Characteristics:

All included studies provided quantitative data on human subjects. The observational studies included both longitudinal cohort and cross-sectional designs and had an average number of 10301 participants. The experimental studies were randomized control trials with either a placebo or an anti-depressant medication with an average number of 80 participants. The experimental studies varied in time duration from two weeks to two years with the most common time frame being eight weeks. The majority of the studies assessed both genders (*n=23),* twelve assessed only females and only two studies assessed only men. Twenty-six of the studies were in adults aged between 23-55 years, ten were in older adults, either postmenopausal or the elderly aged between 40-80 years, and only one study was in young adults aged 18-25 years. Twelve studies looked at depression in disease states. These include major depressive disorder[269-273] chronic fatigue syndrome[274], osteopenia[275], obesity[276,277], breast cancer[278], type 2 diabetes[279] and irritable bowel syndrome[280]. An overview of these study characteristics can be viewed in **Table 3.**

Critical Appraisal:

Over all the results from the critical appraisal tools showed good methodology. Results can be seen in Supplemental Tables 1 and 2. A common weakness observed in the experimental studies was the lack of information in regards to blinding. Although the majority of studies claimed to be double blinded in either the title or the abstract, many failed to provided details of how the assessors and those delivering the interventions were blinded in the methodology

section. In the observational studies common weaknesses included failure to explain how loss of follow-up was addressed, not describing study design bias, not providing a flow diagram to show included participants and failing to indicate number of participants with missing data for each variable of interest. These limitations were considered when synthesising the results from this review.

Depression scales:

The most common depression scale used in the observational studies was the Center for Epidemiologic Studies Depression Scale (CESD) which was used in six of the twenty studies[281-284]. The CESD is a 20-item measure that asks subjects to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely[285]. In the experimental studies the most common scale used was the Hamilton Depression Rating Scale (HDRS) which was used in five of the seventeen studies[269,271,273,286,287]. The second most popular scale was the Hospital anxiety and depression scale (HADS) which was used in four of the studies[272,274,280,288]. HADS is a fourteen-item scale used to measure anxiety and depression in a hospital or community setting[289]. Another popular depression scale used was the Zung Self Rating Depression Scale (ZSDS) which was used in both observational[290,291] and experimental designs[275,286]. ZSDS is a 20-item self-report questionnaire covering affective, psychological and somatic symptoms associated with depression[292].

Polyphenols:

A variety of different polyphenols are assessed in the articles included in this review. The observational studies looked at polyphenols consumed in their biological whole food form and the majority of experimental studies assessed the effect of polyphenols consumed via a capsule[269-273,275-277,280,286-288], powder[293], dried herbal tea[294] or liquid[295]. Only two experimental studies assessed polyphenols consumed in their whole food form[274,296]. The most commonly tested group of polyphenols were flavanols from tea (n=9 observational) and cocoa (n=2 experimental), isoflavones from soy (n=3 observational and n=4 experimental) and hydroxycinnamic acids from coffee (n=5 observational) and curcumin (n=6 experimental). Other classes of polyphenols tested include flavanones in the form of citrus (n=2 experimental), stilbenes in the form of resveratrol (n=1 experimental) and flavonols in the form of nuts (n=1 observational and n=1 experimental). Three of the observational studies

considered the combined effect of all dietary sources of polyphenols in depression risk[282,283,297].

Intervention/variable effect:

The majority of studies (*n*=29) found a statistically significant positive and protective effect of consuming polyphenols on the symptoms and risk of depression. Five studies noted a positive effect which was not statistically significant[269,271,274,290,296] two studies reported mixed result[281,291] and only two studies showed no difference after the intervention[277,295]. An overview of polyphenol effect on depression is displayed in **Table 4.** *P*-values are given for experimental studies in Table 1 and odds ratios, relative risk and *P*-values are given for observational studies in table 2.

Table 1. Data Summary of Experimental Trials assessing polyphenols in depressed participants

Author	Year	Country	Study Design	Intervention	Subjects	Depression Scale	Other Measurements	Results
Sathyapalan et al.[274]	2010	England	Randomized placebo-controlled trial. Duration: 8 weeks of initial intervention followed by a 2 week wash out period followed by 8 weeks of the crossover intervention.	1: Polyphenol rich chocolate with 85% coco solids 2: Placebo chocolate	10 subjects (*n*=6 women) (*n*=4 men) Condition: Chronic fatigue	Hospital anxiety and depression scale (HADS)	Chalder fatigue scale and London handicap scale	Depression scores improved after the high polyphenol chocolate but deteriorated after the placebo chocolate. Coco group HADS median scores: Baseline = 10, conclusion = 5.5. Placebo baseline = 6, conclusion = 12. However, the results were non-significant: Wilcoxon signed rank sum test *Z* value: -2.68 (0.01)
Bergman et al.[269]	2013	Israel	Randomized, double blinded, placebo controlled, pilot clinical trial. Duration: 5 weeks	1: 500 mg/d curcumin plus antidepressant 2: Placebo plus antidepressant	40 subjects (*n*=23 women) (*n*=17 men)	Hamilton Depression rating scale and Montgomery-Asberg Depression Scale (MADRS)	Global Impression Severity Scale	Both groups had a significant improvement in depressive symptoms. MADRS Score for the Curcumin group 95% CI, 7.2-13.7; *P= <0.001* and Placebo group 95% CI. 2.1-8.5; *P*= <0.01. Although no

								significant differences were observed between the intervention and placebo, the curcumin group displayed a more rapid improvement in symptoms compared to the placebo. Curcumin group MADRS mean scores: Baseline = 34.4, conclusion = 14.0. Placebo baseline = 32.8, conclusion = 15.4.
Nina Estrella et al.[286]	2014	Dominican Republic	Pilot randomized clinical study. Duration: 3-month duration with four intervention arms	1: Fluoxetine (10mg/day) 2: Soy isoflavones concentrate (100mg/day) 3: Sertraline (50mg/day) 4: Soy (100mg/day) and Sertraline (50mg/day)	40 women aged 45-55yrs. Condition: menopausal depressive	Zung self-rating depression scale (ZSDS) Hamilton Rating Scale for Depression (HAMD)	Not reported	ANOVA for both ZSDS and HAMD showed statistically significant differences between groups (F= 24.06, *P* = < 0.0001) and (F= 31.73, -*P* = < 0.0001) respectively. Soybean has antidepressant effect and may increase the effects of anti-depressants.

Atteritano et al.[275]	2014	Italy	Double blinded randomized control trial Duration: 2 years	1: Isoflavone Genistein (45mg/day) 2: Placebo	262 women Condition: Osteopenic postmenopausal	Zung self-rating depression score (ZSDS)	Health rated quality of life (HRQL) assessed via Italian version of Short Form-36 (SF-36)	The genistein group saw a decrease in depression scores after 1 and 2 years. The difference between groups was statistically significant (*P*=<0.01 vs placebo). Genistein group ZSDS mean scores: Baseline = 41, conclusion = 36. Placebo baseline = 41, conclusion = 43.
Lopresti et al.[270]	2014	Australia	Randomized double blinded, placebo control trial Duration: 8 weeks	1: 500mg twice daily of Curcumin 2: Placebo	56 subjects (*n*=40 women) (*n*=16 Men)	Inventory of Depressive Symptomatology self-rated scale (IDS-SR 30)	Spielberger State-Trait Anxiety Inventory	From weeks 4-8 the Curcumin group demonstrated significantly more efficacy that placebo. IDS-SR Total Score ($F_{1,53}$ = 4.22, *P*= 0.045) and Mood Score ($F_{1,53}$ = 6.51, *P*= 0.014). Curcumin group IDS-SR Total mean scores: Baseline = 33, conclusion = 22.7. Placebo baseline = 33, conclusion = 25.8.

Sanmukhani et al. [271]	2014	India	Double blinded randomized control trial. Duration: 6 weeks	1: Fluoxetine 20mg/day 2: Curcumin 1000mg/day (500mg BD) 3: Fluoxetine 20mg/day plus curcumin 1000mg/day (500mg BD)	40 subjects (*n*=24 women) (*n*=16 men)	Hamilton Depression Ratting Scale ($HAM\text{-}D_{17}$)	Clinical Global Impression – severity of illness scale	A greater response was observed in the combined Fluoxetine and curcumin group (77.8%) compared to the fluoxetine group (64.7%) and curcumin group (62.5%). However, the differences between groups were not statistically significant (*P*=0.58). Group 1 HAM-D mean scores: Baseline = 21, change from baseline at conclusion = -13.6. Group 2 baseline = 19.3, change at conclusion = -13.3. Group 3 baseline = 21.9, change at conclusion = -14.6.
Esmaily et al. [277]	2015	Iran	Double blind, cross over, placebo controlled randomized control trial	1: Curcumin 1g/day 2: Placebo	30 subjects (*n*=24 women) (*n*=6 men) Condition: Obese	Becks Depression Inventory (BDI)	Beck Anxiety Inventory (BAI)	No significant differences in BDI scores were observed for the curcumin group *P*= >0.05

			Duration: 4 weeks with a 2 week wash out between groups					
Panahi et al. [272]	2015	Iran	Open label randomised control trial Duration: 6 weeks	1: Standard anti-depressant therapy 2: Standard antidepressant therapy plus curcuminoids 1000mg and 10mg piperine.	111 subjects (*n*=60 women) (*n*=51 men)	Hospital Anxiety and Depression Scale (HADS) and Becks Depression Inventory (BDI)	Not Reported	Significantly reduced HADS and BDI scores in the curcumin group compared to the control group. HADS Score *P*= <0.001 and BDI Score *P*= <0.001. Curcuminoids group BDI mean scores: Baseline = 38.66, conclusion = 29.66. Placebo baseline = 40.44, conclusion = 37.60. Curcuminoids group HADS mean scores: Baseline = 42.59, conclusion = 30.90. Placebo baseline = 38.82, conclusion = 36.10.
Yu et al. [273]	2015	China	Double blinded, placebo controlled, pilot randomized control trial	1: Curcumin 1000mg/day 2: Placebo soybean powder	108 male subjects	Chinese version of the 17-item Hamilton Depression Rating Scale and	Blood pathology: plasma cytokines IL-1β, TNF-α and	Significant reduction in depressive symptoms in the curcumin group for both the HDRS and MADRS *P*=<0.05. Significant reduction in

			Duration: 6 weeks			Montgomery-Asberg Depression Rating Scale	brain-derived neurotropic factor (BDNF)	cytokines IL-1β, TNF-α and BDNF for the curcumin group *P*=<0.001. Curcumin group HDRS mean scores: Baseline = 14.06, change from baseline at conclusion = 4.52. Placebo baseline = 14.28, change from baseline at conclusion = 3.30. Curcumin group MADRS mean scores: Baseline = 18.22, change from baseline at conclusion = 6.26. Placebo baseline = 18.68, change from baseline at conclusion = 4.52.
Ibero-Baraibar et al.[276]	2016	Spain	Double blinded, randomized, placebo-controlled trial. Duration: 4 weeks	1: 15% energy restriction diet plus 1.4g coco extract (645mg total polyphenols) 2: 15% energy restriction diet only	50 subjects (*n*=27 women) (*n*=23 men) Condition: Overweight or obese adults	Spanish translation of the Beck Depression Inventory (BDI)	3-day food recall questionnaire	Depressive symptoms were reduced significantly in both experimental groups (*P*=<0.05). However, no differences were observed in depression scores between the two groups. Coco group BDI mean scores: Baseline = 9.4, conclusion = 5.7. Placebo

								baseline =11.8, conclusion = 6.1.
Pribis [296]	2016	USA	Double blinded, randomized, placebo-controlled, cross over design. Duration: 8-week intervention followed by 6 weeks wash out period followed by 8 weeks cross over intervention	1: Banana bread with 60g of ground walnuts 2: Banana bread without walnuts	49 subjects (*n*=29 women) (*n*=20 men) Condition: Students between 18-25yrs	The profile of mood states (POMS)	Lifestyle survey and Food frequency questionnaire (FFQ)	Males, but not females, had a significant medium effect size improvement in total mood disturbances. Both men and women had a non-statistically significant improvement in depression *P*=0.103.
Hirose et al.[288]	2016	Japan	Randomized, double blinded, placebo-controlled trial Duration: 8 weeks	1: Isoflavone aglycone (12.5mg/day) 2: isoflavone aglycone (25mg/day) 3: Placebo	90 women aged 40-60yrs Condition: Menopausal	Hospital Anxiety and Depression Scale (HADS)	Menopausal symptom scale and Athens Insomnia Scale	Low dose (25mg/day) isoflavone aglycone significantly reduced symptoms of depression (*P*=0.033).

Mirghafourvand et al.[295]	2017	Iran	Randomized control trial Duration: 8 weeks	1: Orange peel essential oil (10 drops 3x/day) 2: Placebo	48 women Condition: Postpartum	The Edinburg Postnatal Depression Questionnaire	The Spielberger state-trait anxiety inventory	No statistically significant difference between intervention and placebo (*P*=0.956). Orange peel group depression mean scores: Baseline = 8.0, conclusion = 6.7. Placebo baseline = 8.1, conclusion = 6.7.
Kamalifard et al.[293]	2017	Iran	Triple blind randomized control trial Duration: 8 weeks	1: Bitter orange powder (500mg/day) 2: Lavender flower powder (500mg/day) 3: Placebo – starch (500mg/day)	156 women aged 45-60 Condition: menopausal	Beck Depression Inventory	Socio-demographic questionnaire	Both orange and lavender were effective at reducing symptoms of depression compared to placebo (*P*=0.001). There was no significant difference between orange and lavender. Bitter orange group BDI mean scores: Baseline = 21.38, conclusion = 14.48. Lavender baseline = 20.82, conclusion = 14.07. Placebo baseline =20.01, conclusion = 16.78.

Davinelli, et al.[287]	2017	Italy	Randomized, double blinded, placebo-controlled trail Duration: 12 weeks	1: Capsule containing 200mg of fermented soy (80mg of isoflavone aglycones and 10mg equol) and 25mg of resveratrol per day 2: Placebo capsule	60 women aged 50-55yrs Condition: menopausal	Hamilton Rating Scale for Depression (HAM-D)	Health rated quality of life (HRQL) Menopause Rating Scale (MRS)	Treatment group saw improvements in depression scores in comparison to the placebo group (*P*=0.001).
Kazemian et al.[280]	2017	Iran	Randomized controlled trial Duration: 1 month	1: Capsule containing Zingiber Officinale (ginger), Boswellia carterii (frankinsence) and Achillea millefolium (yarrow) daily.	42 subjects (*n*=19 women) (*n*=23 men) Condition: Irritable bowel syndrome (IBS)	Hospital Anxiety and Depression Scale (HADS)	IBS-severity scoring system (IBS-SSS)	Symptoms of depression reduced significantly in the intervention group (*P*=0.001) with no significant changes in the placebo group (*P*=0.31). Herb group HADS mean scores: Baseline = 17.4, conclusion = 12.5. Placebo baseline = 18.0, conclusion = 17.22.

				2: Placebo				
Chang et al. [298]	2018	Taiwan	Single blinded. Placebo controlled, randomized clinical trial Duration: 2 weeks	1: camomile tea (1 cup per day which included 2g of dried flowers and 300ml hot water steeped for 10-15 minutes) 2: Regular care with no camomile tea.	80 women Condition: 6 weeks postpartum	Edinburgh Postnatal Depression Scale	Postpartum Fatigue Scale	The camomile teat group significantly lowered depressive symptoms compared with the control group (T=-2.372, P=0.020). Camomile group depression mean scores: Baseline = 7.86, conclusion = 7.26. Placebo baseline = 9.71, conclusion = 9.51.

Table 2. Data Summary of Observational Studies assessing polyphenols on depressive symptoms

Author	Year	Country	Study Design	Main Variable	Subjects	Depression Scale	Other measures	Results
Hintikka et al. [299]	2005	Finland	Cross Sectional Study	Tea consumption	2011 participants from the Kuopio Depression Study aged 25-64 (*n*=1121 women) (*n*=890 men)	Beck Depression Inventory (BDI)	Food Frequency Questionnaire	Daily tea drinkers had a significantly reduced risk of being depressed (*OR* 0.46, 95% *CI* 0.3-0.7).
Niu et al. [300]	2009	Japan	Cross Sectional Study	Green tea consumption	1058 elderly participants >70 years old	30-item Geriatric Depression Scale	Height and weight, blood tests for C reactive protein. A 75-item diet history questionnaire	The prevalence of depressive symptoms was 44% lower for participants who consumed ≥4 cups of green tea compared to those who consumed ≤1 cup per day 9Bonferroni corrected *P*=<0.01.
Chen et al. [278]	2010	China	Prospective Cohort Study	Tea consumption	1399 women Condition: Breast cancer survivors	20-item Center for Epidemiological Studies	Quality of Life and Medical outcome	Regular tea consumption (>100g dried tea leaves/month) was inversely associated with

						Depression Scale	short form 36 health survey	overall depression (*OR*, 0.64; 95% CI, 0.41-0.99).
Ruusunen et al. [301]	2010	Finland	Prospective Cohort Study	Coffee and tea consumption	2232 middle aged men	18-Item Human Population Laboratory (HPL) Depression Scale	4 day food record, BMI.	Heavy coffee drinkers had a decreased risk of depression compared to non-drinkers (*RR*=0.28, 95% CI 0.08, 0.98). No associations were observed for tea consumption and depression (*RR*=1.19, 95% CI 0.54, 2.23).
Li et al.[281]	2010	USA	Longitudinal cohort study Duration: cohort from 1971-1982	Legume consumption	4869 adults who participated in the National Health and Nutrition Examination Survey (NHANES I)	Centre for Epidemiological Studies Depression Scale (CES-D)	3-month food frequency questionnaire (FFQ)	In premenopausal women, consumption of legumes was associated with an increased risk of depression (*P*=0.0148). However, moderate consumption was associated with a lower risk of depression among perimenopausal women (*RR*=0.52 (0.27,1.00).

								No significant association was found among men and postmenopausal women.
Lucas et al. [302]	2011	USA	Prospective longitudinal study Duration: 10 year follow up.	Coffee consumption	50739 women (mean age 63 years)	36 item short form health survey	Food frequency questionnaire	Depression risk decreases with increasing coffee intake. Multivariate relative risk for those consuming 4 cups per day or more was 0.80 (95% CI, 0.68-0.95; *P* for trend = 0.02).
Feng et al. [303]	2012	Singapore	Prospective Cohort Study	Tea consumption	1615 older participants aged 55-93 years	15-item Geriatric Depression Scale	Food frequency questionnaire	Risk of depression decreased with increasing tea consumption. Odds Ratio for low, medium and high tea consumption was 1.15, 0.55 and 0.37, respectively. (*P* for linear trend = 0.01).
Feng et al. [304]	2013	China	Cross Sectional Study	Tea consumption	1368 older aged participants ≥60 years	15-item Geriatric Depression Scale	Mini mental state examination. Tea	Daily tea consumption is associated with a reduced risk of depressive symptoms. Weekly tea consumption

							consumption questionnaire	OR=0.86; 95% CI=0.56-1.32 and daily consumption OR=0.59; 95% CI=0.43-0.81. (*P* for linear trend = 0.001).
Omagari et al. [279]	2014	Japan	Cross Sectional Study	Coffee consumption	89 participants with type 2 diabetes (*n*=34 women) (*n*=55 men)	Japanese version of the Hospital Anxiety and Depression Scale (HADS)	Food frequency questionnaire and BMI	Coffee consumption was inversely associated with depressive symptoms with participants who drink 3 or more cups per day having a significantly reduced risk of depression (*P*=0.032)
Pham et al. [305]	2014	Japan	Cross Sectional Study	Green tea and coffee consumption	537 men	Center for Epidemiological Studies Depression Scale	Diet history questionnaire C reactive protein and folate blood test.	Higher green tea consumption ≥4 cups/day was associated with a lower prevalence of depressive symptoms (51% significantly lower prevalence odds) (*P* for trend = 0.01). Coffee consumption was also inversely associated with depressive symptoms with ≥2 cups/day compared to 1

								cup/d: (*OR*=0.61; 95% CI 0.38, 0.98).
Yu et al. [306]	2015	China	Cross Sectional Study	Soybean and soybean product consumption	1717 Liaoning Province residence aged>65 years (*n*=849 women) (*n*=868 men)	Patient Health Questionnaire-9	Food frequency questionnaire	Frequent consumption of soybeans and soybean products is associated with a decrease in the likeliness of depressive symptoms. Consumption 2-3 times per week (*P*=0.23) *OR* 95% CI= 0.36 (0.15,0.87) Consumption >4 times per week (*P*=0.001), *OR* 95% CI= 0.50 (0.34,0.74).
Li et al. [307]	2016	China	Cross Sectional Study	Tea consumption	9371 elderly (≥60 years of age) participants (*n*= 4853 women) (*n*= 4518 men)	Patient Health questionnaire (PHQ-9)	Daily living scale and the Mini Mental State Examination. Food frequency questionnaire	The black tea drinkers had a significantly decreased risk of depressive symptoms (*P*= < 0.01), Compared with non-drinkers, the adjusted OR 95% CI =0.48 (0.23, 0.99) and 0.35 (0.17, 0.72) for participants consuming

								< 3 cups and ≥3 cups of black tea per day, respectively (*P* for trend: <0.01
Chang, et al. [282]	2016	USA	Longitudinal cohort study Duration: 1976-2001	Dietary flavonoid intake	82648 women who participated in the Nurses' Health Study	The 5 item mental health index and the Center for Epidemiologic Studies Depression Scale (CESD-10) and the Geriatric Depression Scale (GDS)	Food frequency questionnaire	Greater intakes of dietary flavonoids were significantly associated with a modest reduction in depression risk. Participants in the highest flavonoid consumption group had a 7-10% reduction in depression risk compared to the lowest intake group. There was evidence of an inverse linear trend across consumption groups (-*P*-trend=0.08, 0.0004 and 0.0007, respectively)
Su et al. [290]	2016	China	Cross sectional Study	Nut consumption	13626 adults who participated in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort.	Zung Self Rating Depression Scale (ZSDS)	Food frequency questionnaire	Frequent nut consumption is associated with lower prevalence of depression. *OR* 95% CI= 0.82 (0.75, 0.90) for consumption 1-3 times per week and *OR* 95% CI= 0.82

					Recruited during 2013-2014			(0.73,0.92) for consumption ≥ 4 times per week.
Chan et al. [298]	2018	Singapore	Prospective Cohort Study	Tea consumption	614 elderly participants aged 60 years and above	15-item Geriatric Depression Scale (GDS)	Geriatric Anxiety Scale. Tea consumption questionnaire	Long term tea consumption was significantly associated with reduced odds of depressive symptoms. Tea consumption for over 15 years resulted in lower GDS Scores (*OR*: 0.82, *P*=0.01).
Navarro et al. [308]	2018	Spain	Longitudinal Cohort Study	Coffee consumption	14413 middle aged participants	Validated physician diagnosis of depression using the Structured Clinical Interview for DSM-IV (SCID-I)	Food frequency questionnaire	Greater coffee consumption is associated with reduced risk of depression. Participants who drank ≥4 cups/day showed a significantly lower risk of depression than participants who drank less than one cup of coffee per day (HR: 0.37 (95% CI 0.15–0.95).
Miyake et al. [284]	2018	Japan	Cross sectional study	Soy isoflavones	1745 pregnant women who participated in the KOMCHS	Center for Epidemiologic Studies	Diet history questionnaire	Isoflavone intake was associated with a lower prevalence of depressive symptoms during pregnancy.

					study (an ongoing prospective pre-birth cohort study)	Depression Scale (CESD)		Prevalence ratios (95 % confidence intervals, *P* for trend) 0.63 (0.47–0.85, 0.002), 0.72 (0.54–0.96, 0.007), 0.74 (0.56–0.98, 0.04), 0.57 (0.42–0.76, <0.0001), 0.73 (0.55–0.98, 0.03), 0.65 (0.49–0.87, 0.003), and 0.63 (0.46–0.86, 0.002).
Yu et al. [291]	2018	China	Cross sectional study	Soy isoflavones	13760 adults who participated in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort.	Zung Self Rating Depression Scale (ZSDS)	Food frequency questionnaire	Moderate intake of soy foods may reduce the incidence of depression while high intakes may worsen depressive symptoms. *OR* 95% CI for <1/week) were 0.80 (0.67, 0.95) for 1-3/week, 0.69 (0.55, 0.86) for 4-7/week, and 1.85 (1.21, 2.80) for ≥ 2/day.
Godos et al. [283]	2018	Italy	Cross sectional study	Dietary polyphenols	1572 adults who participated in the Mediterranean Healthy Easting and Lifestyle and	Center for Epidemiologic Studies Depression Scale (CESD)	Food frequency questionnaire	Higher dietary flavonoid intake may be inversely associated with depressive symptoms. (-*P* for trend <0.001) Dietary intake of phenolic acid (*OR* = 0.64, 95% CI: 0.44, 0.93), flavanones (*OR* =

					Aging (MEAL) Study			0.54, 95% CI: 0.32, 0.91), and anthocyanins (*OR* = 0.61, 95% CI: 0.42, 0.89) showed significant inverse association with depressive symptoms, when comparing the highest with the lowest quartile.
Mofrad et al. [297]	2019	Iran	Cross sectional study	Dietary phytochemicals	488 women aged 20-50yrs	Depression, anxiety, stress scale (DASS)	Food frequency questionnaire	Higher consumption of dietary phytochemicals is associated with a decrease in depressive symptoms (*OR*: 0.22; 95% CI: 0.12–0.38; -*P* = <0.001)

Table 3. Characteristics of included articles

Author	Sex			Age					Disease	Polyphenols								
Experimental	**M**	**F**	**B**	**Young adult**	**Adult**	**Pregnant or post-partum**	**Meno-pause**	**Post-menopausal or elderly**	**Disease state**	**Soy**	**Citrus**	**Resveratrol**	**Cocoa**	**Nut**	**Legume**	**Herb and spice**	**Coffee**	**Tea**	**All poly-phenols**
Sathyapalan et al. [274]			X						X				X						
Bergman et al. [269]			X		X				X							X			
Nina Estrella et al. [286]		X			X		X			X									
Atteritano et al. [275]		X						X	X	X									
Lopresti et al. [270]			X		X				X							X			
Sanmukhani et al. [271]			X		X				X							X			
Esmaily et al. [277]			X		X				X							X			
Panahi et al. [272]			X		X				X							X			
Yu et al. [273]	X				X				X							X			
Ibero-Baraibar et al. [276]			X		X				X				X						

Pribis [296]			X	X													X						
Hirose et al. [288]		X			X			X				X											
Mirghafourvand et al. [295]		X			X		X						X										
Kamalifard et al. [293]		X			X			X					X										
Davinelli et al. [287]		X			X			X				X		X									
Kazemian et al. [280]			X		X						X									X			
Chang et al. [294]		X					X													X			

Author	**Sex**		**Age**						**Disease**	**Polyphenols**									
Observational	**M**	**F**	**B**	**Young adult**	**Adult**	**Pregnant or postpartum**	**Menopause**	**Post-menopausal or elderly**	**Disease state**	**Soy**	**Citrus**	**Resveratrol**	**Cocoa**	**Nut**	**Legume**	**Herb and spice**	**Coffee**	**Tea**	**All poly-phenols**
Hintikka et al. [299]			X		X													X	
Niu et al. [300]			X					X										X	
Chen et al. [278]		X			X				X									X	

Ruusunen et al. [301]	X			X						X	X	
Li et al. [281]			X	X	X				X			
Lucas et al. [302]		X			X					X		
Feng et al. [303]			X		X						X	
Feng et al. [304]			X		X						X	
Omagari et al. [279]			X	X		X				X		
Pham et al. [305]			X	X						X	X	
Yu et al. [306]			X		X		X					
Li et al. [307]			X		X						X	
Chang et al. [282]		X		X	X							X
Su et al. [290]			X	X				X				
Chan et al. [298]			X		X						X	
Navarro et al. [308]			X	X						X		

Miyake et al. [284]	X		X	X	X	
Yu et al. [291]		X	X		X	
Godos et al. [283]		X	X			X
Mofrad et al. [297]	X		X			X

Key: M = Male , F = Female, B = Both Genders

Table 4. Effect of Polyphenols on Symptoms of Depression

Author	Positive Effect: Statistically Significant	Positive Effect: Not Statistically Significant	Mixed results	No Difference Observed
Experimental:				
Sathyapalan et al. [274]		X		
Bergman et al. [269]		X		
Nina Estrella et al. [286]	X			
Atteritano et al. [275]	X			
Lopresti et al. [270]	X			
Sanmukhani et al. [271]		X		
Esmaily et al. [277]				X
Panahi et al. [272]	X			
Yu et al. [273]	X			
Ibero-Baraibar et al. [276]	X			
Pribis [296]	X*	X		
Hirose et al. [288]	X			
Mirghafourvand et al. [295]				X
Kamalifard et al. [293]	X			
Davinelli et al. [287]	X			
Kazemian et al. [280]	X			
Chang et al. [294]	X			
Observational:				
Hintikka et al. [299]	X			
Niu et al. [300]	X			
Chen et al. [278]	X			
Ruusunen et al. [301]	X			
Li et al. [281]			X	
Lucas et al. [302]	X			
Feng et al. [303]	X			
Feng et al. [304]	X			
Omagari et al. [279]	X			
Pham et al. [305]	X			

Yu et al. [306]	X			
Li et al. [307]	X			
Chang et al. [282]	X			
Su et al. [290]		X		
Chan et al. [298]	X			
Navarro et al. [308]	X			
Miyake et al. [284]	X			
Yu et al. [291]			X	
Godos et al. [283]	X			
Mofrad et al. [297]	X			

Key:

X indicates that the study contains this item.

*Only significant in males

DISCUSSION

This systematic review provides important insights into the role polyphenols play in depression. The cross-sectional and cohort studies reported on represent the polyphenol intake of individuals in a real life setting and estimate the prevalence of depression among low, moderate and high consumers of polyphenols. The majority (*n*=17) of these studies found a statistically significant result[278,279,282-284,297-308] suggesting that a higher polyphenol intake is associated with decreased prevalence of depression. Polyphenol intake was measured via various different food frequency questionnaires and diet history forms. Several challenges exist with these methods such as under or over reporting consumption and measurement error[309] and these factors must be considered when interpreting the results. However, the results from these observational studies provide a strong foundation for suggesting that polyphenols play a role in depression, but they can only infer correlation about disease risk and prevalence.

The seventeen experimental trials included in this systematic review can provide more information about causation in regards to polyphenols exerting a therapeutic benefit for depressive symptoms. These experimental results demonstrate a positive therapeutic benefit for depression with various different polyphenols appearing to reduce depressive symptoms. In contrast to the observational studies which looked at depression risk in healthy individuals, the experimental studies assessed individuals presenting with depressive

symptoms or who were diagnosed with depression prior to the commencement of the intervention. The majority (*n*=9) looked at depressive symptoms[274-277,280,288,294-296] with eight of the studies assessing participants with diagnosed clinical depression[269-273,286,287,293]. Of these studies, several also included anti-depressant use either as the active control or in combination with a polyphenol. These include escitalopram[269,273], venlafaxine[269], fluoxetine[271,286] and sertraline[286]. The studies which used polyphenols in combination with antidepressants found that the anti-depressive effects of the polyphenol/anti-depressant combination was greater when compared to the anti-depressant as a monotherapy [269,271,273,286]. Further investigations into the effects of polyphenols in individuals with clinical depression are needed and should be the focus of future studies in this area.

The findings of this systematic review of polyphenols are in part supported by a recent meta-analysis which highlighted the protective role of adhering to a Mediterranean diet for depression risk[310]. The authors suggest that the protective role of the Mediterranean diet could be multidimensional, encompassing both anti-inflammatory functions and protection from oxidative stress[310,311]. Depression is commonly associated with a subclinical inflammatory status characterised by an increase in pro-inflammatory cytokines and neuronal damage[283] which could be the pathways targeted by this dietary pattern.

The polyphenols that this review has highlighted as being effective include soy isoflavones[275,284,286,288,291,306], tea[278,298-300,303-305,307] and cocoa flavanols[274,276], curcumin[270,272,273] and coffee hydroxycinnamic acid[279,301,302,305,308], walnut flavonols[290,296], citrus flavanones[293] and the stilbene resveratrol[287]. Polyphenols are naturally produced plant compounds which form part of the plants defence mechanisms protecting it from pathogens and ultraviolet radiation[264]. Several animal studies have demonstrated that polyphenols reduce depression like behaviour in rodents[263]. Studies have suggested an interaction between polyphenols and monoamine oxidase (MAO), an enzyme utilised in the catabolism of monoamines thus reducing the breakdown of monoaminergic neurotransmitters, and increasing serotonin and dopamine levels[264]. Another possible mechanism for how polyphenols exert their beneficial effects on mental health include their anti-inflammatory properties via inhibition of proinflammatory cytokines, free radical scavenging and antioxidant activity as well as neuroprotective properties[312].

However, the antioxidant activity, bioavailability and enzyme and cell-receptor interactions vary greatly depending on the chemical structure of different polyphenols[265]. The structure of polyphenols effects the rate and extent of intestinal absorption which in turn, effects the metabolites circulating in the plasma[265]. In addition, the polyphenols which are the most common in the diet may not necessarily be the most active due to poor intestinal absorption or from high metabolism and excretion from the body[313]. Studies suggest that the majority of polyphenols are not actually absorbed through the intestinal barrier, but are metabolised by colonic microflora further down the digestive tract[265]. Research even suggests that metabolism pathways and metabolites of polyphenols may be one of the responsible characteristics for their therapeutic effects[313]. A recent review found that gallic acid and isoflavones have the best absorption rates with proanthocyanins displaying the poorest absorption[314]. The differences in bioavailability and absorption rates of various polyphenols is an important limitation of this review and should be considered when interpreting the results.

Several studies have demonstrated that the absorption rate of curcumin is relatively poor[315-317] and the inclusion of piperine in order to enhance absorption is often recommended[317]. Of the six studies included in this review which tested curcumin, three included an absorption enhancer[269,272,277] and three did not[270,271,273], which may have affected the results. All six studies were randomized clinical trials, with three displaying statistically significant results [270,272,273]. More studies on the therapeutic use of curcumin for depression are needed before firm conclusions can be drawn. Other promising polyphenols include those from tea and coffee. Tea and coffee are two of the most commonly consumed beverages worldwide[318] and act as a major source of total dietary polyphenol intake[265]. All of the twelve studies on tea and coffee included in this review were observational studies. Randomised control trials are needed to determine if a cause and effect relationship also exists for these polyphenols.

A common theme present throughout several of the studies is the use of isoflavones for women, either during menopause or in postmenopausal and elderly women. Isoflavones are flavonoids abundant in legumes which are able to influence hormone levels by binding to some estrogen receptors and are thus referred to as phytoestrogens[288]. It has been suggested that isoflavones may alleviate the symptoms of depression which commonly accompany menopause by modulating the dramatic fluctuations in ovarian hormones which

occurs during this period[284]. This potential mechanism of action suggests that isoflavones may only be effective in this specific demographic.

This hypothesis is further supported by the study by Li et al which found mixed results when comparing the results between men, women and menopausal status[281]. The researchers found that in premenopausal women consumption of legumes was associated with an increased risk of depression. However, moderate consumption was associated with a lower risk of depression among perimenopausal women. No significant association was found among men and postmenopausal women[281]. Together, these finding support the theory that isoflavones may exert their beneficial effect for depression by acting as phytoestrogens and therefore may only be appropriate for use in specific population groups.

This review has limitations of its own which need to be acknowledged. The initial search resulted in a large number of very diverse studies. Refinement of the inclusion and exclusion criteria allowed for a more focused review, however, the large exclusion criteria may limit the applicability of this review. The limited number of studies per polyphenol intervention is another key limitation of this review, which may have impacted the overall findings and conclusions drawn from this review. Given the heterogeneous mix of studies included in this review, no cumulative statistical meta-analysis was conducted. This was due to the large diversity of polyphenols tested and variety of depression scales used. The lack of reported data on effect sizes is another important limitation of this review which effects both the meaningfulness and practical importance of these results. A narrative synthesis of the results has been provided which comes with a risk of interpretation bias from the authors. Only published trials available on the preselected databases were available to be reviewed, which may have skewed the findings.

The review also highlighted a lack of research assessing polyphenols for depression in both men and young adults. Emerging research is beginning to highlight differences in which men and women express symptoms of depression, however, it still remains unclear if these differences affect treatment outcomes[77]. Studies in young adults are also needed. Over 75% of mental health problems occur before the age of 25[319]. According to the Australian Bureau of Statistics (ABS) National Survey of Mental Health and Wellbeing: Summary of Results 2007, younger people were more likely to have a mental disorder than older people[320]. The lack on

studies on young adults and men included in this review limits the relevance of these finding to a broader audience.

CONCLUSION

This was the first systematic literature review to assess the effects of polyphenols on the symptoms of depression. The review has identified a strong foundation for suggesting that polyphenols do play an important role in the disorder. The inclusion of both observational and experimental designs has allowed for a comprehensive synthesis of both depression prevalence as well as intention to treat analysis. There appears to be a protective role of consuming higher amounts of polyphenols in reducing depression risk across several populations. In addition to the reduced prevalence, there also appears to be a therapeutic benefit of consuming certain polyphenols in reducing depressive symptoms. In the case of isoflavones this could be due to their phytoestrogen effect. Of the polyphenols included in this review, coffee and curcumin, soy isoflavones, tea and cocoa flavanols, walnut flavonols, citrus flavanones and the stilbene resveratrol show the most promise and would be good candidates for future research. The review also identified that further research is required to investigate the role of polyphenols for depression in men and young adults. Additional studies are needed to confirm these finding.

ACKNOWLEDGMENTS

The authors' contributions were as follows: JB, DS, and JS designed the research question and developed the search terms; JB conducted the literature search, analysed the data and drafted the manuscript with edits from DS and JS. All authors read and approved the final manuscript. JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist.

3.3 CHAPTER SUMMARY

This literature review highlights the important role of polyphenols in depression. Polyphenols are found in richly coloured fruits and vegetables, nuts, legumes, herbs and spices. These foods constitute the bulk of the Mediterranean diet. Thereby adding weight to the pool of evidence suggesting that polyphenols represent a significant mechanism of action for the efficacy of Mediterranean diet for improving depression.

4. CHAPTER 4: The Men's Diet and Depression Survey (the MENDDS study)

4.1 PREFACE

The literature review presented in the previous chapter highlights a number of important issues. Firstly, that there appears to be a protective role of consuming higher amounts of polyphenols in reducing depression risk. Secondly, that there also appears to be a therapeutic benefit of consuming polyphenols in reducing depressive symptoms. In addition, it was apparent that young adults and men are underrepresented in the literature.

This chapter aims to address this specific demographic of young adults and men by exploring different factors relating to their diet. Firstly, to explore the diet quality of young men with depression and examine the frequency of intake of several pertinent food items. Next, to assess the nutritional knowledge and dietary opinions of young men with depression. Lastly, to examine any associations between certain foods or dietary patterns and severity of symptoms in young men with depression.

In order to explore these factors, an online questionnaire was used to survey 384 young men who had previously been diagnosed with depression. The survey used several questionnaires which have been previously validated in depressed populations. These included the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) and a 26-item validated dietary screener questionnaire (DSQ). This questionnaire was slightly adapted for an Australian population with the word "candy" changed to "sweets and lollies". The nutrition knowledge/food symptom association questions were developed specifically for the MENDDS study.

This chapter includes the accepted manuscript presenting the results which was published in *Nutrition* (IF: 4.0) in July 2020. It is reproduced here with permission from Elsevier.

Bayes, J, Schloss, J, Sibbritt, D, 2020, 'An Investigation into The Diets and Nutritional Knowledge of Young Men with Depression (The "MENDDS" survey).' *Nutrition.* 78: 110946.

Supplementary Materials can be found in the Appendix:

- Figure 1 Participant CONSORT flowchart - Appendix 8
- Table 1 Diet History – Appendix 9
- MENDDS Questionnaire – Appendix 10
- The MENDDS Survey Poster Presentation for the 16th World Congress on Public Health – Appendix 11

The last section of this chapter includes two infographics which were created to aid with translation and dissemination of this research. The first infographic is aimed at educating young men with depression about the impact that diet can have on their depressive symptoms and the second infographic is aimed at health practitioners, providing them with some practical suggestions in the treatment of young men with depression.

4.2 THE MENDDS STUDY

An Investigation into The Diets and Nutritional Knowledge of Young Men with Depression (The "MENDDS" survey).

ABSTRACT

***Background*:** Currently 1 million Australians are living with depression each year, with an average of one in eight men experiencing the disorder. Studies have shown that individual nutrients, fruit and vegetable intake, polyphenols and whole dietary patterns can have a positive impact on depressive symptoms. In particular, the Mediterranean diet has shown promising preliminary findings.

Objectives: To assess the diet quality and knowledge of young men in relation to depressive symptoms.

Design: A cross-sectional online survey collected data from 384 young Australian men aged between 18-25 with diagnosed depression. Pearson's chi-square test was used for ordinal categorical variables.

Results: Dietary intake amongst this demographic was poor. Discretionary foods were consumed 2-3 times per week, including pizza (41%), fried potato such as French fries or hash browns (29%) and chocolate (25%). Roughly half of participants (47%) report never consuming wholegrains or legumes and only 9% consume vegetables twice or more per day. Healthy eating is perceived as both time consuming (82%) and expensive (70%). One third (32%) of participants perceive diet to have a big impact and 29% a slight impact on their mental health with only 5% reporting that diet has no impact on their mental health. However, the majority of participants (84%) believe it is 'important' or 'very important' to eat an overall healthy diet and 77% reported being willing to change their diet if it improved their depression symptoms.

Conclusions: These results highlight the relatively poor diets of this demographic who would greatly benefit from a quality diet such as the Mediterranean diet. The reported willingness to change their diets is encouraging and supports the viability of dietary intervention trials in this demographic. The dietary data presented in this study can be used to develop targeted interventions aimed at improving the diets of depressed young men.

Keywords: Depression; major depressive disorder; diet; Mediterranean diet; young adults; men

INTRODUCTION & BACKGROUND

Currently 1 million Australians are living with depression each year[3]. Depression is one of the most common mental health problems experienced by young people. Approximately 1 in 8 men experience depression each year and at least one third of young people have had an episode of mental illness by the age of 25 years[321]. Additionally, only 13% of young men aged 15-24 seek help for their mental health[322] and mental disorders are the largest contributor to disability in young Australians aged 10-24 and cause more prevalent years lived with disability (PYLD) than any other disorder[323]. Depression also presents a significant economic burden with the cost of productivity loss due to sickness absence being nearly double for a person with mild depression and nearly triple for a person with moderate depression compared to individuals without depression[7]. The annual financial burden placed on

businesses due to depressed workers is estimated just under $8 billion Australian dollars (AUD)[7].

Standard treatments for depression include psychological therapies such as cognitive behavioural therapy (CBT) and pharmaceutical medications[324]. These standard therapies are effective for the many patients, however, treatment resistant depression (TRD) commonly occurs in clinical practice, with up to 60% of patients not achieving adequate response following antidepressant treatment[325]. Additionally, it is common for patients to report one or more side effects from selective serotonin reuptake inhibitor (SSRI) medications, with the most common complains being sexual dysfunction, sleepiness and weight gain[326].

Furthermore, men are less likely to seek out medical care then women[3]. Additionally, men who sought help for depression were likely to engage in self-blame and held a fear of being seen as weak, thus causing many to hide their illness in order to minimise damage to their masculine self-image[71]. This can lead to self-medicating and other negative coping mechanisms which further impact health and quality of life.

The combination of reluctance to seek out standard therapies, high treatment resistance and the numerous reported side effects of standard antidepressant medications demands a need for additional treatment options. Recently, several studies have shown that diet can have a positive impact on the symptoms of depression[193,233,327,328]. Several recent literature reviews have explored diets for mental health including papers on individual nutrients[329-333], fruit and vegetable intake[334,335], polyphenols[336] and whole dietary patterns[230,233,337]. In particular, the Mediterranean diet (MD) has shown some promising preliminary findings[156,239,327].

Gender specific research on dietary patterns consistently shows differences in the food choices and behaviours of men and women[338-340]. Numerous studies have reported that men eat fewer fruits and vegetables and other high-fibre foods, eat fewer low-fat foods, and consume more high sugar drinks and alcohol than women[341]. A study of young adults found that men are more than twice as likely to consume takeaway food twice a week or more compared to women[342], a survey of young adults found that men were significantly less likely to engage in food preparation behaviours compared to women[343] and a survey of undergraduate students found that young men are less likely than young women to believe they need to lose weight or try a weight loss diet[340]. It is clear that several differences exist

in the eating habit between men and women with men generally displaying poorer food choices, however, studies assessing the diet quality of young men in relation to depressive symptoms is lacking.

Understanding the nutrition knowledge of this demographic will be important in developing experimental studies to test dietary interventions. Further, investigating the observations made by young men between certain foods and dietary patterns and their symptoms of depression could provide valuable insights for future research. This project aimed to investigate the diets and nutritional education of young men with depression, specifically the current dietary patterns of young men with depression, the knowledge and attitudes young men with depression have about nutrition, and if young men with depression notice any associations between certain foods and the severity of their symptoms.

METHODOLOGY

Design and Data Collection

The study used a cross-sectional design, collecting data via an online questionnaire. Advertising and recruitment for the survey was via several online social media platforms including Facebook, twitter and LinkedIn. Several mental health service and support organisations such as Gotcha4life and Beyond Blue were invited to share the link on their social media and email lists. The survey was open for 4 months between August and November 2019. The inclusion criteria consisted of young men aged between 18-25 with self-reported general practitioner or psychologist diagnosed depression and living in Australia.

Questionnaire

The questionnaire consisted of 62 items, and included a 26-item validated dietary screener questionnaire (DSQ)[344], the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10)[345], nutrition knowledge and food/symptom association questions. The survey was piloted by three subjects who fit the inclusion criteria, but did not participate in the main study, to assess language clarity, the time required and relevance, with corrections made accordingly.

Ethics

Ethical approval was granted by the University of Technology Sydney (UTS) Human Research and Ethics Committee (HREC) on 2nd August 2019. UTS HREC REF NO. ETH19-3828. Informed

consent was obtained electronically from participants before the commencement of the survey.

Statistical Analysis

Descriptive statistics are reported in the text and tables. Bivariate analyses included Pearson's chi-square test for ordinal categorical variables such as Likert-type items. Statistical analysis was undertaken using STATA v16. To adjust for multiple testing, a Bonferroni correction was conducted, thus results were considered significant if $p < 0.002$.

Sample Size Calculation

Estimates from the *National Health Survey: First results - 2014-15 ABS* suggests the proportion of young men in Australia with depression to be roughly 150,000 individuals. With a 95% confidence interval and width of ± 5% a sample size of 384 is needed.

RESULTS

A total of 384 participants completed the survey. Incomplete survey responses are not included in the results or statistical analysis. These include where the participant opened the survey link but did not proceed to answer any questions or where the participant did not meet the inclusion criteria, for example the participant indicated that they were female, had not been diagnosed with depression by a medical doctor or did not consent to participate. The most common income before tax was less than $10,000 (n=131; 34%) and education level was Year 12 or equivalent (n=193; 50%). Participant demographics are displayed in Table 1.

Depression Scores

All participants indicated that they have been diagnosed with depression by their medical doctor or psychologist. The 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10)[345] was used to measure current depressive symptoms, as participants may be utilising anti-depressive therapies in their current mental health care plan and have improved symptoms. A score of 10 or above is considered depressed with a maximum score of 30. The mean score of the survey participants was 21 (SD = 4.7).

Table 1. Demographic Characteristics of Study Participants

Item	Number of Participants (n=384)	% of Participants
Age (in years)		
18	34	8.9
19	38	9.9
20	58	15.1
21	37	9.6
22	53	13.8
23	53	13.8
24	62	16.1
25	49	12.8
	SD = 2.2	*Mean = 21.7*
Income		
less than $10,000	131	34.2
$10,000-$29,999	114	29.8
$30,000-$40,999	62	16.2
$50,000-$60,999	49	12.8
$70,000-$80,999	18	4.7
$90,000-$109,999	4	1.0
$110,000 or more	5	1.3
Education		
Less than Year 12 or equivalent	42	10.9%
Year 12 or equivalent	193	50.3%
Diploma or Vocational Certificate	71	18.5
Bachelor degree (including honours)	72	18.8
Master's degree	5	1.3%
Doctorate	1	0.3

Nutrition Beliefs

Participants were asked to rate how important they believe it is to eat an overall healthy diet. A "healthy" diet being high in vegetables and fresh foods, low in processed and packaged foods which was outlined to them in the survey. A total of 322 (84%) participants believe is it *important* or *very important* to eat an overall healthy diet When asked to rate how healthy their diets are on a typical day the majority of participants rated their current diets as only 'fair' (n=131).

Half of the participants (50%) think it is *important* to eat a large variety of different foods and when asked how often it is ok to consume "fast" or processed foods the most common response was *once per week* (39%). The majority of participants claim to *rarely (*27%) read the nutrition fact labels on food products. When asked what degree of impact diet has on their personal physical health 51% responded *a large impact* and 26% *a slight impact*. When

asked what degree of impact diet has on their personal mental health 32% responded with *a large impact* and 29% with *a slight impact*.

A total of 70% of participants report that they perceive healthy eating to be expensive and 82% find healthy eating to be time consuming. When asked how likely they would be to change their diets if it improved their depressive symptoms 77% responded *very likely* or *likely* to change it. Table 2 displays these results.

Participants answer to the question "how healthy is your diet on a typical day?" was tested against various dietary components in the FFQ. Participants who rated their diets as healthier tended to eat healthy foods more frequently such as vegetables (p=0.0001) and fruit (p=0.0001) and consume discretionary foods less frequently such as fizzy or sugary drinks (p=0.0001) and chocolate, sweets and lollies (p=0.001).

A positive association for reported diet healthiness (poor, fair and good) was also found between several other variables, including frequency of reading nutrition fact labels (p=0.0001), importance of eating a healthy diet (p=0.0001), importance of eating a variety of foods (p=0.0001), finding healthy eating time consuming (p=0.0001) and the likeliness of changing their diet (p=0.002). A positive association for reported diet importance was found between importance of eating a variety of foods (p=0.0001), how often it is ok to eat processed foods (p=0.0001) and the impact of diet on their mental health (0.0001). These results are displayed in Table 3 and Table 4.

Table 2. Nutrition Beliefs of study participants

Question	**Number of Responses (% of respondents)**				
	Poor	**Fair**	**Good**	**Very Good**	**Excellent**
How healthy is your overall diet on a typical day?[1]	73 (19.0%)	131 (34.1%)	111 (28.9%)	56 (14.6%)	13 (3.4%)
	Never	**Rarely**	**Sometimes**	**Most of the time**	
How often do you read the Nutrition Facts labels?	94 (24.5%)	105 (27.3%)	95 (24.7%)	90 (23.4%)	
	Not important	**Low importance**	**Unsure**	**Important**	**Very important**
How important is it to eat an overall healthy diet?[1]	1 (0.3%)	29 (7.6%)	32 (8.3%)	164 (42.7%)	158 (41.1%)
	9 (2.3%)	31 (8.1%)	51 (13.3%)	193 (50.3%)	

How important is it to eat a large variety of different foods?					100 (26.0%)
	<once per month	**2-3/month**	**1/week**	**2-3/week**	**2-3/day**
How often is it ok to eat fast foods/processed foods?	32 (8.3%)	78 (20.3%)	148 (38.5%)	122 (31.8%)	4 (1.0%)
	No impact	**Low impact**	**Unsure**	**Slight impact**	**Big impact**
In your personal experience: What degree of impact does a healthy diet have on **your physical health**?	8 (2.1%)	19 (4.9%)	63 (16.4%)	98 (25.5%)	196 (51.0%)
What degree of impact does a healthy diet have on **your mental health**?	19 (4.9%)	30 (7.8%)	99 (25.8%)	112 (29.2%)	124 (32.3%)
	Yes	**No**			
Do you find: Healthy eating to be expensive?	268 (69.8%)	116 (30.2%)			
Healthy eating to be time-consuming?	313 (81.5%)	71 (18.5%)			
	Very unlikely	**Unlikely**	**Unsure**	**Likely**	**Very likely**
How likely would you be to change your diet if it improved your symptoms of depression?	7 (1.8%)	19 (4.9%)	61 (15.9%)	161 (41.9%)	136 (35.4%)

[1] Healthy: high in vegetables and fresh foods, low in processed and packaged foods

Table 3. Association Between Participants' Belief of Diet Healthiness and Diet

	How Healthy is Your Diet?						**p-value**
	Poor		Fair		Good		
	n	(e)	n	(e)	n	(e)	
Vegetable Consumption							
1/week or less	46	(24)	49	(43)	32	(60)	0.0001
2-6 times/week	25	(35)	71	(63)	89	(87)	
1/day or more	2	(14)	11	(25)	59	(34)	
Fruit Consumption							
1/week or less	55	(33)	67	(59)	51	(81)	0.0001
2-6 times/week	16	(25)	44	(44)	69	(61)	
1/day or more	2	(16)	20	(28)	60	(38)	
Sugary/fizzy drinks							
4/week or more	33	(18)	43	(33)	20	(45)	0.0001
1-3/week	23	(24)	40	(43)	63	(59)	
3/month or less	17	(31)	48	(55)	97	(76)	
Chocolate and Sweets/lollies							

4/week or more	21	(19)	46	(33)	31	(46)	
1-3/week	30	(34)	62	(60)	84	(83)	0.001
3/month or less	22	(21)	23	(38)	65	(52)	
Reading of Nutrition Fact Labels							
Rarely/Never	56	(38)	81	(68)	62	(93)	
Sometimes	13	(18)	32	(33)	51	(45)	0.0001
Most of the time	4	(17)	18	(30)	67	(42)	
Healthy Diet Importance							
Not Important	9	(6)	17	(10)	4	(14)	
Unsure	13	(6)	9	(11)	9	(15)	0.0001
Important	51	(61)	105	(110)	167	(151)	
Importance to Eat a Variety of Foods							
Not Important	13	(8)	15	(14)	12	(19)	
Unsure	14	(10)	26	(17)	9	(24)	0.0001
Important	46	(56)	88	(100)	159	(138)	
How Often Can You Eat Processed Foods							
2-3 times/week or more	23	(24)	57	(43)	46	(59)	0.015
Once Per Week	26	(28)	46	(51)	76	(69)	
2-3 times/month or less	24	(21)	28	(38)	58	(52)	
Impact of Diet on Mental Health							
No Impact	9	(9)	20	(17)	20	(23)	
Unsure	29	(19)	36	(34)	34	(46)	0.005
An Impact	35	(45)	75	(81)	126	(111)	
Is Healthy Eating Expensive							
No	20	(22)	30	(40)	66	(54)	0.028
Yes	53	(51)	101	(91)	114	(126)	
Is Healthy Eating Time Consuming							
No	7	(14)	15	(24)	49	(33)	0.0001
Yes	66	(60)	116	(107)	131	(147)	
Likeliness to Change Diet							
Unlikely	11	(5)	6	(9)	8	(12)	
Unsure	15	(12)	25	(21)	21	(29)	0.002
Likely	47	(57)	100	(102)	151	(140)	
Depression Score Severity							
Mild	6	(12)	22	(22)	35	(30)	
Moderate	27	(35)	69	(63)	89	(87)	0.003
High	40	(26)	40	(46)	56	(64)	
Yearly Income							
$29 999 or less	54	(47)	81	(83	110	(115)	
$30 000 - $69 999	14	(21)	37	(38	60	(52)	0.166
$70 000 or more	5	(5)	12	(9)	10	(13)	
Education Level							
Year 12 or less	52	(45)	78	(80)	105	(110)	

Diploma or Vocational Certificate	9	(14)	26	(24)	36	(33)	0.398
Bachelor Degree or above	12	(15)	27	(27)	39	(37)	

Pearson's chi-square test. Results considered significant when p=<0.0002
n = number of observations
(e) = expected number of observations under chi-square distribution

Table 4 Associations Between Participants' Belief of Diet Importance and other Nutrition Beliefs

	Healthy Diet Importance						p-value
	Not Important		Unsure		Important		
	n	(e)	n	(e)	n	(e)	
Reading of Nutrition Fact Labels							
Rarely/Never	22	(16)	23	(16)	154	(167)	0.007
Sometimes	4	(8)	5	(8)	87	(80)	
Most of the time	4	(7)	3	(7)	82	(75)	
Importance to Eat a Variety of Foods							
Not Important	21	(3)	6	(3)	13	(34)	0.0001
Unsure	4	(4)	13	(4)	34	(43)	
Important	5	(23)	12	(24)	276	(247)	
How Often Can You Eat Processed Foods							
2-3 time/week or more	20	(10)	13	(10)	93	(106)	0.0001
Once Per Week	9	(12)	13	(12)	126	(125)	
2-3 times/month or less	1	(9)	5	(9)	104	(93)	
Impact of Diet on Mental Health							
No Impact	11	(4)	8	(4)	30	(41)	0.0001
Unsure	10	(8)	13	(8)	76	(83)	
An Impact	9	(18)	10	(19)	217	(199)	
Is Healthy Eating Expensive							
No	7	(9)	7	(9)	102	(98)	0.404
Yes	23	(21)	24	(22)	221	(225)	
Is Healthy Eating Time Consuming							
No	3	(6)	2	(6)	66	(60)	0.073
Yes	27	(24)	29	(25)	257	(263)	
Likeliness to Change Diet							
Unlikely	5	(2)	3	(2)	17	(21)	0.093
Unsure	6	(5)	3	(5)	52	(51)	
Likely	19	(23)	25	(24)	254	(251)	
Yearly Income							
$29 999 or less	23	(19)	23	(20)	199	(206)	0.361
$30 000 - $69 999	6	(9)	6	(9)	99	(93)	

$70 000 or more	1	(2)	2	(2)	24	(23)	
Education Level							
Year 12 or less	19	(18)	23	(19)	193	(198)	0.631
Diploma or Vocational Certificate	5	(6)	4	(6)	62	(60)	
Bachelor Degree or above	6	(6)	4	(6)	68	(66)	
	Likeliness To Change Diet						**P-value**
Yearly Income							
$29 999 or less	15	(16)	49	(39)	181	(190)	0.018
$30 000 - $69 999	6	(7)	9	(18)	96	(86)	
$70 000 or more	4	(2)	3	(4)	20	(21)	

Pearson's chi-square test. Results considered significant when p=<0.0002
n = number of observations
(e) = expected number of observations under chi-square distribution

Food/symptom observations

Immediately after consuming high fat processed foods 22% noticed an *improvement* while 21% noticed a *worsening* of symptoms. Several hours after consuming these foods, roughly a third of participants (34%) noticed a *worsening of symptoms* and only 4% noticed an *improvement.* Immediately after consuming high sugar processed foods 37% noticed an *improvement* in symptoms while 15% noticed a *worsening* of symptoms. Several hours after consuming these foods 33% noticed a *worsening* of symptoms and only 6% noticed an *improvement.* Approximately a third of participants (34%) noticed an *improvement of symptoms* after consuming fruits and vegetables. Additionally, around two thirds of participants notice negative effects of alcohol on their depressive symptoms with 34% indicating a *worsening of symptoms* and 32% indicating a *significant worsening of symptoms* several hours after consuming alcohol (Table 5).

Table 5. Participant Food/Symptom Observation

Question	**Participant observations**				
	Significant worsening of symptoms	**Worsening of symptoms**	**No difference in symptoms**	**Improvement of symptoms**	**Significant improvement of symptoms**
Instant differences: When you eat high fat processed foods (Cheese burgers/pizza/fried chicken) do you notice any instant differences in your depression symptoms?	1 (0.3%)	79 (20.6%)	203 (52.9%)	85 (22.1%)	16 (4.2%)
Delayed differences: When you eat high fat processed foods (Cheese burgers/pizza/fried chicken) do you notice any	10 (2.6%)	132 (34.4%)	224 (58.3%)	17 (4.4%)	1 (0.3%)

delayed differences (several hours later) in your depression symptoms?					
Instant differences: When you eat high sugar processed foods (chocolate/cookies/cake) do you notice any instant differences in your depression symptoms?	13 (3.4%)	57 (14.8%)	148 (38.5%)	141 (36.7%)	25 (6.5%)
Delayed differences: When you eat high sugar processed foods (chocolate/cookies/cake) do you notice any delayed differences (several hours later) in your depression symptoms?	28 (7.3%)	125 (32.6%)	204 (53.1%)	23 (6.0%)	4 (1.0%)
Instant differences: When you eat fruits and vegetables do you notice any instant differences in your depression symptoms?	0 (0%)	2 (0.5%)	241 (62.8%)	131 (34.1%)	10 (2.6%)
Delayed differences: When you eat fruits and vegetables do you notice any delayed differences (several hours later) in your depression symptoms?	0 (0%)	2 (0.5%)	233 (60.7%)	132 (34.4%)	17 (4.4%)
Instant differences: When you consume alcohol do you notice any instant differences in your depression symptoms?	47 (12.2%)	72 (18.8%)	79 (20.6%)	188 (30.7%)	68 (17.7%)
Delayed differences: When you consume alcohol do you notice any delayed differences (several hours later) in your depression symptoms?	121 (31.5%)	130 (33.9%)	104 (27.1%)	22 (5.7%)	7 (1.8%)

Dietary Analysis

The dietary analysis used a validated 26-item validated dietary screener questionnaire (DSQ)[344] adapted for an Australian audience. In answering questionnaire items, participants were asked to reflect on foods and drinks they consumed in the last 30 days.

Wholegrain consumption was low with 47% reporting to consume cooked wholegrains 'never or once per month' and only 2% consuming cooked whole grains once or more per day. Whole grain bread consumption once or more per day was reported by 12% of participants. Breakfast cereal consumption was low with 41% reporting to never eat cereal, while daily cereal consumption was reported by 12% of participants.

Participants reported low consumption for fruit and vegetables. Participants reported only consuming fruit and vegetables 2-3 times per week (20% and 29% respectively). Only 11% of participants reported consuming fruit twice or more per day and only 9% consume vegetables twice or more per day.

For protein, the participants reported consuming red meat 2-3 times per week (35%), followed by 23% consuming red meat 4-6 times per week, while 8% indicated that they never eat red meat. When asked about processed meats 23% of participants reported consuming these foods 2-3 times per week and 22% consumed these foods once per week, with 21% (n=79) reporting never or once per month.
Bean consumption was low with the majority stating to eat beans 'never or once per month' (47%). Only 3% consumed beans 4-6 times per week.

Participants reported consuming most discretionary foods 2-3 times per week such as pizza (41%), fried potato such as French fries or hash browns (29%) and chocolate (25%). The full Diet History can be found in Supplementary Table 1.

DISCUSSION

This research has presented a number of interesting results for this population group. Firstly, the majority of participants find that diet has a big impact on their mental health. The results also show that the participants who rate their diets as poor notice a bigger impact of diet on mental health. This supports the findings of several systematic reviews which show that diet effects depression[229,233,334].

When asked about specific foods, participants had varied responses. When considering the instant effects of high sugar processed foods on their mental health some participants notice an improvement while others notice a worsening of symptoms. Several biological mechanisms may explain these effects. Mood may be worsened in some people due to the increased inflammatory response from high carbohydrate intake while mood may be temporarily improved in others due to the addiction-like effects of sugar affecting dopaminergic neurotransmission[346]. The delayed effect of high sugar processed foods was more commonly reported to worsen symptoms than to improve them, suggesting that the initial improvement is only temporary. Several theories have been postulated to explain the

link between high sugar intake and low mood including the effect on brain derived neurotrophic factor (BDNF), inflammation and insulin response[346].

A similar finding was presented when comparing the instant verses delayed effects of alcohol on depressive symptoms. Many participants notice an improvement instantly after consuming alcohol, however two thirds notice a worsening of symptoms several hours after consuming alcohol. Epidemiological studies indicate that heavy alcohol use and depression are strongly linked, however the responsible mechanism remains unclear[347]. The use of alcohol to relieve affective symptoms is common among individuals with mood disorders, however it is associated with substantial psychiatric comorbidity[348]. Studies examining male coping behaviours regularly report alcohol being used to "numb" or "escape from" emotional distress[349]. However alcohol abuse is also a major risk factor for suicide[350]. Educational campaigns which directly target young adults with depression to reduce alcohol consumption as part of their mental health care plan could be useful in improving depression outcomes.

Further, the majority of respondents think it is *important* or *very important* to eat an overall healthy diet, however a large proportion only rate their diet as either fair or poor, with only 15% describing their diets as *very good.* This shows an important disconnect between knowing and doing. It has been suggested that individuals are prevented from acting on their positive intentions by the so-called obesogenic environment. The obesogenic environment is characterized by the high availability and accessibility of palatable energy-dense foods, coupled with the ability to avoid physical activity[351]. The participants who rated the importance of a healthy diet higher were more likely to have a healthier diet and read nutrition fact labels indicating that an education strategy that focuses more on the *importance* of healthy eating rather than the individual components could be a useful strategy.

Other possible barriers to diet change included time and money. The majority of respondents perceived healthy eating to be expensive and time consuming. This was more likely to be reported in the participants who also rated their current diets poorly. This belief that healthy eating is expensive and time consuming supports the findings of a similar study which investigated the perceived barriers to healthy eating in middle aged Australian men[352]. The authors suggest that finding more time will not be the solution and that the focus should be on educating people on how to prioritise their time instead. Health professionals should

focus on developing strategies in which food preparation and cooking fit into the context of daily living[352].

In regards to cost, our results agree with similar findings which report a public perception that healthy foods are expensive[353-355]. In Australia data suggests that the cost of healthy food is still a particular burden to welfare dependant families[356]. Further, it has been reported that a high proportion in Australia will spend their money on discretionary items with around 14% spent on alcoholic drinks, and 15% on take-away foods[357]. Our survey also reported a high intake of discretionary and fast food consumption among depressed young men. Providing information around low cost healthy food options could be a key strategy when promoting healthy eating to this demographic.

It is therefore encouraging that despite these perceived challenges the majority of participants reported that they would be likely to change their diet if it improved their depressive symptoms. The current dietary patterns of this demographic were relatively poor with the majority of participants reporting that they only consume fruits and vegetables 2-3 times per week. Almost half report never or rarely consuming beans and over half never or rarely eat cooked wholegrains such as brown rice. Fruits, vegetables, wholegrains and beans are staple foods included in a Mediterranean dietary pattern which has frequently been linked to reduced depression risk[240]. Participants intake of discretionary foods were high with participants reporting consuming pizza, chocolate and fried potato such as French fries and hash browns 2-3 times per week. Unhealthy 'Western' dietary patterns high in fast foods, processed meats, salty snacks, sweets and desserts has been linked to increased depression risk[358].

Limitations

This survey has limitations which must be acknowledged. Firstly, the study sample may not be representative of all young adult males with diagnosed depression in Australia, in particular, only young men who have access to the internet and social media accounts were able to take part, so caution is needed when generalising our findings to the wider population. In addition, the information reported by participants is self-reported. Hence, there may be biases in our study data caused by social desirability bias as well as recall bias and measurement error. However, when comparing reported diet healthiness and the results from the FFQ, participants responses appeared to be fairly accurate; with the

participants who describe their usual diets as good consuming healthy foods such as fruits and vegetables more frequently and discretionary foods such as chocolate and sugary drinks less frequently.

CONCLUSION

Understanding the nutrition opinions and beliefs of young men with depression is crucial for developing experimental trials testing dietary interventions in this population. Additionally, examining the current diets of this demographic highlights areas for clinicians, health promotion policy and researchers to focus. The results of this survey have demonstrated that dietary intake amongst this demographic was poor, while healthy eating is perceived as both time consuming and expensive. More research is needed to fully understand the implications of cost and time restraints on this demographic in order to overcome these barriers. The majority of participants perceive diet to have a big impact on their mental health and would be willing to change their diet if it improved their depression symptoms. The willingness reported to change their diets is encouraging and supports the viability of dietary intervention trials in this demographic.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

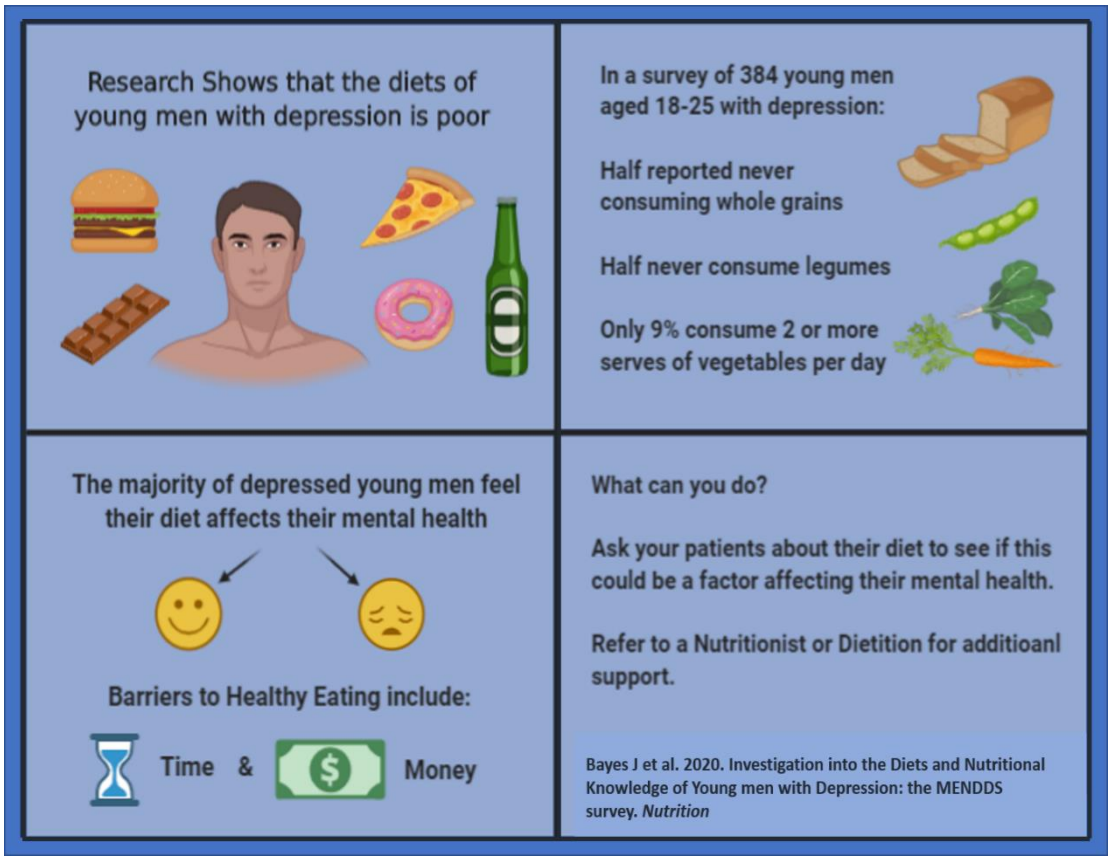
JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship. All authors contributed to the design of the questionnaire. JB was responsible for collecting data, statistical analysis and drafting the manuscript with edits from JS and DS. All authors have read and approved the final manuscript.

4.3 TRANSLATION AND DISSEMINATION

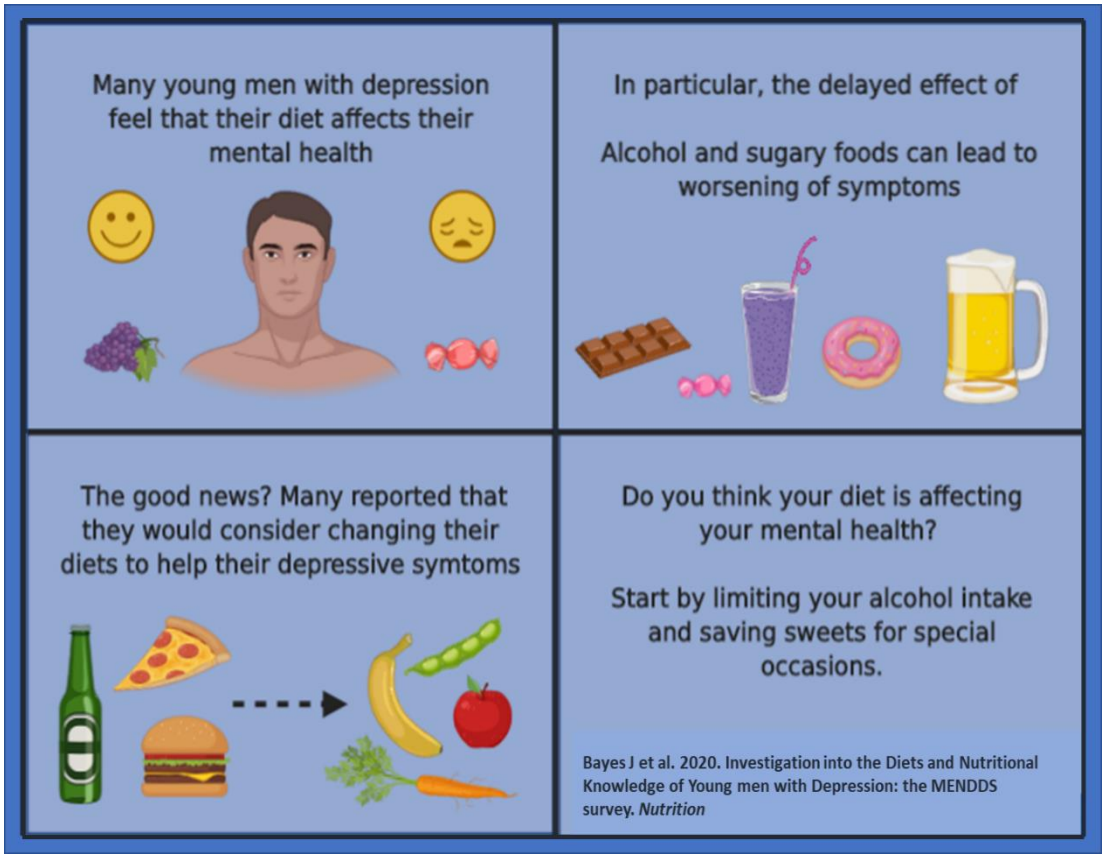
In addition to the peer reviewed publication above, a poster was presented at *16th World Congress on Public Health,* 12-17 October 2020, Rome, Italy, which can be found at Appendix 6. This poster was presented virtually in October 2020 and the abstract published in the *European Journal of Public Health* (Vol 30, Issue Supplement 5, September 2020. Supplement: 16th World Congress on Public Health 2020 Public Health for the future of humanity: analysis, advocacy and action)

Infographics were also created for the translation of our findings to important stakeholders; health practitioners and depressed young men. Infographic 1 is aimed at educating health practitioners about the diets of depressed young men. Infographic 2 is aimed at creating awareness of the link between diet and depression for young men with depression.

Infographic 1 for Health Professionals



Infographic 2 for Depressed Young Men



A video was also created to summarise the key findings from the MENDDS study and introduce the next research project. The video was created via VideoScribe and can be found here: https://sho.co/1DKPE

4.4 CHAPTER SUMMARY

This chapter explored the diets, nutritional knowledge, and opinions of young men with depression. It addressed the following research questions: 1) What are the current dietary patterns of young men with depression? 2) What knowledge and attitudes do young men with depression have about nutrition? And 3) Do young men with depression notice any associations between certain foods and the severity of their symptoms? The results show that the diets of young men are poor, they do feel as though their diet affects their mental health and they notice associations between some foods and their symptoms of depression.

5. CHAPTER 5: A Mediterranean Diet for Men with Depression (AMMEND) Protocol

5.1 PREFACE

The previous chapter outlined the results from the MENDDS questionnaire. It highlighted a number of important issues. Firstly, that young men view healthy eating as both time consuming and expensive. Secondly that the vast majority think that their diets impact their mental health and finally that despite young men reporting relatively poor diets, they would be willing to change it if it could help their depressive symptoms. These results suggest that an intervention study in this demographic may be both worthwhile and viable and also informed the methodology of the next project, a randomised control trial.

The AMMEND trial is a 3-month randomised control trial testing the effect of a Mediterranean diet on the symptoms of depression in young men. The trial is registered with Australia and New Zealand Clinical Trials Registry (ANZCTR) Trial Id: ACTRN12619001545156 and has also been registered with the World Health Organization (WHO) International Clinical Trials Registry Platform's (ICTRP) Universal Trial Number: U1111-1242-5215. It received ethics approval form UTS in February 2020 (HREC REF NO. ETH19-4413).

Lived experience data was collected from 20 young men with depression which assisted in the design of the AMMEND trial. Participants interested in volunteering their time for the 10-minute interview either registered their interest via the contact form at the end of the MENDDS questionnaire or via the contact page on the MENDDS study website. The purpose of the interview was to gain insights into how to make the trial easy and successful. The proposed study design, aims and objectives were explained to the men as well as a description of the MD and befriending intervention.

The men were asked the following questions: 1) Do you think that you could follow any specific diet for three months and why or why not? 2) What time frame do you think you could stick to a Mediterranean diet for? 3) What aspects of following a Mediterranean diet do you think would be most challenging and why? 4) Would you find recipes helpful?

Why/why not? 5) Would you find weekly meal plans and suggestions helpful? Why/why not? 6) Can you think of anything which would make the diet easier to follow? 7) Do the number of meetings seem reasonable to you? And 8) Are there any last comments you feel would help us in conducting this trial? The responses of the young men helped guide planning and execution of the AMMEND trial.

Within the first few weeks of recruitment for the AMMEND trial the global COVID-19 pandemic escalated within Australia. All research activities were ordered to stop, and a contingency plan was put in place. Amendments were made to the original research protocol which included moving from face-to-face appointments to telehealth. Additionally, all anthropometric measurements were removed, and recruitment was opened to all of Australia, instead of just Melbourne. All of these amendments were approved by the UTS ethics committee in April 2020.

This chapter presents the accepted manuscript outlining the protocol for the AMMEND trial which has been published in *The British Journal of Nutrition* (IF:3.7) in November 2020. It is reproduced here with permission from Cambridge University Press.

> Bayes, J, Schloss, J, Sibbritt, D, 2020. 'A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study): A study protocol.' *British Journal of Nutrition*. 126(5), 730-737.

Supplementary Materials can be found in the Appendix:

- Figure 1 Participant CONSORT flowchart - Appendix 12

5.2 THE AMMEND STUDY PROTOCOL

A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study): A study protocol

ABSTRACT

Depression affects approximately 350 million people worldwide. Evidence suggests that diet plays an important role with the Mediterranean diet displaying promising preliminary results. Currently, most of the research is conducted on women and older adults however, the majority of mental illnesses occur before the age of 25. Men are less likely to seek help than women with only 13% of young men aged 15-24 seeking help for their mental health. Young men are hugely underrepresented in the current research which poses a significant issue. A 12-week randomised control trial will be conducted to examine the effect of a Mediterranean diet on the symptoms of depression in young men aged 18-25. Participants will be randomised to either follow a Mediterranean diet or receive the inactive control therapy befriending. Participants will attend 3 appointments at baseline, week 6 and week 12. The main outcome will be changes to the Beck depression Inventory score. This research aims to answer the question of whether diet can be used effectively in this population. This will be the first trial to examine the effect of a Mediterranean diet on the symptoms of depression in young men. This trial will help fill a significant research gap, contribute to the growing field of nutritional psychiatry, guide future research and inform advice given by clinicians to this specific demographic.

Keywords: Young adults; Men; Mediterranean diet; depression; major depressive disorder;

INTRODUCTION

The following protocol paper has been written in accordance with the SPIRIT guidelines[359].

BACKGROUND

Depression is a common mental health disorder affecting approximately 350 million people worldwide[2]. It is the leading cause of disability globally and in Australia it's estimated that 45 per cent of people will experience a mental health condition in their lifetime[3]. It costs an estimated $AUD 8 billion in national employer costs annually due to loss of productivity and

sick leave. A recent report suggested that even sub-clinical levels of depression represent a significant burden to the economy[7]. The standard treatment options include antidepressant medication and talking therapies[324], and although these options help many people, they may be expensive, sometimes ineffective and the medications have been found to be associated with a number of side effects[326]. New evidence-based treatment options are urgently needed to assist with this growing health crisis.

To date, evidence suggests that diet may be a good place to start. A growing body of epidemiological evidence suggests that diet plays an important role in depression[156]. Studies have looked at individual nutrients such as vitamins[329,331,333] and polyphenols[336], specific foods such as fruits and vegetables[334] and whole dietary patterns[233] such as traditional diets and modern diets looking at the impact these have on depression. So far, these studies have shown that healthier diets, high in vegetables and low in processed foods are linked to better depression outcomes[230]. Currently, the diet with the most evidence is the Mediterranean diet (MD) which has also been the focus of the first intervention studies in this area. The SMILES study[327] and the HELFIMED study[240] both showed that a Mediterranean dietary pattern can help reduce depressive symptoms in adults with depression.

In these intervention trials the average age of participants was 40 and 44 and both studies recruited more women than men. However, three quarters of mental illnesses occur before the age of 24[319] and common mental health disorders, such as major depressive disorder, are commonly episodic and risk re-emergence during young adulthood. Additionally, the disability-adjusted life years (DALYs) and rates of mortality due to mental health are also highest among emerging adults (aged 18-29 years) compared to any other age-group[6], thus prevention or early treatment of mental disorders should focus on this demographic.

A recent systematic literature review assessed the associations between diet quality and common mental disorders in emerging adulthood (EA)[360]. The authors highlight that EA presents a particularly risky period for unhealthy dietary behaviour and poor mental health due to significant transitions between home, employment and education[360]. Additionally, EA represents a transfer of agency where many young people become responsible for their meals and eating habits for the first time[360]. Therefore, dietary interventions aimed during this critical period warrant attention. Research has also found that men are less likely than women to seek help for their depression[3] with only 13% of young men aged 15-24 seeking

help for their mental health[322]. Interventions targeting young adults, and young men specifically, is therefore of high importance. A healthy MD may provide a tangible goal for new mental health treatment and prevention in this demographic.

Studies consistently show differences in the food choices and behaviours of men and women[338-340]. Men tend to eat fewer fruits and vegetables and consume more high sugar drinks and alcohol than women[341]. A survey of young adults found that men were significantly less likely to engage in food preparation behaviours compared to women[343]. With another study of young adults finding that men are more than twice as likely to consume takeaway food twice a week or more compared to women[342]. A recent study explored the diets, nutritional knowledge and opinions of 384 young men aged 18-25 with depression[361]. Two thirds of participants stated that they notice an impact of diet on their mental health and 77% reported that they would be likely to change their diet if it helped their depression[361].

Clearly, there are several differences in the eating habits of men and women, with men generally displaying poorer food choices. When considering both the poorer diet quality and reduced help seeking behaviour of young men, coupled with the need to target early depression treatments on youth, more studies in this demographic would be beneficial. Thus, young men with depression and poor dietary habits are an ideal group to test the effect of a healthy MD.

METHODS

RESEARCH AIMS AND OBJECTIVES

The primary outcome of this study is to evaluate the effect of a MD on young men with major depressive disorder. The study aims to determine if the effect of the MD differs significantly from that of the control group by comparing the 21-item Becks Depression Inventory (BDI-II)[362] results between the intervention and control group. Secondary aims are to see if there is a difference in outcome measures between participants who display a high versus low diet compliance. This will be achieved by comparing the depression scores between participants who have a high MD compliance score to those who have a low MD compliance score on an adapted validated 15 item MD adherence questionnaire. Lastly, the study aims to understand the attitudes, perceived benefits and challenges of continuing to follow a MD by young men with depression by uncovering the perceived challenges and benefits to following a MD in the End of Project Evaluation Survey.

STUDY DESIGN

Data was collected from 20 young men aged 18-25 diagnosed with depression which helped inform the design of this study. The men completed a short qualitative questionnaire consisting of 7 open ended questions which invited them to share their opinions on the methodology of this trial. The following research protocol incorporates that data and informed several aspects of the trial including, dietary support documents, number and duration of follow up visits and diet recording and reporting methods.

The AMMEND study is a 12-week randomised control trial testing the effect of a MD on the symptoms of depression in young men. Participants will be randomly allocated to either the MD group or the control group which consist of the social support procedure, befriending. Participants will attend three 45-minute online appointments at baseline, week 6 and week 12. Data collection will include case report forms and several questionnaires.

STUDY POPULATION AND SAMPLING

The study population consists of young men aged 18-25 who have been diagnosed with major depressive disorder by a general medical practitioner. The study sample will be selected using random sampling.

POWER ANALYSIS

The sample size calculation was based on being able to detect a minimum clinically important change of >5 points in BDI[363] while comparing diet and placebo group, with α=0.05 and 80% power. In previous studies[364,365] the response within each subject group was normally distributed with an approximate standard deviation of 7.5. Based on this, 36 participants are needed per group. Allowing for a 15% dropout rate, we are aiming to recruit 86 participants.

RECRUITMENT

Recruitment will be online and consists of the following strategies. Social media advertisements via Facebook and Twitter which target the following demographic: Individuals who are male, aged 18-25, live in Australia and have 'liked' or 'followed' pages relating to depression such as the Back dog institute, beyond blue and Sane. An email campaign which includes a link to the online website (https://mendds.wixsite.com/ammend) and has all the relevant information about the trial will be sent to Australian based medical

doctors, psychologists, natural health practitioners and health clinics, with a view to these practitioners notifying patients who meet the study criteria, about the study and providing the patients with the website link. Practitioners contact details will be collected from a thorough internet search. All participants who are referred by allied health practitioners will be screened to check eligibility. A referral letter stating that the participant has been diagnosed with major depressive disorder will also be requested.

INCLUSION AND EXCLUSION CRITERIA

The study population will consist of young men aged 18-25 who have been diagnosed with major depressive disorder by their medical doctor. They must also score 20 or above on the 21-item BDI-II indicating moderate to severe depression and have scored <40 on the CSIRO Diet Survey[366] indicating a poor baseline diet. Participants will be excluded for the following reasons: 1. If they cannot speak or understand English or if they are not capable of understanding or consenting to what is involved with this trial. 2. If they have also been diagnosed with any of the following mental health disorders: bipolar disorder, post-traumatic stress, personality disorders, eating disorders, psychotic disorders such as schizophrenia or a substance abuse disorder such as alcoholism. 3. If they suffer from any gastrointestinal disorders such as Crohn's disease, ulcerative colitis or irritable bowel syndrome. 4. If they have any food allergies, intolerances or eversions (avoiding foods based on religious or ethical grounds) which would prevent them from following the diet. 5. If they are unavailable to attend the scheduled follow up appointments. 6. If they are unwilling to change their diet if allocated to the MD group. 7. If they score below 20 on the BDI-II or if the BDI-II indicates suicidal thoughts or ideations.

SCREENING PROCEDURE

A phone screening tool specifically developed for this study will be used to cover all aspects of the inclusion and exclusion criteria. This includes the Becks Depression Inventory to assess depressive symptoms and the CSIRO diet questionnaire to assess current diet quality. If the participant is deemed eligible, they will be sent the participant information sheet and scheduled a baseline appointment. A computer-generated random number sequence will be used for randomising participants. The Chief Investigator will generate the sequence and the Principal Investigator will conceal the sequence in numbered sealed opaque envelopes. Participants will be allocated a sequential number upon screening. The sealed envelope corresponding to the allocated participant number will be opened at the baseline

appointment by the researcher and the participant will be informed which group they have been randomised in to. As this is an open-label study blinding is not required. A Consort Flow Chart outlining the study schedule is displayed in Figure 1.

DIET INTERVENTION GROUP

Participants allocated to the MD intervention group will receive nutrition consultations by a qualified nutritionist explaining the components of the diet. The MD used in this study is based on the dietary guidelines of Greece and Spain. The diet is rich in vegetables, legumes and wholegrains, oily fish, olive oil and raw unsalted nuts. The primary focus is on increasing diet quality with fresh wholefoods while reducing intake of energy dense, nutrient poor "fast" foods. They will be provided with a booklet containing sample meal plans, recipes, dining-out options, simple diet "swaps", eating-on-a-budget tips, compliance checklists and online diet history survey link.

Participants will also receive a food hamper at the commencement of the trial. The follow up appointment at 6 weeks will involve a 45-minute consultation where participants will complete another Case report form (CRF) including BDI-II and World Health Organisation (WHO) Quality of Life (QOL-BREF) form. Participants will be asked about their experiences so far and will receive additional nutritional counselling. Participants will attend a final appointment at the conclusion of the study where the final BDI-II will be taken. Diet history will be collected daily from participants via a widget on their mobile device. Participants will be invited to take part in an End of Project Evaluation Survey at week 12, collecting information about their experiences following a MD and their depressive symptoms.

CONTROL GROUP

Participants allocated to the control group will receive 45-minute befriending support sessions. These will be scheduled for the baseline appointment, 6 weeks and 12 weeks in order to mimic the visit schedule and duration of the diet intervention group. Befriending consists of the researcher talking to the participant about neutral topics of interest to the participant such as sports, movies and hobbies. The objective is to keep the participant engaged and interested. The befriending protocol has been selected because it controls for several factors including client expectations, the therapeutic relationship and time spent with the nutritionist. Befriending is often used as a controlled condition for clinical trials of psychotherapy[367] and was used recently in the SMILES trial[327]. Befriending has shown to be

an effective, credible and acceptable validated control therapy for psychological studies and appropriate to participants suffering from mental illness[367]. Participants will also complete the CRF, BDI-II and WHO QOL forms at their baseline appointment, 6 week follow up and final appointment at week 12. Participants in the control group will also receive a $50 Hoyts gift card to thank them for their participation and to act as incentive to return for their final appointment for data collection.

DATA COLLECTION METHODS AND INSTRUMENTS

Data will be collected from all participants via Case Report Forms and will include the 21-item Becks Depression Inventory (BDI-II) depression scale and the World Health Organisations (WHO) Quality of Life (QOL-BREF) form. Adherence to the MD will be measured via an adapted validated 15 item Mediterranean Diet Adherence Scale. All participants, both the diet and control groups, will be required to report everything they eat and drink online daily.

CASE REPORT FORM (CRF)

The CRF includes demographics questions, a section to report all current medications, both prescription and over the counter, nutritional supplements and herbs as well as complementary medicine use. Participants are asked not to change any aspect of their usual routine for the duration of the trial, particularly exercise and use of vitamins. These activities will be recorded at each appointment. Energy, stress levels and other lifestyle factors will also be recorded. An adverse events log is also included.

BECK DEPRESSION INVENTORY (BDI-II 21-ITEM)

The 21 item BDI-II is one of the most popular self-assessment tools for depression and has been used in over 7000 studies worldwide[368]. The 21 items in the BDI-II reflect symptoms and attitudes observed in the criteria for depressive disorders in the *DSM-IV* (Diagnostic and Statistical Manual of Mental Disorders). It demonstrates high reliability and good correlation with measures of depression and anxiety[369]. Each of the 21 items have four possible answers rating from zero to three. These reflect their intensity and create a score which ranges from 0 to 63[368]. A score of 20 and above indicates moderate depression and forms part of the inclusion criteria for the trial. The BDI-II has also demonstrated a high level of validity, sensitivity and specificity for detecting depression in both the general population as well as psychiatric and medical settings[370]. A systematic literature review of the psychometric properties of the BDI-II found that it reports an average alpha reliability coefficient of 0.9,

ranging from 0.83 to 0.96[368]. It also reports the retest reliability (Pearson's r) as relatively stable with good to excellent coefficients (range, 0.73 to 0.96)[368].

THE COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION (CSIRO) HEALTHY DIET SCORE

The CSIRO Healthy Diet Score Survey asks questions about the quantity, quality, and variety of foods consumed[366]. Individuals receive a personalised Diet Score out of 100 which reflects their overall compliance with the Australian Dietary Guidelines. Over 145,000 Australians have completed the survey since it was launched in May 2015[366]. The average Diet Score was 58.8 out of a possible 100. A score of 75 has been proposed as a benchmark of a "good" score[366]. A score of 40 or below would thus indicate a "poor" score and forms part of the inclusion criteria for the AMMEND trial.

WORLD HEALTH ORGANISATION (WHO) QUALITY OF LIFE (QOL) FORM

The WHO QOL-BREF is a 26-item version of the WHOQOL-100 assessment. The WHOQOL form has demonstrated to be a thorough, cross-culturally valid assessment of QOL, as reflected by its four domains: physical, psychological, social and environment[371]. WHOQOL BREF has been used previously in participants with major depressive disorder and was sensitive to improvement after treatments[372]. It has shown to be a psychometrically reliable instrument that it is suitable for evaluating quality of life.

THE MEDITERRANEAN ADHERENCE SCORE (MEDAS)[373]

The MEDAS is a 14-item questionnaire which asks about the frequency of consumption or amount consumed of 12 main components of the MD and two food habits related to the MD. Each of the 14 items is scored 1 or 0, depending on whether participants adhere to each MD component or not[373]. Participants total score will be categorised into two groups: <7 points (low adherence) and ≥7 points (high/ medium adherence). The English version of the MEDAS has displayed acceptable accuracy and reliability for assessing MD adherence[373] and has been used in depressed populations previously[374]. An additional question about wholegrain servings has also been included in our adapted version of this questionnaire: How many serves of whole grains (wholemeal bread, brown rice, oats etc.) do you consume per day? A point is awarded for ≥ 3 serves. Participants daily diet entries will be scored against the MEDAS and given an average score at the conclusion of the study.

DIET GUIDELINES

The term Mediterranean Diet has often been misused. There is no evidence that one "Mediterranean Diet" is followed by everyone living in the countries around the Mediterranean Sea. However, the foods that are common among the various countries of the Mediterranean regions are somewhat similar. The healthy MD is a moderate diet characterised by some typical Mediterranean food groups: cereals, legumes, fish, virgin olive oil, fresh fruit, nuts, vegetables, wild plants, and wine as an optional alcoholic beverage. The MD used for the AMMEND study is based on the dietary guidelines of Greece and Spain. It is abundant in plant foods including vegetables, fruits, cereals, legumes, nuts and seeds. Olive oil is the principle source of fat, dairy products (principally cheese and yogurt) and fish and poultry are consumed in low to moderate amounts, zero to four eggs consumed weekly and low red meat consumption. Participants will document all meals and snacks consumed during their time in the study via a widget on their mobile device. A score is calculated based on the MEDAS detailed earlier.

END OF PROJECT EVALUATION SURVEY

The End of Project Evaluation Survey is a 20-item questionnaire consisting of 16 multiple choice questions and 4 open ended questions asking participants in the diet group to reflect on their experiences following the MD. The Survey asks participants to reflect on several different topics including, their weekly food budget, time commitment, motivation, enjoyment level, challenges and perceived impact on their depressive symptoms.

DATA ANALYSIS METHODS

Statistical analysis will be performed using STATA. Descriptive statistics will be reported using means and standard deviations providing baseline demographics and measurements. The two groups will be compared across baseline measurements, using chi-square or t-tests where appropriate, to ensure that there are no differences between randomised groups. If differences between the two groups are identified, those variables will be included in linear regression modelling of the outcome variable. Possible confounders such as changes to exercise, stress, sleep, recreational drug use, over the counter medications and supplement use will be considered in the statistical analysis.

The main outcome will be the BDI-II score which will be analysed as a continuous variable and reported as a mean. A one-tailed analysis will be used to detect differences in BDI-II

scores between the intervention and control groups. Intention to treat analysis will be used exploring dose–response effects associated with the Mediterranean diet adherence. Changes between BDI-II score at baseline and the conclusion of the study will be analysed using paired t-tests. Differences in BDI-II scores between both groups will be assessed using a linear regression model. The BDI-II can also be split into two subgroups. Cognitive-affective items (Cognitive-Affective subscale) and somatic and performance complaints (Somatic and Performance subscale). Analysis of the effect of the MD on the two subscales will also be performed.

To investigate whether dietary change is associated with positive outcomes in depression, changes in diet scores will be entered into regression analyses as appropriate with changes in BDI-II scores as dependent variables. Sub-group analyses by depression severity score will be conducted to determine if the severity of depression effects the results.

Secondary aims are to see if there is a difference in outcomes measures between participants who display high verses low compliance to the MD. The final BDI-II score of participants who display low compliance (<7 on the MEDAS) will be compared to those who display moderate to high compliance (≥7 on the MEDAS) with linear regression modelling.

DATA MANAGEMENT

All data will be collected and stored according to Good Clinical Practice Guidelines. All hard copy data such as consent forms, CRF's, dietary screening forms and BDI-II scores will be stored in a locked filing cabinet which can only be accessed by the lead researchers. Electronic data will be stored securely in REDcap and a Research Data Management Plan created via Stash. Data will be stored for 5 years and all information will be treated confidentially. Data will only be used for the purpose of this research project.

ACCESS TO DATA

Data can only be accessed by members of the research team. If requested, participants can access their individual results at the completion of the trial by contacting the lead researcher.

DATA MONITORING & AUDITING

Data monitoring and auditing of the trial will be conducted by the senior researchers and supervisory team DS and JS.

ETHICAL CONSIDERATIONS

Due to this trial involving participants with depression extra caution will need to be taken. Participants will have been previously diagnosed with depression by their general practitioner and will be under their primary care. Participants will continue with their prescribed treatment protocol whether that be medications and/or counselling during the course of the trial. If there are any changes to their depression treatment during the course of the trial these will be noted on the case report form and reported as confounders. This is a pragmatic trial and represents real life events. Participants will be specifically asked about any changes to medications, either type or frequency, psychology appointment frequency or complementary therapies/herbal remedies at the follow up appointments. A letter communicating the participants involvement in this study will be given to the participants primary care doctor explaining all aspects of the trial. During the study the BDI-II will be completed at baseline, week 6 and week 12. While we don't expect that a Mediterranean diet or befriending will cause a significant worsening of symptoms, as both have used safely in previous depression clinical trials, we will still carefully monitor BDI-II results.

ANCILLARY AND POST-TRIAL CARE

If the results indicate a worsening of symptoms during or after the study, the participants doctor/counsellor will be contacted. If the participants health is at risk they may be withdrawn from the study. A complementary counselling session will also be organised with the study Psychologist. Participants will be aware that they can withdraw from the trial at any time and for any reason. A detailed handout of depression resources will also be given to participants at the commencement of the trial. There is also a possible risk of minor gastrointestinal symptoms as a result of dietary changes. These include bloating, altered bowel movements and abdominal pain as a result of increased fiber and introduction of new foods. If these symptoms occur, they will be ameliorated by the qualified clinical nutritionist and recorded in the Adverse Events Log. The trial may be terminated early if the results suggest that the diet or social support are causing harm. This decision will be made by senior members of the research team, DS and JS.

STUDY INTEGRITY

This trial has been designed following Good Clinical Practise (GCP) principles in line with the declaration of Helsinki and all researchers hold current GCP certificates. Ethical Approval was granted by the University of Technology Sydney (UTS) on 4th February 2020: UTS HREC REF

NO. ETH19-4413. The trial is registered with Australia and New Zealand Clinical Trials Registry (ANZCTR) Trial Id: ACTRN12619001545156 and has also been registered with the World Health Organisation (WHO) International Clinical Trials Registry Platform's (ICTRP) Universal Trial Number: U1111-1242-5215.

DECLARATION OF INTERESTS

This project is funded by Endeavour College of Natural Health. This is an independent research project. The funding body has no involvement with the design, implementation or analysis of the project. Their only role is providing the money awarded by the grant approval. There are no potential commercial interest to declare.

DISSEMINATION POLICY

The results from this study will be published in a peer reviewed academic journal. Participants in the trial will also be notified of the outcomes. A progress report will also be completed for Endeavour College of Natural Health.

DISCUSSION

The SMILES[327] and HELFIMED[240] trials have both shown that a MD can be effective at reducing depressive symptoms in adults with depression and are supported by a growing body of observational research. This project aims to assess the MD in a very specific population group often underrepresented in diet research. Unfortunately, young men rarely seek help for their depression, which suggests that the current treatment options are particularly unappealing for this demographic and the stigma of depression still significant. Evidence based treatment options for young men are urgently needed and this research aims to answer the question of whether diet can be used effectively in this population.

Changing behaviours is challenging and diet research requires intense commitment from participants. A previous study found the following facilitators and barriers for adopting a Mediterranean diet in a non-Mediterranean country[375]. Participants reported that the diet was enjoyable and that they experienced pleasure and fulfilment at meal times but that stress or work pressures often got in the way and made it difficult to prepare food[375]. The authors also recommend challenging assumptions about what a Mediterranean diet looks like and educating participants that the MD is not a “salad only” diet. They also recommend education on where to find certain foods and meal planning skills[375]. These factors have all

been considered in the design of this study and appropriate time set aside to discuss these issues with participants.

Potential limitations of this trial include selective dropout/retention from participants not being allocated to their preferred intervention group. To control for this, participants in each intervention group will be offered the opportunity to try the alternative intervention at the conclusion of the study. For example, participants allocated to the social support group can receive nutritional counselling if they wish, once they have finished their trial period. Other behavioural exposures could also impact the trial results. These will be controlled for by asking extensive questions in the case report form about possible confounders such as exercise, stress, sleep, recreational drug use, over the counter medications and supplement use. These factors will then be considered in the statistical analysis. As this is a whole diet intervention this trial cannot be double blinded, however, the two intervention groups will be presented as equal in their possible treatment efficacy to reduce client expectancy.

Despite these limitations, this study has a number of strengths. These include that the participants depression is diagnosed by a GP rather than being self-reported and the randomised nature of the trial preventing intervention selection bias and confounding. Another strength is the use of befriending for the social support group which controls for several potential confounders including the therapeutic relationship and the time and attention received by the participant. This will also be the first trial to assess a whole diet approach in young men with depression. Whole diet approaches consider food synergy and how foods work together naturally within the diet. This reflects a more natural way of eating rather than consuming isolated nutrients. An additional strength of this design is that by collecting diet history information daily, there is a reduced risk of recall or measurement error. Further, the follow up survey included at the conclusion of this trial will help inform future research by highlighting the positive and negative aspects of following a MD by this demographic and will help researchers and clinicians implement this diet in a real-world setting.

CONCLUSION

This will be the first randomised clinical trial to assess the impact of a Mediterranean diet on the symptoms of depression in young men. This study will not only help fill a significant research gap but also contribute to the growing field of nutritional psychiatry. The results

from this study may also help guide future research in this area and inform advice given by clinicians to this specific demographic.

FUNDING

The authors would like to thank Endeavour College of Natural Health and the Australian Research Centre in Complementary and Integrative Medicine (ARCCIM), University of Technology Sydney (UTS) for providing funding for this research.

ACKNOWLEDGMENTS

JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

STATEMENT OF AUTHORSHIP

JB conceptualised and designed the study; JS and DS assisted with the development of the study design, methodology and statistical analysis plan. JB obtained the funding and ethics approval with assistance from JS and DS; JB drafted the study protocol with edits from JS and DS; all authors contributed to the manuscript and approved the final version.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist.

5.3 CHAPTER SUMMARY

This chapter has presented the published protocol paper for the AMMEND trial. It outlined the study design, power analysis, recruitment strategy, inclusion and exclusion criteria, screening procedure, details of the intervention and control group, data collection methods and instruments, the diet guidelines, data-analysis methods, data management plan, ethical considerations, study integrity and the dissemination policy.

After the protocol paper was published, several changes were made to the AMMEND trial methodology due to the impact of COVID-19. These changes included, moving to telehealth appointments, removing the anthropometric measurements, opening the trial up to all of Australia and changing the recruitment strategy, including the use of a clinical trial recruitment company.

6. CHAPTER 6: A Mediterranean Diet for Men with Depression (AMMEND) Results Article

6.1 PREFACE

The previous chapter outlined the AMMEND study protocol. This next chapter presents the results from this research trial in the article "A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study). Which has been published in the *American Journal of Clinical Nutrition* (IF:7.05) in April 2022. It is reproduced here with permission from Oxford University Press.

> Bayes, J, Schloss, J, Sibbritt, D, 2022. 'A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study), *The American Journal of Clinical Nutrition,* nqac106, https://doi.org/10.1093/ajcn/nqac106

Supplementary Materials can be found in the Appendix:

- Figure 1: Participant CONSORT flowchart - Appendix 13
- Supplemental Figure 2: WHO QoL (BREF) Domain Score Results for MD and Befriending Groups – Appendix 14
- Supplemental Figure 3: WHO QoL (BREF) Total Raw Score for MD and Befriending Groups – Appendix 15

Additional Documents:

- Phone Screening Tool – Appendix 16
- Participant Information Sheet and Consent Form – Appendix 17
- Case Report Form – Appendix 18
- Participant Documents – Appendix 19
- Adapted 15-item Questionnaire of Mediterranean diet adherence – Appendix 20
- Table 1. Demographic Characteristics of Study Participants – with included p-values – Appendix 21

6.2 THE AMMEND STUDY DEPRESSION RESULTS

A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study)

ABSTRACT

Background: Depression is a common mental health condition which affects 1 in 8 males each year, especially young adults. Young adulthood offers an opportunity for early dietary interventions, with research suggesting that a Mediterranean diet (MD) could be beneficial in treating depression.

Objective: This study aimed to determine if a MD can improve depressive symptoms in young males with clinical depression.

Methods: A 12-week, parallel-group, open-label, randomized control trial was conducted to assess the effect of a MD intervention in the treatment of moderate to severe depression in young males (18-25 years). Befriending therapy was chosen for the control group. Assessments were taken at baseline, week 6 and week 12. MD adherence was measured with the Mediterranean Adherence Score (MEDAS). The primary outcome measure was the Beck Depression Inventory Scale (BDI-II) and secondary outcome was Quality of Life (QoL).

Results: A total of 72 participants completed the study. After 12 weeks, the MEDAS scores were significantly higher in the MD group compared to the befriending group (Mean diff: 7.8, 95% CI: 7.23, 8.37, $p<0.001$). The mean change in BDI-II score was significantly higher in the MD group compared to the befriending group at week 12 (Mean diff: 14.4, 95% CI: 11.41, 17.39, $p<0.001$). The mean change in QoL score was also significantly higher in the MD group compared to the befriending group at week 12 (Mean diff: 12.7, 95% CI: 7.92, 17.48), $p<0.001$).

Conclusion: Our results demonstrate that compared to befriending, a MD intervention leads to significant increases in MEDAS score, decreases in BDI-II score and increases in QoL scores. These results highlight the important role of nutrition for the treatment of depression and should inform advice given by clinicians to this specific demographic population.

Keywords: young adults; male; Mediterranean diet; Major depressive disorder, Quality of Life

INTRODUCTION

Depression is a common mental health disorder affecting approximately 350 million people worldwide[2]. In Australia, approximately 1 million Australian adults have depression in any given year and early onset can mean that sufferers face varying degrees of disability for many years of their lives[3]. Depression can present differently in each individual, however the main characteristics include anhedonia, a depressed mood and altered cognitive function[38]. The overwhelming burden of mental illnesses affect young people, with the transition from adolescence through to adulthood presenting many challenges, such as significant transitions between home, educations and employment[360].

From a developmental perspective, the ages 18–24 years has been described as *emerging adulthood*, which is a transitional developmental stage between late adolescence and adulthood[79]. A sharp increase in depression rates are observed with rates of mental illness peaking in emerging adulthood[80]. Unfortunately, young males rarely seek help for their mental health, with only 13% of young males aged 15-24 seeking professional help[322]. However, research shows that emerging adulthood also offers an opportunity for early lifestyle interventions, such as dietary change, as many are learning to cook and are taking control of their food choices for the first time[360]. In addition, research consistently shows that males tend to display poorer diets when compared to women[338-340], making young males aged 18-25 with depression particularly in need of additional support.

Standard treatment of major depressive disorder includes psychotherapies such as cognitive behavioral therapy and anti-depressant medications, such as selective serotonin-reuptake inhibitors[376]. However, roughly 30% of patients with depression fail to adequately respond to antidepressant medications[377]. Recently, researchers have been exploring the effect specific nutrients[329,331,333,336], certain foods[334,378] and various dietary patterns[233] have on mental health in the emerging field, *nutritional psychiatry*[379]. Currently, the diet with the most evidence for exerting a positive effect on depressive symptoms is the Mediterranean diet (MD)[236].

The MD is high in fruits, vegetables, wholegrains, legumes, seafood, nuts, seeds and olive oil, while being low in processed “fast” foods, red meat and sugar[380]. While much observational evidence shows that those following a Mediterranean diet have a reduced risk of developing depression[381-384], only a few experimental trials have been conducted, showing that a MD can

also help treat active Major Depressive Disorder (MDD)[140,240]. However these two trials have been performed on older adults, with a mean age of 40[140] and 44[240], with no studies to date exploring a MD in young adults with clinical depression. Interventions aimed at prevention or early treatment of depression are urgently needed.

Additionally, there is limited research on the effect of a MD on quality of life (QoL) in patients with depression, particularly young males. QoL questionnaires typically assesses the participants experiences of an illness, such as disability, fatigue and pain, and may also include questions about participants physical, social and emotional wellbeing[385]. Therefore, examining the impact of diet on QoL could provide additional insights into the efficacy of interventions across various domains of health[385].

Therefore, the aim of this research trial is to determine if nutritional counselling, focusing on the MD, can improve the diet quality, depressive symptoms and QoL of young males with depression. We executed a randomized controlled trial examining the effect of a MD versus befriending therapy for the treatment of depression in young males with clinical depression. We hypothesize that following the MD would result in improved diet quality, depressive symptoms and QoL in the MD group at week 12.

METHODS

Study design

This was a 12-week, parallel-group, open label, randomized control trial (RCT) of a MD intervention in the treatment of moderate to severe depression. A detailed study protocol has been published elsewhere[386] . The trial was registered with Australia and New Zealand Clinical Trials Registry (ANZCTR) Trial Id: ACTRN12619001545156 prior to commencing recruitment. It has also been registered with the World Health Organization (WHO) International Clinical Trials Registry Platform's (ICTRP) Universal Trial Number: U1111-1242-5215.

Participants were recruited from Australia over an 18-month period. Participants were randomized 1:1 to receive either dietary support or befriending[367]. Participants in both groups completed assessments at baseline (week 0), midway (week 6) and at program completion (week 12). Ethics approval was received from the Human Research Ethics Committees of the University of Technology Sydney (UTS) on the 4th February 2020: UTS

HREC REF NO. ETH19-4413. Written informed consent was obtained from all participants after they had received a complete description of the study. The study's protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[387]. Primary and secondary outcomes were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines and their extension to non-pharmacologic treatments[388].

Patient and Public Involvement:

During the development of the study protocol 20 young males with depression were invited to participate in a telehealth interview to give their opinion on the design of the trial, research questions and outcomes measures. Modifications were then made to the study design to account for their priorities and preferences. At the conclusion of the trial, the results were disseminated to all trial participants via email.

Study population and sampling

The study population consisted of young males aged 18-25 years who had been diagnosed with major depressive disorder (MDD) by a general medical practitioner. Potential participants were recruited using targeted campaigns of flyers/posters, social media advertisements, databases from previous studies and via a research participant recruitment company (Trialfacts, Melbourne, Australia).

Inclusion and exclusion criteria

The eligibility criteria included participants who were aged 18-25 years, identified as male, and had previously been diagnosed with depression by their medical doctor. They must also have scored 20 or above on the twenty-one-item Beck Depression Inventory (BDI-II), indicating moderate to severe depression and have scored 40 or less on the Commonwealth Scientific and Industrial Research Organization (CSIRO) Diet Survey. The CSIRO Healthy Diet Score Survey asks questions about the quantity, quality, and variety of foods consumed. Individuals receive a personalized Diet Score out of 100 which reflects their overall compliance with the Australian Dietary Guidelines. A score of 75 has been proposed as a benchmark of a "good" score[366]. A score of 40 or less on the CSIRO Diet Survey, was considered poor.

If participants were on antidepressant medications or undergoing psychotherapy, they were required to be on the same treatment for at least 2 weeks prior to enrolment into the study. Participants were excluded if they had been diagnosed with any of the following disorders: bipolar disorder, posttraumatic stress, personality disorders, eating disorders, psychotic disorders such as schizophrenia or a substance abuse disorder such as alcoholism. Participants were also excluded if they had: gastrointestinal disorders such as Crohn's disease, ulcerative colitis or irritable bowel syndrome; or food allergies, intolerances or aversions (avoiding foods based on religious or ethical grounds) which would prevent them from following the diet. In addition, participants were required to attend all appointments in order to complete the trial. Therefore, participants were excluded if they were unavailable to attend the scheduled follow-up appointments, were unwilling to change their diet if allocated to the MD group, or unwilling to participate in the befriending sessions.

Randomization

A computer-generated random number sequence was used in excel to randomize participants using block randomization (Block size 20). The Chief Investigator generated the sequence, and the Principal Investigator concealed the sequence in numbered sealed opaque envelopes. Participants were allocated a sequential number upon screening. The sealed envelopes corresponding to the allocated participant number were then opened at the baseline appointment by the researcher. The participant was then informed if they were randomized to the MD intervention group or the befriending group.

Diet Intervention group

The dietary intervention was delivered by a clinical nutritionist at the commencement of the trial during a 60-minute appointment which comprised of personalized dietary advice, motivational interviewing, goal setting and mindful eating to support optimal adherence to the Mediterranean diet (MD). Participants also attended a 60 minute follow up appointment at week 6 and week 12 which focused on additional goal setting, motivational interviewing and overcoming any challenges they were facing following the MD. The MD used in this study is based on the dietary guidelines of Greece and Spain[389-391]. The diet is rich in vegetables, legumes and wholegrains, oily fish, olive oil and raw unsalted nuts. The primary focus is on increasing diet quality with fresh wholefoods while reducing intake of energy-dense, nutrient-poor 'fast' foods. The following servings of food groups were recommended: wholegrains (5-8 servings/day), vegetables (5+ servings/day), fruit (2+ servings/day), legumes

(1 servings/day), fish (2 servings/week), nuts and seeds (1 servings/day), extra virgin olive oil (3 servings/day), dairy foods (1-2 servings/day), eggs (no more than 6 per week), poultry (2-3 servings/week), red meat (1 servings/week). Consumption of discretionary foods, such as sweets, fried food, processed meats and sugary drinks were limited no more than 3 servings per week.

In addition to the 60-minute nutritional counselling appointment, participants were also provided with a booklet containing information on serving sizes, sample meal plans, recipes, dining-out options, simple diet 'swaps', eating-on-a-budget tips, compliance checklists and an online daily diet history survey. Participants also received a food hamper valued at $50 at the commencement of the trial with a selection of Mediterranean foods. The diet was designed to be easy to follow, palatable, satiating and aimed to fit within their usually weekly food budget. Participants were advised that calorie restriction and weight loss were not an aim of the MD, and they may consume permitted foods freely.

Control group

Participants allocated to the control group received befriending support sessions. These appointments followed the same visit schedule and duration as the diet intervention group. Befriending involves the researcher talking to the participant about neutral topics of interest such as movies, sports and hobbies. The aim is to keep the participant engaged and interested. Befriending is an effective, credible and acceptable validated control therapy for psychological studies and appropriate to participants suffering from mental illness[367]. Befriending was chosen for its ability to control for some of the important factors that have been shown to confound RCTs. It controls for the client's expectations, the therapeutic relationship and time spent with the nutritionist. Participants in the control group received a $50 Hoyts gift card at the program completion to thank them for their participation.

Data collection methods and instruments

Data was collected at Baseline (week 0), midway (week 6) and project completion (week 12) using the following instruments: A Case Report Form (CRF) which collected demographic data, medical history, and medications. The Beck Depression Inventory (BDI-II 21-Item) which measures depressive symptoms[392]. The Commonwealth Scientific and Industrial Research Organization (CSIRO) Healthy Diet Score which measures diet quality[373]. The World Health Organization (WHO) Quality of Life (QOL) form which includes 26 questions on the

individual's perceptions of their health and wellbeing over the previous two weeks[393]. Responses to questions are on a 1-5 Likert scale where 1 represents "disagree" or "not at all" and 5 represents "completely agree" or "extremely". The WHO QoL-BREF has been used in previous populations with major depressive disorder and has shown to be a psychometrically valid and reliable instrument, appropriate for evaluating quality of life in depressed patients[372]. Four domain scores can also be derived from the QoL results. Domain scores are scaled in a positive direction with higher scores denoting a higher quality of life[393]. The mean score of items within each domain is used to calculate the domain score. Mean scores are then multiplied by 4 in order to make domain scores comparable with the scores used in the WHOQOL-100[393].

An adapted Mediterranean Adherence Score (MEDAS)[373] which is a 15-item questionnaire assessing dietary habits considered characteristic of the Mediterranean diet in addition to assessing consumption of specific food groups was also used. Each item is scored 1 or 0, depending on whether participants adhere to each MD component or not, and is summed for each individual providing a total score out of 15; with higher scores indicating greater adherence to the M [373]. In order to measure compliance and assess diet quality, participants documented all meals and snacks consumed during their time in the study via a widget on their mobile device. A detailed description of each can be found in the study protocol[386]. The primary outcome measure was the BDI-II. This was used to assess depressive symptomatology at baseline and at the primary endpoint of 12 weeks.

Sample Size Calculation

The sample size calculation was based on being able to detect a minimum clinically important change of >5 points in BDI[363] while comparing diet and placebo group, with α=0.05 and 80% power. In previous studies [364,365] the response within each subject group was normally distributed with an approximate standard deviation of 7.5. Therefore, 36 participants were needed per group and 72 participants in total.

Data analysis methods

Statistical analysis was conducted using STATA (version 16). The descriptive statistics reported included percentages, means and standard deviations. The main outcome was the BDI-II score which was analyzed as a continuous variable and reported as a mean. Assumptions for the repeated measures ANOVA were assessed and included the Bartlett's

Test for Homogeneity of Variances. Kolmogorov–Smirnov test for normality was also used to assess the distribution of the residuals in the data sets. Two-way repeated measures ANOVA was used to determine differences in BDI-II scores between each group across three time points, with time as the repeated measure. The Tukey HSD test was used to determine pairwise differences in mean BDI-II scores between the intervention and control group at week 6 and week 12. Two-way repeated measures ANOVA was also used to determine differences in MEDAS score between each group across three time points, with time as the repeated measure. The Tukey HSD test was also used to determine pairwise differences in the MEDAS score between the intervention and control group at week 6 and week 12. Two-way repeated measures ANOVA was also used to determine differences in total QoL score between each group across three time points, with time as the repeated measure. The Tukey HSD test was also used to determine pairwise differences in total QoL scores between the intervention and control group at week 6 and week 12**.**

RESULTS

Baseline Characteristics

A total of 165 participants were screened for eligibility, with 75 participants recruited into the trial between March 2020 and August 2021. Three participants (4%) withdrew from the study: one from the control group and two from the intervention group. All three withdrawals were due to commitment clashes meaning they were unable to attend appointments, and all withdrew within 48 hours of enrolling. Therefore, their data was omitted from data analysis. A Consolidated Standards of Reporting Trials (CONSORT) flow chart outlining the study schedule and number of participants is displayed in **Figure 1**.

The mean age of participants was 22 years old and 71% (n=51) of participants were born in Australia. A total of 45% (n=33) of participants were seeing a psychologist and 35% (n=26) were taking medication for their depression, with 73% (n=19) of those medications being selective serotonin reuptake inhibitors (SSRI's). Despite some participants receiving these therapies, all participants still had baseline depression scores indicating moderate to severe depression. The average timeframe that participants had been taking medications was 1 year and the average time frame participants had been undergoing psychotherapy was 8 months. A total of 30% (n=22) use phone applications focused on mental health (calm/headspace etc.) and 75% (n=54) have a family history of mental illness. The mean baseline depression score

on the BDI-II scale was 34.8 for the MD group and 33.5 for the befriending group. All baseline measurements are reported in **Table 1**.

On average, the participants undertook 2 exercise sessions per week. When asked who is usually responsible for cooking and preparing their food and meals, 32% (n=23) cook their own meals, 43% (n=31) have their meals prepared by someone else (parents/student accommodation/partner), and 25% (n=18) rely entirely on fast food/take out. A total of 41% (n=31) indicated that they have followed a specific diet in the past. The most frequently reported previous diet was intermittent fasting (n=9). When asked to rate their overall sleep quality, 68% (n=51) indicated poor sleep. When asked to rate their energy out of 10, the mean score was 4/10. When asked to rate their stress levels out of 10, the mean score was 6.

Outcome Measure comparisons

The Mediterranean diet adherence scores (MEDAS) was similar at baseline for both the MD and Befriending group. Significant within group changes were observed at the 6 week and 12 week mark for the MD group but not the befriending group. The mean change between baseline and week 12 was 8.0 (95% CI 7.41, 8.59) for the MD group and 0.2 (95% CI -0.27, 0.67) for the befriending group. At week 12 the mean difference in MEDAS score between the MD group and the befriending group was 7.8 (95% CI: 7.23, 8.37, $p<0.001$). There were no side effects or adverse reactions from the MD reported. The results are displayed in **Table 2**.

The BDI-II scores were similar at baseline for both groups and both groups saw a decrease in BDI-II scores. The mean change between baseline and week 12 was 20.6 (95% CI 17.08, 24.33) for the MD group and 6.2 (95% CI 1.83, 10.57) for the befriending group. The mean difference in BDI-II score between the MD group and the befriending group at week 12 was 14.4 (95% CI: 11.41, 17.39, $p<0.001$). These results are displayed in **Table 3.**

At the conclusion of the study, 100% (n=36) of participants in the MD group saw an improvement in their symptoms, with 36% (n=12) of those participants reporting a final BDI-II score between 0-10, which indicates low or minimal depression. In the befriending group, none of the participants in the befriending group had a BDI-II score between 0-10 at the conclusion of the study.

For QoL, **Table 4** shows the statistical comparisons made between the MD and befriending group, for the baseline and week 12 scores. Significant increases were observed in the MD group compared to the befriending group at week 12 for Domain 1 – Physical Health ($p<0.001$) and Domain 2 – Psychological Health ($p<0.001$). No significant differences between the MD and befriending group at week 12 were observed for Domain 3 – Social Relationships ($p=0.676$) and Domain 4 – Environment ($p=0.512$). For the total QoL score, the mean change between baseline and week 12 was 18.3 (95% CI 13.91, 22.69) for the MD group and 5.6 (95% CI 0.26, 10.94) for the befriending group. The mean difference in total QoL score between the MD group and the befriending group at week 12 was 12.7 (95% CI: 7.92, 17.48, $p<0.001$).

DISCUSSION

In our cohort of young males with moderate to severe major depressive disorder, we hypothesized that nutritional counselling which focused on implementing a Mediterranean diet with a qualified nutritionist over 12 weeks would result in improved diet quality as measured by increases in the Mediterranean diet adherence (MEDAS) score in the MD group. We also hypothesized that improvements in diet from following a MD would result in reduced depressive symptoms, as measured by the BDI-II. In line with our hypothesis, our results demonstrate that nutritional counselling can effectively improve both the diets and depressive symptoms of young males with clinical depression after 12 weeks of following a MD intervention.

We observed a mean reduction of 20.6 points on the depression scale for the MD group at 12 weeks. We also observed 36% of participants in the MD group reporting low to minimal depressive symptoms at the completion of the trial. These findings build on the work of previous studies which suggest a beneficial effect of diet on depressive symptoms in older adults[240,327]. Our results show that a MD can be effective in young males with moderate to severe clinical depression.

Dietary change comes with many challenges, and compliance over the long term poses significant difficulties for researchers, clinicians and patients alike[394]. Past research has also shown that males rate many health behaviours, including healthy food choices, as less important than women rate them[341], potentially leading to difficulties in engaging this demographic in dietary interventions. In addition, significant stigma around males following

a “healthy diet” still exists in relation to hegemonic masculinity[395]. Furthermore, fatigue and lack of motivation are common symptoms associated with depression and may pose additional challenges when making dietary changes.

However, a recent survey of young males with depression, demonstrates that this demographic feel that their diet has a significant impact on their depressive symptoms and would be willing to change their diet in order to improve their mental health[361]. The low dropout rate observed in our intervention group suggests high acceptability of the dietary intervention by the participants. The significant dietary improvements observed in the intervention group also demonstrates that dietary improvement is achievable for young males with clinical depression, regardless of potential diet stigma, and the challenging symptoms of their condition.

Our results also show that significant improvements can be seen in depressive symptoms over a short time period and these improvements can be sustained for the duration of the diet change. Previous research shows similar results, with a recent RCT demonstrating that following a healthier eating pattern for just 3 weeks can lower self-reported depression symptoms in 17-35 year old males and females[396]. Additionally, our trial had less nutritional counselling appointments compared to the two previous randomized control trials (RCT’S) which have assessed a MD in adults with depression, the SMILES study[327] and the HELFIMED study[240]. Both RCT’s incorporated seven appointments over 12 weeks, which is considerably more than the three appointments involved in our study. When designing the protocol for this trial, we invited young males with depression to give their opinion on the design of this RCT. As a result of this feedback, we chose to reduce the number of appointments to help with compliance and completion rates. Our results show that significant improvements in diet and depression can still be observed with less frequent appointments.

The mechanisms by which the MD may exert its beneficial effect on depression are complex and multifaceted[139]. Numerous biological pathways appear to be involved which affect inflammation, oxidative stress, epigenetics, mitochondrial dysfunction, the gastrointestinal tract microbiome, tryptophan–kynurenine metabolism, the hypothalamic-pituitary (HPA) axis, neurogenesis and brain derived neurotrophic factor (BDNF)[139]. At present, depression is thought to arise from a combination of biological, psychological and social factors[37]. While the benefits of nutritional psychiatry have primarily focused on the biological mechanisms[139],

social and psychological benefits may also play an important role[397]. Learning to prepare new foods and cooking with family and friends may also have a therapeutic effect[398].

Improvements to physical QoL were also reported in the MD group. These include improvements in concentration, sleep and energy. Fatigue, poor sleep and trouble concentrating are common physical symptoms of depression[399], therefore the improvements in depression could partially explain these findings. Additionally, individual components of the MD have shown to affect each of these physical factors in previous research. Omega 3 fatty acids found in fish and flavonoids found in fruits and vegetables show promise for improving cognitive function[400,401], concentration and memory[402]. In addition, a low fiber diet, high in sugar and saturated fat has shown to impair sleep quality and is associated with lighter, less restorative sleep[403]. Significant improvements in overall QoL were also reported in the MD group compared to the control. This suggests that following a MD may have a broader impact on young males with depression then expected, influencing many aspects of their health and wellbeing.

While this is the first study to show that a MD can improve the symptoms of depression in young males with clinical depression, there are limitations to our trial which must be considered. Firstly, the short duration of this trial means we cannot determine the effect of long-term adherence to a MD and the effect this may have on depressive symptoms in young males with clinical depression. Secondly, we did not ask participants to stop their depression medications or psychotherapy appointments due to ethical reasons. Despite some of the participants receiving these therapies, all participants still had baseline depression scores indicating moderate to severe depression. There were also no significant differences in the number of participants using these therapies in the MD group and the control group and as such we do not believe this to have significantly affected the results in any way. Per-protocol analysis was used and thus the data from the three participants who withdrew from the study was not included in the final analysis.

Another potential limitation was the inability to blind participants to their treatment group, which could potentially affect the expected outcomes by participants. To combat this, the potential benefits of both diet and social support for mental health were presented as equal in their possible treatment efficacy, thereby reducing client expectancy bias. Additionally, information regarding the research hypothesis was withheld from the trial participants. As

the active control therapy of befriending has shown to be somewhat effective for participants suffering from depression[404], we expected some improvement in this group. However, our results show that the MD is significantly more effective compared to befriending therapy.

CONCLUSION

This was the first randomized clinical trial to assess the impact of a Mediterranean diet on the symptoms of depression in young males with clinical depression. Considering the overall poor diet quality of depressed young males, coupled with the need for early interventions, this research provides a promising treatment option. Our results demonstrate that depressed young males can significantly change their diet quality over a short time period under the guidance of a clinical nutritionist. These dietary improvements lead to significant improvements in depressive symptoms with no observed side effects. We also found that when compared to the control group, the MD group had significant increases in the physical and psychological heath domains, as well as overall QoL. The results from this study may help guide future research in this area and inform advice given by clinicians to this specific demographic. Medical doctors and psychologists should consider referring depressed young men to a nutritionist or dietitian as an important component of treating clinical depression.

FUNDING

The authors would like to thank Endeavour College of Natural Health and the Australian Research Centre in Complementary and Integrative Medicine (ARCCIM), University of Technology Sydney (UTS) for providing funding for this research.

ACKNOWLEDGMENTS

JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

STATEMENT OF AUTHORSHIP

JB conceptualized and designed the study; JS and DS assisted with the development of the study design, methodology and statistical analysis plan; JB conducted research and was responsible for data collection; JB performed the statistical analysis which was reviewed by DS and JS; JB drafted the manuscript with edits from JS and DS; all authors contributed to the manuscript and read and approved the final version.

CONFLICTS OF INTEREST

There are no conflicts of interest, and no competing financial interests exist. This project was funded by Endeavour College of Natural Health. The funding body had no involvement with the design, implementation or analysis of the project. Their only role was providing the money awarded by the grant approval. There are no potential commercial interest to declare

Table 1. Demographic Characteristics of Study Participants

Item	MD Group	Control Group
Number of Participants	**36**	**36**
Age (Mean ± SD)	21.5 (2.9)	22.5 (2.5)
Born in Australia (%)	n=27 (75%)	n=27 (75%)
Habits:		
Baseline CSIRO diet score /100	35.1(4.9)	35.3 (4.7)
Caffeine intake, drinks/week (Mean ± SD)	11 (8.2)	9 (7.9)
Alcohol intake, drinks/week (Mean ± SD)	6.6 (7.3)	5.4 (5.3)
Exercise sessions/week (Mean ± SD)	2.3 (2.1)	2.5 (2.7)
Cigarette smokers (%)	n=5 (13.8%)	n=7 (19.4%)
Recreational drug use (%)	n=12 (33.1%)	n=13 (36.1%)
Depression:		
Baseline BDI-II Score	34.8 (8.1)	33.5 (9.0)
Taking anti-depressant medication (%)	n=11 (31%)	n=15 (41%)
Undergoing psychotherapy (%)	n=16 (44%)	n=17 (47%)
Using phone apps[1] focused on mental health (%)	n=11 (31%)	n=11 (31%)
Home:		
Living at home with parents (%)	n=14 (39%)	n=15 (42%)
Living in student accommodation (%)	n=4 (11%)	n=1 (3%)
Share housing (%)	n=13 (36%)	n=14 (39%)
Living alone (%)	n=5 (14%)	n=6 (17%)
Money spent on food/week ($AUD) (Mean ± SD)	$110 (54.1)	$104 (56.7)
Time spent cooking/day (minutes) (Mean ± SD)	44 (29.2)	37 (30.7)
Other Factors:		
Energy/10 (Mean ± SD)	4.2 (1.5)	4.0 (1.9)
Stress/10 (Mean ± SD)	6.5 (1.8)	6.4 (1.8)
Family History of Mental Illness (%)	n=26 (72%)	n=28 (77%)

[1]Phone applications such as Calm, Headspace, Smiling Mind etc. which have a focus on mental health

Table 2. Comparison of MD and Befriending groups using the Mediterranean Diet (MEDAS) Score

Group	Baseline Mean (SD)	Week 6 Mean (SD)	Week 12 Mean (SD)	Baseline – Week 12 Mean Change (95% CI)	Week 12 Between Group Mean Diff (95% CI)	p value[1]
MD	3.3 (1.1)	10.6 (1.3)[3]	11.3 (1.4)[4]	8.0 (7.41, 8.59)	7.8 (7.23, 8.37)	<0.001[2]
Befriending	3.3 (1.0)	3.5 (1.0)[3]	3.5 (1.0)[4]	0.2 (-0.27, 0.67)		

[1]p values are for two-way repeated measure ANOVA
[2]p value is <0.001 for the interaction of group, time and group by time.
[3]Tukeys HSD for MD vs Befriending at week 6 p=0.001
[4]Tukeys HSD for MD vs Befriending at week 12 p=0.001

Table 3. Depression Score (BDI-II) differences for MD vs Befriending

Group	Baseline Mean (SD)	Week 6 Mean (SD)	Week 12 Mean (SD)	Baseline – Week 12 Mean Change (95% CI)	Week 12 Between Group Mean Diff (95% CI)	p value[1]
MD	34.8 (8.1)	19.8 (9.7)[3]	14.1 (7.3)[4]	20.6 (17.08, 24.33)	14.4 (11.41, 17.39)	**<0.001[2]**
Befriending	33.5 (9.0)	29.7 (9.9)[3]	27.3 (9.6)[4]	6.2 (1.83, 10.57)		

[1]p values are for two-way repeated measure ANOVA
[2]p value is <0.001 for the interaction of group, time and group by time.
[3]Tukeys HSD for MD vs Befriending at week 6 p=0.001
[4]Tukeys HSD for MD vs Befriending at week 12 p=0.001

Table 4. WHO QoL-BREF total scores and domain scores for the MD and Befriending group

Group	Baseline Mean (SD)	Week 6 Mean (SD)	Week 12 Mean (SD)	Baseline – Week 12 Mean Change (95% CI)	Week 12 Between Group Mean Diff (95% CI)	p value[1]
Domain 1 Physical Health[3]						
MD	49.3 (14.8)	64.9 (12.8)[4]	73.7 (10.5)[5]	24.4 (18.37, 30.43)	17.7 (10.67, 24.74)	**<0.001[2]**
Befriending	53.3 (15.4)	57.6 (13.3)[4]	59.9 (14.7)[5]	6.6 (-0.48, 13.68)		
Domain 2 Psychological[3]						
MD	32.0 (14.1)	51.7 (16.4)[6]	61.0 (13.6)[7]	29.0 (22.49, 35.51)	22.1 (16.07, 28.13)	**<0.001[2]**
Befriending	35.7 (13.3)	40.8 (13.4)[6]	42.6 (15.3)[7]	6.9 (0.16, 13.64)		
Domain 3 Social Relationships[3]						
MD	46.5 (18.8)	52.9 (17.2)	58.2 (15.2)	11.7 (3.66, 19.74)	5.7 (-2.41, 13.81)	0.676
Befriending	45.9 (21.1)	50.5 (21.5)	51.9 (21.4)	6.0 (-3.99, 15.99)		
Domain 4 Environment[3]						
MD	67.5 (16.0)	72.9 (12.4)	77.0 (12.4)	9.5 (-3.99, 15.99)	4.8 (-1.21, 10.81)	0.512
Befriending	66.8 (14.6)	69.5 (13.8)	71.5 (14.4)	4.7 (-2.12, 11.52		
Total Raw Score						
MD	71.9 (10.1)	83.7 (9.3)[8]	90.2 (8.5)[9]	18.3 (13.91, 22.69)	12.7 (7.92, 17.48)	**<0.001[2]**
Befriending	73.8 (10.8)	77.5 (10.3)[8]	79.4 (11.9)[9]	5.6 (0.26, 10.94)		

[1]p values are for two-way repeated measure ANOVA

[2]p value is <0.001 for the interaction of group, time and group by time.

[3] Transformed Scores (/100)

[4-9] Means sharing a common superscript number are significantly different at p<0.05 (Tukey's HSD)

6.3 CHAPTER SUMMARY

This chapter has outlined the results from the AMMEND study. The results show that young men with moderate to severe clinical depression and poor baseline diets are able to significantly change their diets and adopt a MD over a short time period. These changes lead to significant improvements in depressive symptoms and quality of life.

7. CHAPTER 7: A Mediterranean Diet for Men with Depression (AMMEND) follow up Survey

7.1 PREFACE

The previous chapter outlined the AMMEND study results article. This next chapter presents the results from the end-of-trial evaluation survey. The questionnaire used was developed specifically for the AMMEND study. This chapter presents the accepted manuscript which has been published in Clinical Nutrition ESPEN (IF: 2.4) in December 2022. It is reproduced here with permission from Elsevier.

Bayes, J, Schloss, J, Sibbritt, D, 2022. 'A Mediterranean diet intervention for young men with depression: patient experiences, challenges and benefits (the "AMMEND study") – A Cross-sectional Study', Clinical Nutrition ESPEN, DOI: 10.1016/j.clnesp.2022.12.016

7.2 THE AMMEND FOLLOW UP SURVEY RESULTS

A Mediterranean diet intervention for young men with depression: patient experiences, challenges and benefits (the "AMMEND study") – A Cross-sectional Study

ABSTRACT

Background: Recent research has highlighted the beneficial effects of following a Mediterranean diet (MD) for depression. Unfortunately, adherence to specific diets presents many challenges and while previous research has aimed to understand these challenges, the focus has primarily been on weight-loss interventions in patients with obesity or cardiovascular disease. There is a limited understanding of the specific challenges faced by those with clinical depression, and for young men.

Aims: The aim of this study is to understand the experiences, challenges and benefits expressed by young men with clinical depression who completed a 12-week Mediterranean diet intervention.

Methods: An online questionnaire was used to collected data from 36 young Australian men aged between 18-25 with diagnosed depression who participated in the Mediterranean Diet arm of the Mediterranean Diet for Men with Depression (AMMEND) study. Descriptive analyses were undertaken for each variable with results reported as percentages and frequencies.

Results: Positive aspects highlighted by participants included enjoying the taste of foods, finding the diet easy to follow, being highly motivated to continue with the diet and a perceived benefit to their depressive symptoms. The main challenges highlighted by participants included difficulties findings food options when eating out, the diet being more expensive or time consuming than their previous diet and the negative attitudes of their friends and family towards the Mediterranean diet intervention.

Conclusion: We recommend that the influence of friends and family attitudes towards the diet and the impact this has on following a Mediterranean diet in young men be explored further, as this posed a challenge for many of our participants. The results from this study may also assist clinicians when promoting a Mediterranean diet to this specific demographic.

Keywords: Young adult; Men; Diet, Mediterranean; depression; Depressive disorder, major.

INTRODUCTION

Depression is a common mental health condition estimated to affect over 350 million people worldwide[2]. Previous observational research has demonstrated that diet quality is often associated with mental health issues, with poorer diet quality associated with a greater risk of depression[381-384]. Additionally, certain diet patterns have shown to be protective against developing depression, these include the Mediterranean diet (MD)[384], the Dietary Approaches to Stop Hypertension (DASH) diet[405] and the MIND diet[406]. Recent experimental research has also demonstrated that dietary change, specifically following a Mediterranean diet (MD), can be effective in the treatment of clinical depression[140,240]. Research also shows that men have a preference for therapy that focuses on action, goals and observable progress[245]. Therefore, diet interventions which focus on motivational interviewing, actionable tasks such as meal preparation, goal setting and progress reports could be more appealing to men.

Despite prevalent symptoms of depression including fatigue and a lack of motivation, previous research in depressed men shows that the majority would be willing to change their

diets if it might improve their depressive symptoms[361]. Substantial evidence also shows that men tend to eat more processed fast foods, and less fruits and vegetables than women[341,407,408]. Therefore, *the Mediterranean Diet for Men with Depression* (AMMEND) study aimed to improve the diet quality of young men experiencing depression with nutritional counselling focusing on a MD. Participants attended three appointments over 12 weeks with a qualified nutritionist, which resulted in significant improvements in depressive symptoms[409].

The MD is a diet high in plant foods, particularly fruits, vegetables, whole grains, legumes, nuts and seeds. The MD is also high in healthy fats from fish and olive oil, but low in processed foods such as sugary snacks, fried foods and preserved meats. Like any new habit, dietary change involves significant motivation, commitment and education[410]. Unfortunately, long-term adherence to diets are notoriously poor[411], with less than a quarter of individuals who begin a healthy eating plan able to maintain it 12 months later[412]. While some research has previously explored challenges to dietary adherence, the focus has primarily been on weight-loss interventions in patients with obesity[413] or cardiovascular disease[414]. There is a limited understanding of the specific challenges faced by those with clinical depression, and for young men, when following a MD.

Therefore, our primary aim was to understand the experiences, challenges and benefits expressed by the participants of the AMMEND trial who completed the 12-week MD intervention. We aimed to explore the perceived challenges of following a MD and examine which aspects the participants found easy to follow. We also assessed whether young men with depression would consider following a MD long-term as part of an adjunctive treatment strategy.

METHODS

Study design

The AMMEND study was a 12-week randomised control trial of a MD intervention in the treatment of moderate to severe depression. A detailed study protocol has been published previously[386]. This research presents the results from the end-of-project evaluation which included an anonymous online survey. Both the trial and the end-of-project evaluation was registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR) Trial Id: ACTRN12619001545156 prior to recruitment. This research has also been registered with the

World Health Organisation (WHO) International Clinical Trials Registry Platform's (ICTRP) Universal Trial Number: U1111-1242-5215.

Participants were recruited from Australia over an 18-month period and randomised to receive either dietary counselling or a social support therapy called befriending[367]. Assessments were completed at baseline, week 6 and at week 12. The follow up survey was completed by participants allocated to the MD group at the completion of the trial at week 12. Ethics approval was received from the Human Research Ethics Committees of the University of Technology Sydney (UTS) on the 4th February 2020: UTS HREC REF NO. ETH19-4413. Written informed consent was obtained from all participants before commencement of any intervention.

Study population and sampling

Young men who had previously received a diagnosis of major depressive disorder (MDD) by a general medical practitioner were recruited into the trial. The sample size calculation for the AMMEND trial was based on being able to detect a minimum clinically important change of >5 points on the BDI-II [363] while comparing the MD and placebo group, with α=0.05 and 80% power. Previous studies[364,365] demonstrated a normally distributed response within groups with an approximate standard deviation of 7.5. Therefore, we calculated that a minimum of 36 participants were needed per group.

Inclusion and exclusion criteria

Eligibility criteria included participants who identified as male, were aged 18-25 years of age, with moderate to severe depression, as measured by the twenty-one-item Beck Depression Inventory (BDI-II) score of 20 or above[415]. Additionally, participants were required to have a poor baseline diet, measuring as <40/100 on the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Diet Survey[386]. The exclusion criteria included the following disorders: bipolar disorder, posttraumatic stress, personality disorders, schizophrenia or a substance abuse disorder. Gastrointestinal disorders or food allergies, intolerances or eversions, including eating disorders, preventing participants from following the diet.

Diet Intervention group

Participants in the MD group attended appointments with a clinical nutritionist at the beginning of the trial. These appointments included personalised dietary advice, goal setting,

motivational interviewing and mindful eating suggestions to encourage optimum adherence to the Mediterranean diet. The MD used in this research is based on the dietary guidelines of Greece and Spain[389-391], which is high in vegetables, wholegrains, oily fish, legumes, nuts and olive oil. The central emphasis was to improve the quality and nutrient density of the diet, while also minimising the consumption of nutrient-poor foods. Participants were supplied with a food hamper containing Mediterranean diet food staples and a booklet including sample meal plans and recipes at their baseline appointment. The diet intervention was devised to be straightforward, cost effective and palatable. Weight loss was *not* an aim of the diet and participants were instructed to consume permitted foods freely.

Data collection methods and instruments

A detailed description of the data collection tools used in the AMMEND trial can be found in the study protocol[386]. Participants who completed the MD intervention arm of the trial were invited to complete an anonymous end-of-project evaluation survey. This was a cross-sectional online questionnaire which consisted of sixteen multiple-choice questions, that followed a Likert style answering system. The questionnaire was created and managed via the research program RedCap and asked participants to reflect on their experiences following the MD. The survey asks participants to reflect on several different topics including their weekly food budget, time commitment, motivation, enjoyment level, challenges and perceived impact on their depressive symptoms and was developed specifically for the AMMEND trial.

Data analysis methods

Participants' experiences were investigated by treating each questionnaire item as a categorical variable. Descriptive analyses were undertaken for each variable with results reported as percentages and frequencies.

RESULTS

All participants who completed the AMMEND trial and were allocated to the MD group completed the end-of-project evaluation survey and interview (n=36). The mean age of participants was 21.5 years. The mean baseline depression score on the BDI-II scale was 34.8 and the mean baseline Commonwealth Scientific and Industrial Research Organisation (CSIRO) diet score was 35.1. A detailed report of all baseline characteristics for the AMMEND

study participants has been published elsewhere[416]. The results for each question on the online survey can be found in Table 1.

Cost and time

When asked about money spent following the diet the responses were evenly split over three answer choices. Roughly one third answered that following the MD was cheaper than their usual food budget (n=11, 30.5%), one third indicated that following the MD was about the same as their usual food budget (n=12, 33.3%) and one third indicated that following the MD was more expensive than their usual food budget (n=12, 33.3%).

Participants were asked to compare the time spent cooking and preparing meals while following the MD to their past routine. The most frequently reported answer was that following the MD was "about the same as their usual routine" (n=17, 47.2%), followed by "longer than their usual routine" (n=15, 41.6%). Only 3 participants indicated that while following the MD cooking and preparing food was "less than their usual routine" (8.3%).

Cooking skills

Participants were asked to rate the difficulty of cooking and preparing MD dishes and recipes. The majority of participants indicated that they found the dishes and recipes easy to make (n=34, 94.4%). The majority of participants also indicated that they had the required cooking equipment and utensils (n=23, 63.8%), while a third indicated that they had to learn to cook (n=11, 30.6%). Most of the participants found locating the required foods and ingredients while grocery shopping easy (n=25, 69.4%), while others indicated that "some foods were easy to find while others were hard" (n=11, 27.7%).

Eating out

When eating out in cafes, restaurants, food courts and ordering food online, 50% of participants indicated that they could easily find options which fit the diet criteria (n=18), while 28% (n=10) struggled find options which fit the diet criteria, and 22% (n=8) had to find new places to eat due to diet requirements

Taste and enjoyment

When eating Mediterranean foods and meals, 75% (n=27) indicated that they enjoyed the taste of the foods and meals, while 22% (n=8) indicated that they enjoyed some foods and

not others. Only 1 participant indicated that they did not enjoy the taste of the MD foods and meals. While following the MD, 64% indicated that they did not feel as though they were missing out on tasty foods (n=23), while 33% indicated that they did feel as though they were missing out on tasty foods (n=12). The majority of participants (n=31, 86%) indicated that the MD was an easy diet to follow, with only 2 participants indicating that the MD was a hard diet to follow.

Attitudes of others

The majority of participants (n=21, 58%) indicated that the MD was received positively by their friends and family, while 28% (n=10) indicated that the MD received mixed responses. Five participants (14%) indicated that the MD was received negatively by their friends and family. When discussing the MD with their healthcare practitioners, the majority of participants (n=19, 53%) indicated that the MD was received positively by their health care practitioner, while 33% (n=12) indicated that their practitioner did not express an opinion.

Perceived and actual impact

When asked to reflect on their expectations before starting the MD, 44% (n=16) participants indicated that they thought the MD would have no impact on their depressive symptoms, while 39% (n=14) though the diet would have some impact. When asked what degree of impact they believe the MD had on their depressive symptoms by the conclusion of the study, 100% of participants indicated that they observed an improvement in their depressive symptoms. The majority indicated that it had a significant improvement on their symptoms (n=24, 67%), and 33% indicated that it had an improvement in symptoms.

Motivation to continue

Participants were asked about their motivation to continue with the MD. The majority (n=20, 56%) of participants indicated that they were highly motivated and 39% (n=14) indicated that they were somewhat motivated to continue. Only 1 participant reported that they were unmotivated to continue following the MD. When asked how likely they were to continue following the MD eating pattern, 56% (n=20) indicated that they were likely to continue and 39% indicated that they were very likely to continue.

DISCUSSION

This was the first research to explore the experiences, challenges and benefits of following a 12-week MD program expressed by young men with moderate to severe clinical depression. We identified a number of factors which had a positive and negative influence on the participants experience as well as specific challenges encountered. We found that all participants observed an improvement in their depressive symptoms and expressed a willingness to continue with the prescribed diet beyond the conclusion of the program. This is encouraging and suggests that the MD could play a pivotal role in depression treatment for young men. It adds to the growing body of evidence suggesting that the MD should be considered an important lifestyle based mental healthcare strategy for individuals with major depressive disorder[417].

The main positive aspects highlighted by participants included enjoying the taste of MD foods, finding the diet easy to follow, being highly motivated to continue following the diet and a perceived benefit to their depressive symptoms. These positive effects support findings from previous research which explored the experiences of middle-aged healthy adults in England who followed an 8-week MD intervention[375]. This study also found that participants enjoyed the taste and experience of eating Mediterranean foods and that trying new foods is an important benefit of following the diet[375]. We therefore recommend that these factors be highlighted by clinicians when talking with patients who may be considering a MD.

The main challenges highlighted by participants in our research included the MD being more expensive and time consuming than their previous diet and difficulties findings food options when eating out. This finding has been reported by other researchers which examined common barriers to healthy eating in young men aged 18-25[418]. They reported that a lack of time to cook and prepare healthy foods due to a busy lifestyle and the ease of access to unhealthy foods to be key barriers to healthy eating[418]. Strategies to overcome these major barriers should be considered by clinicians implementing a MD with young men. In the AMMEND study, participants were provided with examples of low-cost alternatives to more expensive food items and given strategies on how to fit meal preparation into busy schedules. This may explain why one third of participants found following the diet to be less expensive than their usual routine.

Some participants reported negative attitudes from their friends and family when discussing the MD. Previous studies in young adults suggests that peer pressure plays a pivotal role in food choices[419]. Research suggests that young adults may attach social meanings to food, and judge peers based on their food choices[420], which may lead to young people choosing less healthy but more socially acceptable options[421]. Some researchers have even suggested that choosing healthy foods is emotionally and socially risky for young people who have an emotional need for identity and belonging[421]. Compounding this issue are the additional barriers and significant stigma which still exist for men following a healthy diet in relation to hegemonic masculinity[395]. Evidently there is a pressing need to further understand these significant barriers and the impact they have on food choices in young men, as well campaigns to normalise the consumption of a healthy diet in young men.

It was interesting to note that a large percentage of participants (44%) indicated that prior to beginning the MD program, they did not believe that the MD would make any difference to their depressive symptoms. A further 14% were unsure of what impact they expected and only 1 participant (3%) thought that a MD would have a significant impact on their depressive symptoms. This suggests two things. Firstly, that the impact of diet on mental health is not widely known by young men with depression, despite recent research and media attention on the topic[140,240,396,422]. Secondly, that the positive impact experienced by all of the participants was not influenced by expectancy bias.

This research has presented a number of important findings, however, there are several limitations which must be acknowledged. Firstly, the survey data collected from participants was self-reported. Hence, there may be biases in our study data caused by social desirability bias as well as recall bias. Additionally, our sample size is small. Even though all participants who completed the MD arm of the AMMEND trial completed this end-of-project evaluation survey and interview, further research on a larger sample are needed to generalise these findings to the wider community.

CONCLUSION

The aim of this research was to explore the experiences, challenges and benefits of following a 12-week MD program expressed by young men with moderate to severe clinical depression. This was the first research study to identify factors which had a positive and negative influence on the participants experience as well as specific challenges encountered.

We recommend that the barriers of cost, time, and the attitudes of friends and family be explored further, as these factors could pose a significant challenge for young men following the MD long term. The results from this study may also assist clinicians when promoting a MD to this specific demographic.

FUNDING

The authors would like to thank Endeavour College of Natural Health and the Australian Research Centre in Complementary and Integrative Medicine (ARCCIM), University of Technology Sydney (UTS) for providing funding for this research.

ACKNOWLEDGMENTS

JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

STATEMENT OF AUTHORSHIP

JB conceptualised and designed the study; JS and DS assisted with the development of the study design, methodology and statistical analysis plan. JB obtained the funding and ethics approval with assistance from JS and DS; JB drafted the manuscript with edits from JS and DS; all authors contributed to the manuscript and approved the final version.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist. The AMMEND trial was funded by Endeavour College of Natural Health. The funding body has no involvement with the design, implementation or analysis of the project. JB is a consulting nutritionist and lecturer. JS is a consulting naturopath. There are no potential commercial interest to declare.

Table 1. Participant questionnaire responses

Questions	Number of Responses (% of respondents)				
The following questions relate to your experiences following the MD.	Was cheaper than my usual budget	Was about the same as my usual budget	Was more expensive than my usual budget	Unsure	Prefer not to answer
The amount of money you spent on food:	11 (30.5%)	12 (33.3%)	12 (33.3%)	1 (2.7%)	0 (0%)
	Was less than my usual routine	Was about the same as my usual routine	Was longer than my usual routine	Unsure	Prefer not to answer
The time spent preparing meals and cooking:	3 (8.3%)	17 (47.2%)	15 (41.6%)	1 (2.7%)	0 (0%)
	Dishes/recipes were easy to make	Some Dishes/recipes were easy while others were hard	Dishes/recipes were difficult to make	Unsure	Prefer not to answer
When preparing and cooking Mediterranean dishes/recipes:	34 (94.4%)	0 (0%)	2 (5.6%)	0 (0%)	0 (0%)
	In enjoyed the taste of the foods and recipes	I enjoyed some foods and not others	I did not enjoy the tastes of the foods and recipes	Unsure	Prefer not to answer
When eating Mediterranean foods and recipes	27 (75%)	8 (22.2%)	1 (2.7%)	0 (0%)	0 (0%)
	I did not feel as though I was missing out on tasty foods		I did feel as though I was missing out on tasty foods	Unsure	Prefer not to answer
While following the Mediterranean diet:	23 (63.8%)		12 (33.3%)	1 (2.7%)	0 (0%)
	An easy diet to follow	A hard diet to follow	Too strict	Unsure	Prefer not to answer
The Mediterranean diet is:	31 (86.1%)	2 (5.6%)	0 (0%)	3 (8.3%)	0 (0%)
	I could find the required foods and ingredients	Some foods were easy to find while others were hard	I could not find the required foods and ingredients	Unsure	Prefer not to answer
When shopping for foods and ingredients	25 (69.4%)	10 (27.7%)	0 (0%)	1 (2.7%)	0 (0%)
	I had the required equipment and utensils	I did not have the required equipment and utensils	I had to learn to cook	I did not know what utensils to use	Unsure

When cooking and preparing meals:	23 (63.8%)	2 (5.6%)	11 (30.6%)	0 (0%)	0 (0%)

	I could easily find options which fit the diet criteria	I struggled to find options which fit the diet criteria	I had to find new places to eat due to diet requirements	Unsure	Prefer not to answer
When eating out in cafes, restaurants, food courts and ordering food online:	18 (50.0%)	10 (27.8%)	8 (22.2%)	0 (0%)	0 (0%)

	Diet was received positively by my friends and family	Diet had mixed responses from my friends and family	Diet was received negatively by my friends and family	Unsure	Prefer not to answer
When talking to friends and family about the diet:	21 (58.3%)	10 (27.8%)	5 (13.9%)	0 (0%)	0 (0%)

	Diet was received positively by my health care practitioner	I had mixed responses from my health care practitioners	Diet was received negatively by my health care practitioner	My practitioner did not express an opinion	Unsure/prefer not to say
When discussing the diet with my health care practitioner:	19 (52.7%)	1 (2.7%)	0 (0%)	12 (33.3%)	4 (11.1%)

	I experienced no unpleasant digestive symptoms	I did experience some unpleasant digestive symptoms	Unsure	Prefer not to say
While following the Mediterranean diet:	36 (100%)	0 (0%)	0 (0%)	0 (0%)

	Highly motivated	Somewhat motivated	Unmotivated	Very unmotivated	Unsure/prefer not to answer
My motivation to continue with the diet:	20 (55.6%)	14 (38.9%)	1 (2.7%)	0 (0%)	1 (2.7%)

	A significant improvement in symptoms	An improvement in symptoms	No difference	A worsening of symptoms	A significant worsening of symptoms	Unsure
Before you started the Mediterranean diet, what outcomes did you expect it to have on your depressive symptoms:	1 (2.7%)	14 (38.9%)	16 (44.4%)	0 (0%)	0 (0%)	5 (13.9%)

	A significant improvement in symptoms	An improvement in symptoms	No difference	A worsening of symptoms	A significant worsening of symptoms	Unsure
Now that you have followed the diet for 12 weeks, what degree of impact do you think the diet had on your						

depressive symptoms:	24 (66.7%)	12 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Very likely	Likely	Unsure	Unlikely	Very Unlikely	Prefer not to say
How likely would you be to continue with a Mediterranean diet?	14 (38.9%)	20 (55.6%)	1 (2.7%)	1 (2.7%)	0 (0%)	0 (0%)

7.3 CHAPTER SUMMARY

This chapter outlines the results from the end-of-trial evaluation survey. It has highlighted the main challenges and barriers to following the MD program by young men with depression. These included difficulties findings food options when eating out, the diet being more expensive or time consuming than their previous diet and the negative attitudes of their friends and family towards the Mediterranean diet intervention. Positive aspects highlighted by participants included enjoying the taste of foods, finding the diet easy to follow, being highly motivated to continue with the diet and a perceived benefit to their depressive symptoms. It is important for clinicians to be aware of these challenges when implementing a MD in clinical practice.

8. CHAPTER 8: AN OVERVIEW OF FINDINGS

8.1 PREFACE

The previous chapter outlined the results from the AMMEND end-of-trial evaluation survey study. This next chapter presents a short report article which provides an overview of the current evidence on diet and depression in young men and collates the findings from each of the projects included in this thesis. The short report article "The use of diet for treating depression in young men: Current evidence and existing challenges" is currently under peer review with *Nutrition*.

8.2 OVERVIEW OF FINDINGS

The use of diet for treating depression in young men: Current evidence and existing challenges

Short Communications

Depression is a leading cause of disability among young adults, and in Australia, depression affects 6.4% of 18-25 year old's each year[423]. Many young adults cannot correctly identify the symptoms of depression[424], and have limited understanding about effective treatment options[425]. Research shows that men are less likely to seek help than women, with only 1 in 4 men who experience depression accessing treatment[3]. Depression is also a high-risk factor for suicide, which is the leading cause of death in young men[426]. Therefore, there is a pressing need for early interventions which appeal to young men with depression. Recently, diet therapy has been proposed as a potential treatment option for major depressive disorder.

Nutritional psychiatry explores the use of specific nutrients, foods and dietary patterns for mental health conditions[137]. A large number of different nutrients have been examined for their effect on depressive symptoms, including vitamins such as folate, B12 and B6[427], amino acids such as tryptophan[428] and SAMe[429], as well as polyphenols[336], probiotics[220] and omega 3 fatty acids[430]. Numerous mechanisms whereby diet may exert beneficial effects on

depressive symptoms have been proposed. These include the role of reducing inflammation, oxidative stress, increasing brain-derived neurotrophic factor (BDNF), balancing the microbiome and tryptophan/serotonin metabolism[139]. Despite known differences in depression characteristics and treatment responses between males and females, there are limited sex-specific studies examining the role of diet in young men specifically.

Specific Nutrients, diets and Depression in Men: Tryptophan, SAMe, Folic acid, Polyphenols and Omega 3 fatty acids

Tryptophan is an essential amino acid that acts as a precursor to serotonin[431]. The role of tryptophan in mood disorders has been the target of much research since the 1980's, however the results are often inconsistent and contradictory[432]. Further, research suggests that men and women respond differently to increases in tryptophan levels[432], with tryptophan supplementation found to affect the emotional processing response of the females, but not males[433]. This indicates that women may be more sensitive to changes in serotonin levels than men[433] with studies showing that estrogen and testosterone exert direct and indirect effects on serotonin transporter proteins[434]. In addition, a large epidemiological study of 29,133 men, found no association between dietary tryptophan intake and self-reported depressed mood, hospital admission for depressive disorders or suicide[435]. The conflicting evidence on the role of tryptophan in men currently limits recommendations for its use at this time.

S-adenosyl methionine (SAMe) is a nutritional compound that plays a crucial role in one-carbon cycle and methylation of neurotransmitters[436]. Several studies have assessed the effect of SAMe supplements for treating mood disorders, with the majority showing a favourable effect[436]. However, research demonstrates that sex might impact the antidepressant efficacy of SAMe, with a greater therapeutic effect observed in men[437]. This finding emerged despite both males and females displaying similar baseline depression severity. The authors suggest this finding could be due to variances in the one-carbon cycle pathways, as a result of hormonal regulation[437]. However, further research is needed in this area to determine to exact mechanisms involved.

Folic acid also plays an important role in the one-carbon cycle, and folate deficiency has consistently been associated with increased depression[438]. A recent systematic literature review and meta-analysis found that folate, as an adjunct to SSRI/SNRIs improves depression

scores, remission and response rates[438]. However, sex differences have been observed, with a 10 week trial demonstrating that a significantly greater percentage of women responded favourably to the folic acid supplementation compared to the men[439]. It has been suggested that the 500-µg/d dose may not have been sufficient for men and that a higher does may be required to achieve a positive treatment effect[440].

Other nutritional compounds which have received recent attention for their potential impact on depression are the various polyphenolic compounds[336]. Polyphenols are natural agents found in a variety of plant foods. [441]. These naturally occurring compounds are found in high quantities in fruits, vegetables, tea, coffee, chocolate, legumes and cereals[441]. Polyphenols are potent antioxidant and anti-inflammatory agents, and have shown to prevent neuro-inflammation[263], and modulate specific cellular signalling pathways involved in cognitive processes [264]. A recent systematic literature review assessed the role of polyphenols for depression[336]. The results highlighted a beneficial role of several different polyphenols, including coffee, curcumin, soy isoflavones, tea and cocoa flavanols, walnut flavonols, citrus flavanones and the stilbene resveratrol[336]. However, the review also highlighted a lack of research on men and young adults specifically[336].

Another nutrient which has gained much recent attention is omega 3 polyunsaturated fatty acids (PUFA's). While much evidence supports the efficacy of omega 3's for depression[430], numerous epidemiological studies have found these beneficial effects apply to females but not to males[442-444]. A recent review has suggested that these differences could possibly be due to sex hormones and their influence on docosahexaenoic acid (DHA)[445]. Estrogen has shown to increases DHA levels within the body, while testosterone decreases them[446]. This further demonstrates the different treatment response experienced by men to certain nutrients.

A recent systematic review and meta-analysis published in 2019 assessed the effect of dietary improvement on the symptoms of depression and anxiety[447]. They found that studies with female samples observed significantly greater benefits from dietary interventions compared to male samples[447]. The authors propose three reasons to explain this finding. First that females have higher rates of mood disorders across the general population[447]. Secondly, due to differences in metabolism and body composition, females may be more responsive to dietary interventions which affect glucose or fat metabolism[447]. Thirdly, the sociocultural

differences between males and females may shape beliefs around diet, nutrition and health thereby influencing the outcome of dietary intervention trials[447].

Dietary Patterns of Young Men with Depression

Currently, there has been a shift away from supplementing with isolated nutritional compounds to a focus on overall dietary patterns[141]. A recent cross-sectional study, *the MEN'S Diet and Depression Survey* (*MENDDS) e*xamined the diets of 384 young men aged 18-25 with clinical depression[361]. The results revealed that their diets were poor and included a high consumption of processed foods and high sugar snacks[361]. The majority of the participants consumed chocolate and sweets three times per week, in addition to a high consumption of sweet pastries and bakery items[361]. Research suggests that high sugar intake is associated with low mood due to its influence on inflammation, insulin response and BDNF[346].

There was also a high consumption of fried foods, with the majority of participants consuming pizza, and fried potato such as French fries or hash browns three or more times per week[361]. These foods are high in processed vegetable oil which has recently been shown to increase the risk of developing depression[448]. Vegetable oil is high in omega 6 fatty acids, and it is thought that an imbalance in the ratio of omega 6 and omega 3 fatty acids contributes to increased inflammation and negative mental health symptoms[448].

Additionally, roughly 40% of participants in the MENDDS consumed processed meats such as bacon, hot dogs and lunch meats such as ham, salami and spam two or more times per week[361]. This is particularly concerning as much epidemiological data has shown that a high intake of processed meat is associated with cardiovascular disease, type 2 diabetes mellitus, and cancer[449]. A recent meta-analysis has also demonstrated that processed meat is associated with a moderately higher risk of depression[449]. Processed meats are high in inflammatory compounds such as saturated fats, nitrates and nitrites, polycyclic aromatic hydrocarbons and heterocyclic amines which could be responsible for these negative effects[450].

Interestingly, the MENDDS study also found that the vast majority of the participants indicated that they feel as though their diets impact their mental health and would be willing to change it in order to help their depressive symptoms[361]. The results showed that their

current diets were low in fruits, vegetables, beans, and wholegrains. Only 9% of participants consumed vegetables twice or more per day and roughly half of the participants reported never consuming wholegrains or legumes[361]. These foods are staple ingredients in the Mediterranean Diet, which is currently the dietary pattern with the most evidence for treating major depressive disorder[140,240].

The use of a Mediterranean diet for treating depression in young men

A recent randomised controlled trial, *A Mediterranean diet for MEN with Depression* (The AMMEND trial) tested the effect of a Mediterranean Diet on the symptoms of depression in young men aged 18-25, with moderate to severe clinical depression[409]. The results demonstrated that young men who experience depression are able to significantly change their diet quality over a short time period (12 weeks) under the guidance of a clinical nutritionist[409]. The Mediterranean Diet intervention in this cohort led to both clinically and statistically significant improvements in depressive symptoms, as measured by the Beck Depression Inventory (BDI-II). Improvements were also observed on the World Health Organisations (WHO), Quality of Life (QoL) measurement scale, with both clinically and statistically significant improvements observed in both the psychological and physical domain, as well the total QoL raw score[409]. These findings suggest that following a Mediterranean Diet has the potential to have a wide impact on young men with depression, influencing many aspects of their health and wellbeing. Additionally, the Mediterranean Diet was well tolerated with no reported side effects[409].

Key challenges of incorporating dietary change in young men

The AMMEND end of project evaluation identified several barriers experienced by the study participants when following the Mediterranean Diet program. These included the cost of Mediterranean Diet foods, time spent cooking and preparing food and struggling to find options which met the diet criteria when eating in restaurants or ordering food online. Some participants also reported negative attitudes from their family and friends towards to the diet. Despite these challenges, excellent adherence to the diet was observed among all participants, suggesting that the motivation to adhere to the diet was greater than the influence of these barriers. However, it is unclear what long-term affect these challenges would have on ongoing adherence to a Mediterranean Diet.

Previous research which examined a Mediterranean Diet intervention in healthy older adults assessed the facilitators and barriers for adopting a Mediterranean Diet in a non-Mediterranean country[375]. They reported similar challenges, including the increased cost of food and time required to prepare food as key barriers affecting their experience. The authors recommended that the assumptions about what a Mediterranean Diet involves should be challenged, as many participants held the view that the Mediterranean Diet predominantly consists of salads[375].

In addition to these barriers, research shows that everyday items, including foods, are permeated with subtle yet pervasive gender associations[451]. Studies have demonstrated that individuals who eat unhealthy food and larger portion sizes are typically seen as more masculine[452,453]. Conversely, individuals who eat healthy food and smaller meals are perceived as more feminine[452]. The food with the strongest association with the masculine identity is meat, with fruits and vegetables frequently viewed as more feminine[452]. The impact of gender stereotypes and the desire for social acceptance and the influence that this may have on food choices should not be underestimated. It is important that these factors are taken into consideration when evaluating the barriers to implementing a Mediterranean Diet in young men with depression.

Suggestions for overcoming these challenges in research trials and within clinical practise

When discussing the Mediterranean Diet in clinical practise and in clinical trials, adequately explaining the components of the Mediterranean Diet is crucial in order to correct assumptions about what a Mediterranean Diet involves. Emphasis should also be given to providing low-cost food items and simple recipes which take minimal time to prepare. Providing examples on how to choose healthier options when ordering food online may also be valuable for young men. Discussing strategies to overcome the potential negative attitudes of their family and peers should also be considered.

Some authors have suggested that the word “diet” comes with many negative associations, especially for individuals who have previously experienced restrictive dietary regimens[454]. Previous research has also demonstrated that men view dieting as a predominantly female activity[455]. Therefore, it is to be expected that a Mediterranean Diet intervention may create conflict with both food-based gender stereotypes and help seeking behaviour in general. It has been suggested that to overcome these negative connotations, the Mediterranean Diet

be referred to as “a lifestyle” rather than “a diet”[456]. It would be interesting to look at what difference, if any, omitting the word “diet” makes to the attitudes of young men. For example, would a “Mediterranean Lifestyle” or “Mediterranean Eating Pattern” be better perceived and understood by this demographic? Determining what words, terms and phrases resonate the most with this demographic may help with clinical trial recruitment and for clinicians suggesting a Mediterranean Diet in clinical practise.

CONCLUSION

When considering isolated nutrient supplementation for men, the current evidence is conflicting. The role of tryptophan on depressive symptoms in men is contradictory, and omega 3 fatty acids appears to have a less pronounced treatment effect in males compared to females. Polyphenols show promise, but more research is required to confirm these results. The shift in nutrition science from isolated nutrients to overall dietary patterns may hold more potential. New evidence shows that a Mediterranean Diet is effective in treating depression in young men with moderate to severe clinical depression. We recommend that clinicians prioritise discussing the role of diet with depressed young men and consider referrals to nutritionists or dietitians for specialist support.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist.

ACKNOWLEDGMENTS

JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

8.3 CHAPTER SUMMARY

This chapter presented an up-to-date overview of the current research on diet and depression in young men. It summarised the main results from the research presented in this thesis and discussed the findings in the context of other research in this field.

9. CHAPTER 9: DISCUSSION

9.1 PREFACE

This thesis has made several original contributions to knowledge. This chapter will discuss these contributions, provide an interpretation of the main research findings from each project and consider the implications of these results. Specific challenges which occurred during the candidature are also discussed and limitations of the research outlined.

9.2 DISCUSSION

The original contributions to knowledge this thesis presents include: 1) The first systematic literature review to assess the effect of polyphenols in a Mediterranean diet on symptoms of depression; 2) The first research to examine the diets of young men with depression and to examine their nutrition knowledge and opinions; 3) The first RCT in young men with clinical depression conducted to explore the effect of a MD on depressive symptoms; 4) The first RCT to demonstrate that a MD can effectively treat clinical depression in young men; 5) The first research to explore and identify the challenges of following a MD for this specific demographic.

The first research project contained within this thesis was the systematic literature review exploring the role of polyphenols in depression. The results highlight that various polyphenols do appear to play an important role in both mediating depression risk, and in treating active clinical depression. In particular, the polyphenols found in citrus, grapes, nuts, soy, cocoa, tea and coffee appear to be most effective. The evidence for tea and coffee were from observational research studies while the evidence for cocoa, citrus and grapes were from experimental interventions. The cocoa was consumed as a food (chocolate), while the others were prescribed as nutraceutical supplements. Soy isoflavones and walnut flavonols efficacy were supported by both experimental and observational evidence. While it is generally considered better to incorporate these polyphenols into the diet through whole foods, due to the synergistic action of nutritional compounds[137], the majority of trials used

oral supplements and still achieved beneficial results. This is important as it means that individuals with allergies, intolerances or aversions to specific foods could still reap the benefits via daily supplementation. It would be interesting to test the effect of a combination supplement, which includes several different polyphenols within the one product, and see if this has a greater effect on depressive symptoms compared to singular polyphenol supplements. While designing the study protocol for the AMMEND trial, we made sure that the participant resources for the MD included recipes and meal suggestions rich in these polyphenols.

The literature review does have some important limitations which should be discussed. The first issue relates to the methodology. I conducted the screening of article titles, abstracts and full text, performed the ROB assessment and undertook data extraction independently. Future studies should utilise two independent reviewers for title, abstract and full-text screening, ROB assessments and data extraction and in order to prevent researcher bias. Secondly, only research studies published in English were included which may have influenced the end results. Future reviews could also consider extracting more data on the methodology of each included study such as measures of adherence, intention to treat (ITT) or per protocol analysis, attrition rates and whether confounders were controlled for.

The next project undertaken within this thesis was the MENDDS survey, which set out to explore the current diets and nutritional knowledge of young men with depression. Much previous research had shown that the diets of men tend to be poorer than women[341]. The Australian Health Survey conducted by the Australian Bureau of Statistics has also reported that the diets of young adults tend to be high in refined and processed foods and drinks[457]. Therefore, we expected the diets of young men with depression to be poor, and thus our results were unsurprising. What was unexpected, was the large number of participants who indicated that they believe that their diet impacts their mental health and would be willing to change it. This laid the foundation for the AMMEND trial as it highlighted that dietary change was something that young men with depression were interested in and would be willing to try.

When considering the high percentage of young men who do not seek help for their depression[322], coupled with the high rates of non-responders to antidepressants[458] and the high out-of-pocket expense of psychotherapy[459], finding effective therapies which appeal to

young men is vitally important. Executing an intervention which does not appeal to or interest the target demographic would be futile, even if in theory, it appears promising. This is why the MENDDS survey was a critical and significant steppingstone in the development of the AMMEND trial.

We had originally set out to compare the BDI-II results of those who demonstrated high compliance to the MD to those who demonstrated low compliance. A score of 7 or less on the MEDAS is considered "low compliance". However, in our 12-week RCT, none of the participants allocated to the MD group displayed low compliance and thus we were unable to perform this subgroup analysis. This suggests that following a MD was very achievable for young men with clinical depression. Despite having poor baseline diets and moderate to severe clinical depression, all participants allocated to the diet group successfully maintained high compliance to the diet over the duration of the trial.

While we hoped for high compliance to the dietary guidelines, we did not expect all participants to achieve this. During the development of the AMMEND study protocol we invited 20 young males with depression to participate in a virtual online interview to give their opinion on the design of the trial, the research questions and the outcomes measures. Based on their opinions, priorities and preferences, modifications were then made to the study design. In particular, the young men we interviewed suggested that we include example meal ideas, shopping lists and budget friendly options in our study material for participants. By directly engaging with the demographic involved in our research, we were able to tailor our methods to meet their needs. This may explain the excellent adherence to the MD we observed in the AMMEND study participants.

The results from the AMMEND trial demonstrate that incorporating dietary change by following a MD can significantly reduce depressive symptoms in depressed young men. In the participants who had the highest adherence to the MD, as indicated by a MEDAS score of 13-15/15 at week 12, all participants had a final BDI score of 10 or less indicating low or minimal depression. This suggests that higher adherence to the diet is correlated with a greater reduction in symptoms. These results built on the work of previous researchers in the growing field of nutritional psychiatry, which suggests that diet plays an important role in the treatment of depression. The AMMEND trial results are the first to highlight that a MD

intervention can be effective in young men, a demographic which faces significant challenges and barriers regarding help seeking and dietary change.

In addition, there were no reported side effects or negative digestive symptoms observed. The end-of-trial evaluation survey also revealed that several participants noticed improvement in their digestive health while following the intervention. The MD is high in fiber, plant diversity, prebiotics and polyphenols which can positively affect the gastrointestinal microbiome and overall digestive health[460], which may explain this finding. Additionally, the microbiome is thought to be a key mechanism by which diet may exert a beneficial effect on depression[139]. The diversity of the gastrointestinal tract microbiome has been strongly associated with major depressive disorder[461]. This association is thought to be due to the bi-directional communication system between the gut and the brain. This communication is mediated by neuroimmune, neuroendocrine and sensory neural pathways[461].

Currently, evidence suggests that the primary neural signalling pathway between the microbiome and the brain is via the vagus nerve[461]. The vagus nerve, also called 10th cranial nerve, is the longest and most complex of the cranial nerves. It runs from the brain through the face and thorax to the abdomen[461]. It is constantly sending sensory information from the digestive tract to the brain and this may be the mechanism by which the microbiome influences mood[461]. Furthermore, the microbiome has shown to influence the modulation of neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), which may communicate via this channel[461].

Some of the AMMEND participants also experienced reduced body weight. Weight loss was not an aim of the trial, and the participants were encouraged to consume the permitted foods freely, however, by swapping out high kilojoule processed foods for whole foods, fruits and vegetables, the overall daily kilojoule intake may have reduced leading to the observed improvements in body weight. Additionally, a recent systematic review assessed the effect of the MD on long-term (≥ 12 months) weight loss[462]. The review concluded that the MD is superior to low-fat diets for long-term weight loss among overweight and obese individuals trying to lose weight[462]. It would be valuable to assess body weight, BMI and waist circumference in future longer-term clinical trials assessing the MD in young men with depression in order calculate the degree of impact the diet has on these measurements.

These anthropometrics measurements were originally included in the AMMEND trial design, however due to COVID-19 restrictions, these outcomes could not be collected. It would also be useful for future studies also conduct correlation analysis between weight loss and BDI-II symptom reduction.

Many clinical trials have been criticised for using outcomes measures and tools which assess outcomes in a highly reductionist approach. Therefore, quality of life (QoL) has recently become an important concept in the field of health and medicine as it encompasses the general wellbeing of patients and involves both objective and subjective indicators[463]. In addition, a shift to patient-centred medicine has occurred due to the increasing importance placed on patients' voices in disease management[464]. Therefore, the AMMEND trial also assessed QoL alongside other outcome measures.

The World Health Organization (WHO) defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns"[465]. Measurements of QoL made using clinical assessment tools aim to determine the benefits of an intervention on the participants overall health status[385], whereas QoL questionnaires typically assesses the participants experiences of an illness, such as disability, fatigue and pain, and may also include questions about participants physical, social and emotional wellbeing[385]. Therefore, examining the impact of diet on QoL provides additional insights into the efficacy of interventions across various domains of health.

A 2011 survey in the *SUN project*, a Mediterranean dynamic prospective follow-up cohort study in Spain, examined the effect of a MD on health-related QoL in healthy adults[466]. The study investigators found that adherence to the MD was associated with all of the physical domains and most of the mental health domains measured[466]. In older Australian participants with depression, the *Healthy Eating for LiFe with a MEDiterranean-style diet (HELFIMED)* study found that the MD significantly improved all domains on the Assessment of Quality of Life (AQoL-8D) questionnaire, except for pain[240]. However, no research had previously examined the effect of a MD on QoL in young males with depression.

AMMEND trial results demonstrate that the MD can effectively improve total QoL as well as both psychological and physical QoL in young males with clinical depression. This suggests

that following a MD may have a broader impact on young males with depression then expected, influencing many aspects of their health and wellbeing. In addition to this, we aimed to assess how a MD might work in a real-world setting and therefore evaluated potential barriers and challenges to following a MD by this demographic in our end-of-project evaluation survey. The results of the survey found that the participants enjoyed following the MD, are motivated to continue following it after the completion of the trial and felt that it positively impacted their depressive symptoms. They observed this positive impact despite the majority thinking that the MD would not have any effect on their depressive symptoms prior to beginning the diet. The participants also reported cost, time and difficulty finding take-out food options as important challenges when following the diet. In addition, mixed or negative attitudes of family and friends to the diet was reported by a number of participants. This could present a significant challenge when following the MD long term, and requires additional investigation in order to fully understand the impact of peers on dietary choices in the context of mental health. In future studies it would also be beneficial to conduct additional follow up surveys at 6 months and 1 year after finishing the trial in order to explore what percentage of participants continue to follow the diet, as well as to report any new challenges which may arise.

IMPACT OF COVID-19

Some of the research included in this thesis was significantly impacted by the SARS-CoV-2 (COVID-19) pandemic which swept the globe in early 2020. Within a few weeks of receiving ethics approval to begin recruitment for the AMMEND trial, the virus took hold within Australia. All face-to-face research activities were required to stop, and a so a contingency plan was developed. This involved a number of changes from the original protocol and involved omitting the collection of anthropometric measurements such as height, weight and blood pressure. This meant that outcome measures such as body mass index (BMI) and systolic and diastolic blood pressure could not be determined, and therefore we recommend that these measurements be included in future trials.

Another change that was implemented in the contingency plan was the switch from face-to-face appointments to virtual telehealth appointments. This change meant that the geographical location of the trial was no longer limited to Melbourne Victoria, and instead participants from all across Australia could now participate. The utilisation of digital technologies and platforms, such as telehealth, comes with both advantages and

disadvantages. It has become popular in regional Australia in recent years due to a decline in the number of health workers in these areas coupled with advances in technology[467]. In the context of COVID-19, telehealth use has increased exponentially across many parts of Australia and is no longer limited to regional areas[468].

While the integration of these innovations into healthcare is generally viewed as positive, it could also be contributing to inequalities in health care[469]. Differences in telehealth use based on age, income, race/ethnicity, poorer health and limited English proficiency are common issues[470]. Previous research has also demonstrated that in order for telehealth services to be utilised, high speed internet and adequate digital literacy are necessary[467]. Our participants were 18-25 years old, which is often referred to as *generation Z*[471]. Research shows that generation Z tend to have excellent digital literacy[471], and thus we do not feel this significantly affected our recruitment. However, we cannot rule out the role of race/ethnicity, English as a second language, and poor internet connection and the impact this may have had on the sample recruited for the AMMEND trial.

Conversely, the change to telehealth may have had a positive impact on other issues affecting recruitment and participation. For example, young men who may have originally been unable to attend due to financial, travel or time restraints were now able to attend. It also meant that the sample did not solely included residents of a large major city, but also included young men from regional and rural Australia, thus increasing the generalisability and external validity of the research findings.

Another significant challenge was the impact the COVID-19 pandemic had on the mental health of our trial participants. Emerging research has explored the impact the pandemic, and the subsequent lockdowns, has had on the mental health of Australians. In September 2021, daily call volumes to *lifeline* had increased by 33%, and calls to *beyondblue* had increased by 30%, compared to September 2019[472]. Additionally, a study of 1157 participants from Victoria, found that in September-2020, a third of participants reported anxiety or depressive disorder symptoms, a fifth indicated suicidal ideation, and a tenth indicated that they seriously considered suicide in the prior 30 days[473]. The researchers also found that young adults, individuals with disabilities, and individuals previously diagnosed with a psychiatric or sleep condition had an increased prevalence of these adverse mental health symptoms[473]. Therefore, participants in the AMMEND trial were also specifically asked if any

major negative or positive events (including lockdowns, changes to work/study, family or social relationship events etc.) occurred which may have impacted their mental health at each follow up appointment.

In addition to the impact on mental health, the COVID-19 pandemic had a significant social and economic impact on young Australians[474]. To control the spread of the virus, the Australian Government enforced border closures, social distancing measures and a number of lockdowns which involved the closure of non-essential businesses. In response to the economic fall-out from these measures, the *Jobkeeper* wage subsidy was introduced by the Australian Government, however, individuals needed to be employed for at least 12 months to qualify. Young people aged between 15 and 24 are more likely to be causal workers and employed with their current employer for less than 12 months[474]. This is more than four times the proportion of casual employees over the age of 25[474]. Young people were also disproportionally affected by the closing of the hospitality and retail sectors which were the industries effected the most[474].

Participants were being recruited and the interventions for the AMMEND trial were being conducted during this time period. Recruitment for clinical trials has many challenges, particularly for projects which have a small financial budget and limited resources[475]. Additionally, recruitment to clinical trials across many sectors in Australia suffered as a result of the pandemic, with most trials experiencing a delay in timelines or a complete halt of operations[476]. Our study demographic in particular was also significantly affected by the challenges of the pandemic such as economic challenges, loss of employment and changes to study and education. These challenges made recruitment especially difficult, and during the first 6 months of advertising only and handful of participants had expressed interest and underwent screening. In order to overcome some of these challenges we made an additional amendment to our original recruitment strategy and enlisted the services of a recruitment agency (Trialfacts). This significantly boosted interest and screening rates for the AMMEND trial. The final number of participants who completed the study was 72. This was the minimum number identified from the sample size calculation, resulting in an adequately powered study.

The pandemic also significantly impacted the dietary choices of Australians. Research has reported some positive changes to eating habits which occurred during this time such as

increased home cooking and eating meals with family members[477]. However, increases in snacking, baking less healthy foods and overall increases in food consumption were also reported[477]. Additionally, overall spending on alcohol increased, with sales 20% higher in July 2020 compared to July 2019[478]. Research has also demonstrated that job loss, eating more, changes to sleep, and depression were factors associated with heavier alcohol consumption during the pandemic[479]. Furthermore, issues of food supply shortages and food insecurity that occurred due to panic buying, led to additional challenges, particularly in reginal and rural and remote communities in Australia[480].

Despite these significant challenges, it is a testament to the strength and resolve of the young men who enrolled, to complete the AMMEND trial during such an incredibly challenging time. Participant retention was excellent, with only three participants withdrawing from the trial. This suggests a high degree of acceptability of both the MD intervention and the control therapy. In addition, enrolment rates were also high. Enrolment rate refers to the number of participants who passed screening and were deemed eligible and decided to enrol. Previous research indicates that roughly 10% of subjects survive the 'recruitment funnel', which is the process of initial screening through to enrolment[476]. For the AMMEND trial, we screened 165 potential participants, 75 of whom enrolled. This is an enrolment rate of 45% which is significantly higher than average enrolment rates. It has been suggested that a number of factors affect the recruitment funnel, including personal, contextual and research related factors[476].

It is possible that contextual and environmental factors played a role in the high enrolment rate observed for the AMMEND trial. In the context of the COVID-19 pandemic, once potential participants were made aware of the trial, expressed interest and passed screening, the desire to contribute to depression research coupled with additional free time may explain this result. In addition, participant related barriers were investigated during the trial development and changes made accordingly, which may have also contributed to this result.

LIMITATIONS

Despite the important findings presented in this thesis, this research has limitations which must be acknowledged. Firstly, we cannot determine the long-term effects of following a MD in young men with depression. Our trial demonstrated that after 12 weeks depressive symptoms greatly improved in the diet group, however long-term consequences cannot be

determined from our research alone. While observational evidence suggests that following a MD long-term is both safe and health promoting[481], more research is needed to assess the effect in young men with clinical depression.

Following a MD is generally considered to be a sustainable, moderate and healthy[482]. However, *diet culture* and strict rules around dietary habits has shown to have negative effects on mental health[483]. These negative effects are predominately seen in relation to weight-loss diets which focus heavily on counting calories/kilojoules or eliminating and demonising certain food groups[483]. Additionally, research suggests a bidirectional association between depression and eating disorders[484]. With recent research highlighting that patients with depression can adopt negative coping strategies such as emotional eating behaviours which can be a risk factor for developing disordered eating[484]. Longer-term trials may therefore benefit from regular check-in's in order to monitor for these negative coping behaviours.

Orthorexia is a relatively new term and refers to a pathological obsession with proper nutrition that is characterised by a restrictive diet and ritualised eating patterns, as well as an intense phobia and rigid avoidance of foods believed to be unhealthy or impure[485]. Individuals with orthorexia obsess over the quality, as opposed to the quantity, of food in one's diet[486]. Often spending much time researching food, weighing and measuring food, and planning future meals, with additional intrusive, food-related thoughts occurring regularly[487]. Psychologically, individuals with orthorexia experience intense frustration when their food-related practices are disrupted and these dietary deviations often prompt a desire for self-punishment, such as by enforcing an even stricter diet or period of fasting[485].

However, the MD is considered a relatively flexible diet when compared to other diets[488]. It does not completely eliminate any food groups and emphasises moderation. Furthermore, a cross-sectional study found that adherence to the Mediterranean diet is inversely related to binge eating disorder in patients seeking a weight loss program[489]. Therefore, the risk of a MD intervention program triggering disordered eating is low, however, participants diagnosed with any form of eating disorder were excluded from participating in our clinical trial. Hence, we do not have data to determine the effect of a MD for treating depression in young men with eating disorders. Trials with a longer duration are needed to determine if

following a MD intervention over a time span of several months to years has any negative effects on those at risk of developing disordered eating.

It is also crucial that this research is *not* used to suggest the following: 1) To lay blame or responsibility onto individuals with clinical depression by suggesting that poor diet has caused depression; 2) To suggest that eating a healthier diet will resolve all of their symptoms of clinical depression; and 3) To imply that dietary change is easy or achievable for all young men with clinical depression.

Chapter 4 presented the results from the survey examining the diets of young men with depression. While poor diet quality was observed in this demographic, we cannot state causation. This research is not sufficient to show that poor diets *lead* to depression. However, the results from the AMMEND trial can demonstrate causation. The results show that in young men with poor diets and clinical depression, following a MD can lead to improvements in symptoms. It is important that clinicians discuss diet quality with this demographic in a non-judgemental way that does not imply that the symptoms the patient is experiencing is their fault due to poor diet.

While the results from the AMMEND trial demonstrate that following a MD can significantly improve depressive symptoms and quality of life, these results should not be overstated as a cure for depression. Even though we were able to meet the target sample size to determine significant differences in the BDI-II score, repeating this study in different countries and locations should be conducted in order to confirm these findings. It would also be valuable to explore any differences in treatment effect for participants with treatment-resistant depression. Longer trials should also explore any long-term challenges or consequences of following a MD and specifically assess if the positive effects plateau over time.

A limitation of the AMMEND trial was the lack of blinding and interactions between participants and researcher. Guidelines and strategies were outlined in the study protocol documents to try to minimise these potential sources of bias. These strategies included spending equal amounts of time discussing both the diet and befriending intervention during screening in order to present both treatments as equal and reduce expectancy bias. Both groups also followed the same study schedule regarding appointment frequency and length, thereby receiving the same time, attention and therapeutic relationship. Finally, both groups

received comparable renumeration for their participation. Future studies could also consider conducting clinician-rated depression scoring via an independent third party.

The AMMEND trial required participants to complete an online daily diet diary to record their food intake over the 12-week intervention. Measuring diet adherence via self-report questionnaires everyday has the potential for response set bias, expectation bias and social desirability bias[490]. However, if this were to occur, we would expect to see improvements in the diet scores of the control group as well. The control group completed the same daily diet diary as the MD group; however, no changes in the Mediterranean Diet Adherence Screener (MEDAS) score were observed. This suggests that the daily diet recording did not lead to overestimations of dietary adherence or diet quality. Furthermore, recall bias and memory error are significant challenges in dietary trials, and may be overcome by monitoring diet intake more frequently[491]. Using the online diet diary, which could be accessed via a mobile phone, provided an easy and convenient way to track daily food intake during the AMMEND trial. Assessing objective nutritional biomarkers via blood and urine may provide more convincing evidence of dietary adherence[492]. However, this would also increase participant burden, particularly in the case of fasting blood tests[492], which may affect trial attrition and compliance. These factors must be carefully considered for future trials.

Our results show that all participants in the MD group maintained high compliance to the MD over the course of the trial. However, it is important to remember that dietary change requires significant effort and motivation. Individuals need to be provided with adequate education, tools and guidance. In the AMMEND trial, participants were provided with meal ideas, recipes, diet 'swaps', an example meal plan, options for eating out or ordering take-out and an example shopping list. Our results demonstrate that under the guidance of a qualified clinical nutritionist, participants can significantly change their diet. Therefore, we recommend that mental health professionals routinely refer their patients to nutritionists or dietitians and that similar resources and guidance are provided to young men with depression in clinical practise.

Recent research has explored Australian mental health practitioners' reported practice, beliefs, and barriers to the prescription of dietary change for mental health conditions[493]. The study investigators surveyed psychologists, psychiatrists, allied mental health clinicians, general practitioners and mental health nurses. They found that the most frequently

mentioned barrier to prescribing dietary change were practitioner barriers, which included insufficient skills and knowledge, lack of qualifications, and dietary advice being outside their scope of practice[493]. These barriers were the most prevalent among the psychologists and less prevalent among the psychiatrists[493]. Mainstream psychology does not include training in nutrition or dietary change, and it has been suggested that psychologists are hesitant to include dietary advice into treatment due to concerns about adhering to their codes of conduct and concerns about litigation[494].

Researchers have also suggested that psychiatrists and other mental health professionals may be better trained in addressing dietary change with their patients[493]. The current clinical practice guidelines for psychiatrists treating major depressive disorder, which was updated in 2020, recommends that patient's diet be addressed, and outlines some basic healthy eating principles[495]. The guidelines recommend that a "diet with high proportions of vegetables, fruit, fish and grain but low animal fats appear helpful in depressive disorders[495]." However, comprehensive dietary advice and nutritional medicine requires specialist training. Therefore, routine referrals to qualified nutritionists, dietitians, or other clinicians with specialist training in nutritional psychiatry should be considered when treating patients with depression.

9.3 CHAPTER SUMMARY

This chapter has discussed the main findings from each of the four projects presented in this thesis. It highlighted the original contributions to knowledge, the implications of these findings as well as limitations which should be considered. A detailed discussion of the impact the COVID-19 pandemic had on the AMMEND trial was also presented.

10.CHAPTER 10: CONCLUSION

10.1 PREFACE

The previous chapter discussed the original contributions to knowledge presented in this thesis as well as the various limitations of the research findings. This chapter presents the impact, relevance, and significance of these findings, as well as suggestions for future research. A concluding statement is also provided.

10.2 RESEARCH QUESTIONS ANSWERED

This thesis asked a number of research questions pertaining to the impact of diet on depressive symptoms of young men. Various research methods and designs were utilised, including a systematic literature review, a cross-sectional online survey, a randomised control trial and a follow-up survey. As a result of these projects, all original research questions were answered and the following conclusions were made:

- The polyphenols found in the Mediterranean diet have an impact on both depression risk and active symptoms of depression via a systematic literature review;
- The current dietary patterns of young men with depression are poor. Their diets are high in processed foods and sugary snacks as well as low in vegetables and wholegrains;
- Young men with depression believe their diet has an impact on their mental health and would be willing to change it in order to help improve their depressive symptoms;
- Young men with depression and poor diets are capable of significantly improving their diets over 12 weeks under the guidance of a clinical nutritionist;
- Following a MD for 12 weeks may significantly improve depressive symptoms in young men with clinical depression;
- Following a MD for 12 weeks can significantly improve quality of life in young men with clinical depression;

- Challenges to following the MD expressed by young men included difficulty finding Mediterranean foods and ingredients, the increased cost of food, increased time required to prepare and cook food, and the negative attitudes of friends/family to the diet; and
- Positive aspects to following the MD expressed by young men included enjoying the taste of the food, finding the diet easy to follow and perceiving an improvement to their depressive symptoms. They also reported a willingness to continue with the diet at the conclusion of the program.

10.3 SIGNIFICANCE

Depression is one of the most disabling conditions affecting young people in Australia, with the Covid-19 pandemic exacerbating mental health conditions such as major depressive disorder[496]. In 2020, Headspace National Youth Mental Health Foundation conducted a national telephone survey of 1035 Australian youth aged 12-25 years[497]. They found that one third of young men aged 18-25 years reported high or very high levels of physiological distress[497]. Current treatment options for depression include psychotherapy and pharmacological medications, however, these treatments are associated with a number of side effects, are often expensive, and in some cases ineffective. Without adequate and effective treatment, young adults may live with the debilitating consequences of depression for many years, affecting their engagement in work, study and social relationships. Additionally, research shows that only a small fraction of young men actually seek help for their depression and many have negative views towards conventional treatments. The need for new evidence-based therapies which appeal to young men is therefore urgently needed.

The emerging field of nutritional psychiatry is a promising new area of research which examines the role of nutrients, foods and dietary patterns in mental health conditions. Despite the growing number of studies assessing the role of diet for depression, no research had explored the effect of diet in depressed young men specifically. This thesis aimed to bridge this important gap in the existing literature by examining the current diets of young men with depression, assessing the effect of a MD intervention on depressive symptoms in young men, and exploring the challenges and barriers they experienced following the diet.

The findings from this thesis will directly benefit young men with depression by providing a new evidence-based treatment strategy which may improve their depressive symptoms and quality of life. Further, the findings may also help to guide the recommendations provided by clinicians to young men with depression. By understanding their diet quality and nutrition knowledge, clinicians can tailor the dietary advice given to this demographic, resulting in better outcomes. In addition, by understanding the challenges and barriers of following the MD, clinicians are provided with guidance on which barriers to focus on and can troubleshoot potential challenges before they occur. These findings also provide an important foundation which further research can build upon.

10.4 RESEARCH IMPACT

This thesis has produced six manuscripts, four of which have been published and two which are currently under peer review. Findings from this thesis have been presented at both local and international conferences: The 16th World Congress of Public Health 2020 and the Lifestyle Medicine Conference in 2021 and in 2022. Lay person summaries, infographics, videos and articles were produced for each research output to maximise translation to key stakeholders including health practitioners, mental health organisations, training and education organisations and the patient group – young men with depression.

At the time of writing (08/12/2022), the published manuscripts have been cited a total of 78 times. The AMMEND results article has received much media attention and has appeared in 80 online news outlets to date. The findings have been published as a feature story in five magazines: 1) Verywell Mind, 2) Inverse Magazine, 3) Medical News Today, and 4) Natural History Magazine and 5) Fartherly Magazine. I have also discussed the AMMEND results findings on ABC Radio Sydney, Eastside FM, and Joy Drive Radio Melbourne, as well as television interviews on Channel 7 News and Channel 9 News. The article currently has an ALTMETRIC attention score of 896.

Several findings from this thesis have already been incorporated into learning and teaching materials for Bachelor of Health Science students studying Nutritional and Dietetic Medicine at Endeavour College (Australia). Specifically, the literature review results on polyphenols, the results from the MENDDS study and the AMMEND trial results have been incorporated

into the learning material for the subject *Clinical Nutritional Medicine*. In addition, BioConcepts, a leading nutritional supplement company and education provider for nutritionists, have included these research findings in their Practitioner Education Series and Between Clinical Minds podcast.

The results from the AMMEND trial have also influenced clinical guidelines and have been included as supporting evidence in the recently published "Clinical guidelines for the use of lifestyle-based mental health care in major depressive disorder: World Federation of Societies for Biological Psychiatry (WFSBP) and Australasian Society of Lifestyle Medicine (ASLM) taskforce"[417].

10.5 FUTURE DIRECTIONS

Building on the work presented in this thesis, future research should explore the following research questions:

- Can the results of the AMMEND trial be replicated in other locations within Australia or in other countries?
- Do the improvements observed in depressive symptoms only last for the duration of time following the diet? Do the positive benefits disappear once the diet is no longer followed?
- Will the positive effects plateau or reduce over time?
- Do other "healthy" diets, such as a Japanese diet, which share many dietary characteristics with the MD, have the same effect?
- What is the minimum length of time needed to observe a significant improvement in depressive symptoms?
- What degree of impact does the negative attitudes of peers on the MD have on the adherence to the diet in young men?
- What strategies are effective in overcoming the challenges young men face when following a MD?
- Are online nutrition interventions or face to face interventions more effective for the treatment of depression?

- How effective are online nutrition programs and phone applications in delivering nutrition interventions for patients with depression?

10.6 FINAL STATEMENT

From the work presented in this thesis, it is evident that diet appears to play a significant role in the mental health of young men. Implementing a MD should be considered in the treatment of depression in young men, and referrals to nutritionists or dietitians should become routine. Further research is needed to determine the long-term effects of a MD in this demographic.

11. APPENDICES

Appendix 1: Literature Review Supplemental Figure 1

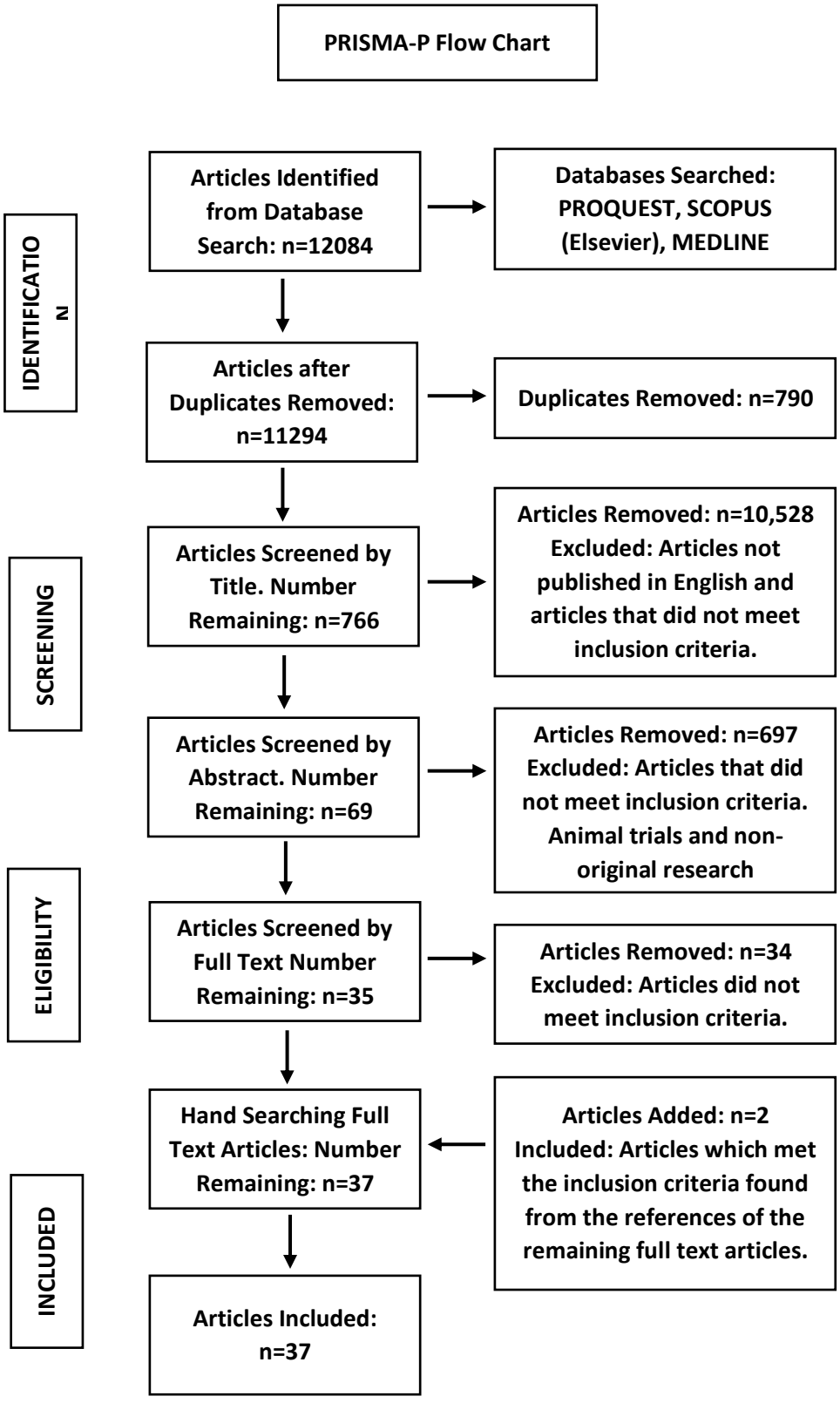


Figure 1. PRISMA-P Flow Chart

Appendix 2: Literature Review Supplemental Table 1.

The Joanna Briggs Institute Critical Appraisal tool for Systematic Reviews

Checklist for Randomized Controlled Trials

Author	Was true randomization used?	Was group allocation concealed?	Were groups similar at baseline?	Were participants blinded?	Were research staff blinded?	Were outcome assessors blinded?	Identical group treatment?	Was follow up completed?	Analysis within each group?	Outcomes measured identically?	Reliable measurements?	Appropriate statistical analysis?	Appropriate trail design	Total no. of Yes' (Y)
Sathyapalan et al. (27)	Y	Y	Y	Y	UC	UC	Y	Y	Y	Y	Y	Y	Y	**11**
Bergman et al. (22)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Nina Estrella et al. (39)	Y	UC	Y	UC	UC	UC	Y	Y	Y	Y	Y	Y	Y	**9**
Atteritano et al. (28)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Lopresti et al. (23)	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y	**12**
Sanmukhani et al. (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Esmaily et al. (30)	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y	**12**
Panahi et al. (25)	Y	Y	Y	UC	UC	UC	Y	Y	Y	Y	Y	Y	Y	**10**

Yu et al. (26)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Chang et al. (60)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	**11**
Ibero-Baraibaret al. (29)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Pribis (49)	UC	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Hirose et al. (41)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Mirghafourv and et al. (48)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Kamalifard et al. (46)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Davinelli et al. (40)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**13**
Kazemian et al. (33)	Y	Y	Y	Y	UC	UC	Y	Y	Y	Y	Y	Y	Y	**11**

Key: Y-Yes; N-No; UC-Unclear; N/A- Not Applicable

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatments groups treated identically other than the intervention of interest?
8. Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?
9. Were participants analysed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Appendix 3: Literature Review Supplemental Table 2. Critical Appraisal for Observational studies assessing polyphenols for depressive symptoms. (STROBE Checklist for cohort, case-control, and cross-sectional studies)

Author/date	Title, abstract & introduction				Methods													
	Title & abstract		Background	Objective	Study deign	Setting	Participants		Variable	Data Source	Bias	Study size	Quant. variables	Statistical methods				
	1a	1b	2	3	4	5	6a	6b	7	8	9	10	11	12a	12b	12c	12d	12e
Hintikka et al. (2005)	-	X	X	X	X	X	-	-	X	X	-	X	X	X	X	X	-	-
Niu et al. (2009)	X	X	X	X	X	X	X	-	X	X	-	X	X	X	X	X	-	-
Li et al. (2010)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
Chen et al. (2010)	X	X	X	X	X	X	-	-	X	X	-	X	X	X	X	-	-	-
Ruusunen et al. (2010)	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	-	-	-
Lucas et al. (2011)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Feng et al (2012)	X	X	X	X	X	X	-	-	X	-	-	-	-	X	X	-	-	-
Feng et al. (2013)	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	X	-

Omagari et al. (2014)	X	X	X	X	X	X	-	-	X	X	-	-	X	X	X	-	-	-
Pham et al. (2014)	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	-	-	-
Yu et al. (2015)	X	X	X	X	X	X	X	X	X	X	-	-	X	X	X	-	-	-
Chang et al. (2016)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	-	-	X
Su et al. (2016)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Li et al. (2016)	X	X	X	X	X	X	-	-	X	X	-	-	X	X	X	-	-	-
Miyake et al. (2018)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Yu et al. (2018)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	X
Godos et al. (2018)	-	X	X	X	-	X	X	X	X	X	X	X	X	X	X	-	-	X
Navarro et al. (2018)	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X
Chan et al. (2018)	X	X	X	X	X	X	X	X	X	X	-	-	X	X	X	-	-	-
Mofrad et al. (2019)	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	-	X	X

Author/date	**Results**	**Discussion & Other information**

	Participants			Descriptive data			Outcome data	Main results			Other Analysis	Key Results	Limitations	Interpretation	Generalisability	Funding
	13a	13b	13c	14a	14b	14c	15	16a	16b	16c	17	18	19	20	21	22
Hintikka et al. (2005)	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-
Niu et al. (2009)	X	X	X	X	-	-	X	X	X	-	X	X	X	X	X	-
Li et al. (2010)	X	X	X	X	-	X	X	X	X	-	X	X	X	X	X	X
Chen et al. (2010)	X	X	-	X	-	X	X	X	X	-	X	X	X	X	X	X
Ruusunen et al. (2010)	X	X	-	X	-	X	X	X	X	-	X	X	X	X	X	X
Lucas et al (2011)	X	X	-	X	-	X	X	X	X	-	X	X	X	X	X	X
Fend et al. (2012)	-	-	-	-	-	-	X	X	X	-	X	X	-	X	X	X
Feng et al. (2013)	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	X
Omagari et al. (2014)	-	-	-	X	-	-	X	X	X	-	X	X	X	X	X	-
Pham et al. (2014)	X	X	-	X	-	-	X	X	X	-	X	X	X	X	X	X
Yu et al. (2015)	-	-	-	X	X	-	X	X	X	-	X	X	X	X	X	X
Chang et al. (2016)	X	-	X	X	-	X	X	X	X	-	X	X	X	X	X	X

Su et al. (2016)	X	X	X	X	X	-	X	X	X	-	X	X	X	X	X	X
Li et al. (2016)	-	-	-	X	-	-	X	X	X	-	X	X	X	X	X	X
Miyake et al. (2018)	X	X	-	X	-	-	X	X	X	-	X	X	X	X	X	X
Yu et al. (2018)	X	X	-	X	-	-	X	X	X	-	X	X	X	X	X	X
Godos et al. (2018)	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	X
Navarro et al. (2018)	X	X	-	X	-	X	X	X	X	-	X	X	X	X	X	X
Chan et al. (2018)	-	-	-	X	-	-	X	-	X	-	X	X	X	X	X	X
Mofrad et al. (2019)	X	X	-	X	-	-	X	X	X	-	X	X	X	X	X	X

Key:

X indicates that the study contains this item.

- indicates that the study does not contain this item

Strobe Questions Version 4 as published in Oct / Nov 2007

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix 4: Literature Review Supplemental Table 3 PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	48
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	48
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	49
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	50
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	51
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	51
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	51
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	51
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	51
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	51
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	51
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	52
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	n/a

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	51
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	n/a
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	n/a
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	52
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	52
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	52
Study characteristics	17	Cite each included study and present its characteristics.	52
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	52
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1 and Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	53
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	79
	23b	Discuss any limitations of the evidence included in the review.	82
	23c	Discuss any limitations of the review processes used.	82
	23d	Discuss implications of the results for practice, policy, and future research.	83
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	51
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	n/a
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	83
Competing interests	26	Declare any competing interests of review authors.	83
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	83

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 5: Literature Review Supplementary Table 4 Literature Search Strategy Log Results

Date of search	Database or Search Engine	Search history	Limits (e.g dates, publication types)	# of Results	# downloaded
18/02/2019	PROQUEST	Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	9417	All
18/02/2019	Scopus (elsevier)	Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	1999	All
21/02/2019	Medline (EBSCO)	Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	8	All
		Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	3	All
21/02/2019	CINAHL	Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	5	All

21/02/2919	Embase	Polyphenols OR Phytochemicals OR flavonoids AND depression OR major depressive disorder OR major depression OR mental health	2000-current	652	All
			Total from combined search 12084		
			No of duplicates: 790		
			Results after duplicates removed: 11294		

Appendix 6: Literature Review Supplementary Material – ROB interpretation

JBI CRITICAL APPRAISAL CHECKLIST FOR RANDOMIZED CONTROLLED TRIALS

The JBI Critical Appraisal Checklist for RCT consists of 13 questions scored as Yes, No or Unclear.

Overall Quality Score:
Poor: <5/13
Average: 6-8/13
Good: 9-12/13
Excellent: 13/13

STROBE CHECKLIST FOR COHORT, CASE-CONTROL, AND CROSS-SECTIONAL STUDIES

The Strobe Checklist for Cohort, Case-Control, And Cross-Sectional Studies consists of 34 questions. Each item is sored as either containing an item or not containing an item.

Methodology quality score:
Poor: <9/34
Average: 10-19/34
Good: 20-29/34
Excellent: 30-34/34

Appendix 7: Literature Review Supplementary Material – Narrative Synthesis Process

A general framework for narrative synthesis based on the work of Popay et al.[498] was used for the literature review process. The narrative synthesis process includes the following key elements:

1. Assessing how the interventions work, why and for whom do they work.
   The aim is to inform decisions about the literature review questions and the type of articles to be included in the literature review. In addition, it aims to contribute to the interpretation of the review's findings and to evaluate how widely applicable those findings may be.
2. Developing a preliminary synthesis.
   The aim is to organise the results from the included articles to describe any patterns which may be evident across the studies in regards to the direction of effects and the size of those effects.
3. Exploring relationships in the data.
   The aim is to evaluate any factors which might explain differences in direction and size of effect across the studies included in the review.
4. Evaluating the robustness of the synthesis.
   The aim is to provide an assessment of the strength of the available evidence and to draw conclusions about the likely size and direction of the effects observed. An additional aim is to provide general conclusions on potential effects for different population groups and/or contexts.

Appendix 8: MENDDS article Supplementary Figure 1 Participant Flow Chart

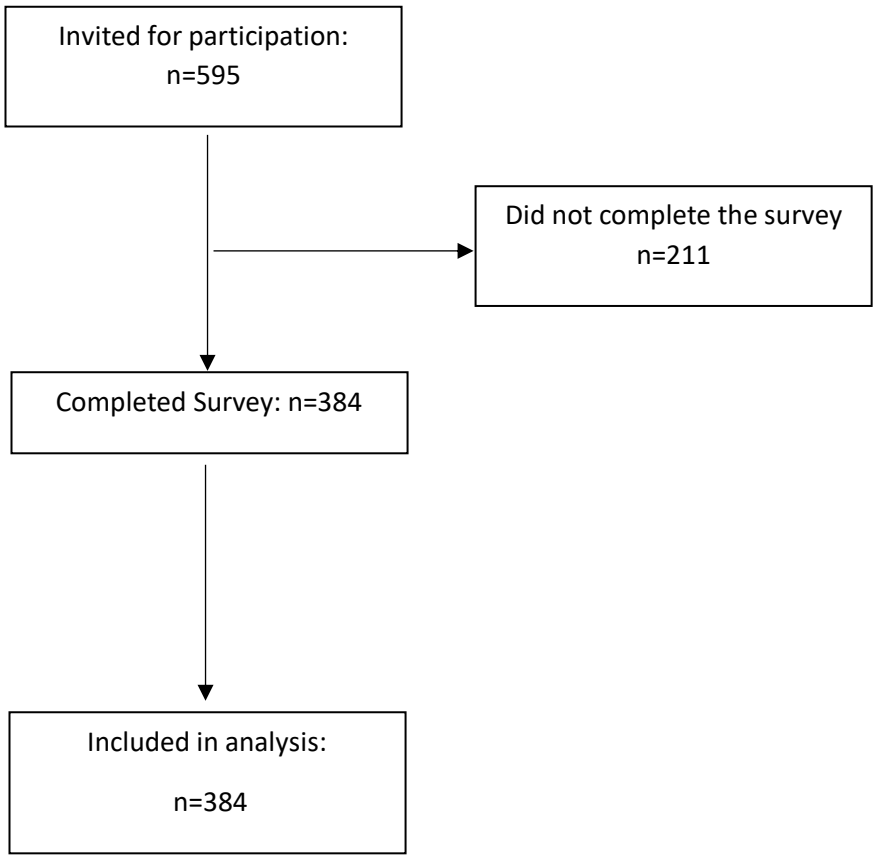


Figure 1. Participant Flow Chart

Appendix 9: MENDDS Article Supplementary Material Table 1. Diet History

Food	Frequency of Consumption							
	Never or 1 time/month	**2-3 times/month**	**1 time/week**	**2-3 times/week**	**4-6 times/week**	**1 time/day**	**2-3 times/day**	**4 or more times/day**
Hot or cold cereal	159 (41.4 %)	48 (12.5%)	36 (9.4%)	52 (13.5%)	42 (10.9%)	42 (10.9%)	5 (1.3%)	N/A
Milk (all types)	54 (14.1%)	51 (13.3%)	38 (9.9%)	57 (14.8%)	56 (14.6%)	71 (18.5%)	43 (11.2%)	10 (2.6%)
Fruit Juice	155 (40.4%)	98 (25.5%)	55 (14.3%)	42 (10.9%)	16 (4.2%)	14 (3.6%)	4 (1.0%)	N/A
Sugary fizzy drinks/soda	85 (22.1%)	77 (20.1%)	59 (15.4%)	67 (17.4%)	29 (7.6%)	30 (7.8%)	29 (7.6%)	8 (2.1%)
Sports or energy drinks *	159 (41.4%)	78 (20.3%)	47 (12.2%)	47 (12.2%)	19 (4.9%)	19 (4.9%)	14 (3.6%)	1 (0.3%)
Sugar sweetened tea & coffee	163 (42.5%)	35 (9.1%)	31 (8.1%)	37 (9.6%)	25 (6.5%)	40 (10.4%)	46 (12%)	7 (1.8%)
Fruit	60 (15.6%)	71 (18.5%)	42 (10.9%)	77 (20.1%)	52 (13.5%)	39 (10.2%)	38 (9.9%)	5 (1.3%)
Vegetables	31 (8.1%)	46 (12.0%)	51 (13.3%)	112 (29.2%)	73 (19.0%)	38 (9.9%)	30 (7.8%)	3 (0.8%)
Green leafy lettuce salad	66 (17.2%)	67 (17.4%)	62 (16.1%)	91 (23.7%)	52 (13.5%)	28 (7.3%)	14 (3.6%)	4 (1.0%)
Fried potatoes**	33 (8.6%)	81 (21.1%)	97 (25.3%)	111 (28.9%)	40 (10.4%)	14 (3.6%)	8 (2.1%)	N/A
Other potatoes***	61 (15.9%)	80 (20.8%)	92 (24.0%)	103 (26.8%)	39 (10.2%)	9 (2.3%)	N/A	N/A
Beans	182 (47.4%)	95 (24.7%)	48 (12.5%)	43 (11.2%)	10 (2.6%)	4 (1.0%)	2 (0.5%)	N/A
Cooked whole Grains****	213 (55.5%)	88 (22.9%)	30 (7.8%)	36 (9.4%)	13 (3.4%)	2 (0.5%)	2 (0.5%)	N/A
Whole grain bread	103 (26.8%)	87 (22.7%)	37 (9.6%)	65 (16.9%)	47 (12.2%)	37 (9.6%)	7 (1.8%)	1 (0.3%)
Pizza	101 (26.3%)	157 (40.9%)	84 (21.9%)	38 (9.9%)	3 (0.8%0	1 (0.3%)	N/A	N/A

Food	Frequency of Consumption							
	Never or 1 time/month	**2-3 times/month**	**1 time/week**	**2-3 times/week**	**4-6 times/week**	**1 time/day**	**2-3 times/day**	**4 or more times/day**
Cheese	27 (7.1%)	45 (11.7%)	62 (16.1%)	133 (34.6%)	77 (20.1%)	29 (7.6%)	11 (2.9%)	N/A
Red Meat	31 (8.1%)	40 (10.4%)	50 (13.0%)	135 (35.2%)	87 (22.7%)	30 (7.8%)	11 (2.9%)	N/A
Processed meat*****	81 (21.1%)	78 (20.3%)	85 (22.1%)	87 (22.7%)	36 (9.4%)	11 (2.9%)	6 (1.6%)	N/A
Chocolate/sweets and lollies	36 (9.4%)	74 (19.3%)	80 (20.8%)	96 (25.0%)	52 (13.5%)	24 (6.3%)	22 (5.7%)	N/A
Sweet pastries & bakery items	120 (31.3%)	115 (29.9%)	78 (20.3%)	49 (12.8%)	15 (3.9%)	6 (1.6%)	1 (0.3%)	N/A
Cookies, cake, pie or brownies	112 (29.2%)	119 (31.0%)	79 (20.6%)	50 (13.0%)	10 (2.6%)	12 (3.1%)	2 (0.5%)	N/A
Ice cream & frozen desserts	126 (32.8%)	114 (29.7%)	71 (18.5%)	46 (12.0%)	16 (4.2%)	9 (2.3%)	2 (0.5%)	N/A
Salted/sweetened popcorn	274 (71.4%)	66 (17.2%)	24 (6.3%)	12 (3.1%)	5 (1.3%)	2 (0.5%)	1 (0.3%)	N/A
Tomato based sauce	73 (19.0%)	127 (33.1%)	92 (24.0%)	76 (19.8%)	13 (3.4%)	3 (0.8%)	N/A	N/A
Mexican style tomato salsa	224 (58.3%)	99 (25.8%)	43 (11.2%)	17 (4.4%)	1 (0.3%)	N/A	N/A	N/A

*Sports or energy drinks, such as KoolAid, Gatorade, Red Bull or Vitamin Water

** Fried potatoes, including french fries, home fries, or hash brown potatoes

*** Other potatoes, such as baked, boiled, mashed potatoes, sweet potatoes, or potato salad

**** Cooked whole grains such as brown rice, bulgur, cracked wheat, or millet

***** Processed meat such as bacon, hot dogs and lunch meats such as ham, salami and spam

Appendix 10: MENDDS Questionnaire

Part 1:

Demographics (6 questions):

- Age?

Input: Select from menu (18; 19; 20; 21; 22; 23; 24 and 25)

Rationale: To check they meet inclusion criteria

- Sex?

Input: Select either male or female

Rationale: To check they meet inclusion criteria

- Have you been told you suffer from depression by a Medical Doctor or Psychologist?

Input: Select either yes or no

Rationale: To check they meet the inclusion criteria

- Which state do you currently live in?

Input: Choose one answer from menu (NSW, WA, QLD, SA, VIC, NT, ACT, TAS)

Rationale: Demographic information

- What is your yearly income before tax?

Input: Select from menu (less than $10,000; $10,000-$29,999; $30,000-$40,999; $50,000-$60,999; $70,000-$80,999; $90,000-$109,999; $110,000 or more)

Rationale: To adjust for confounding factors in analysis and also to see if diet and nutrition education differs across income levels.

- What is the highest degree or level of school you have completed? (If you're currently enrolled in school, please indicate the highest degree you have *received.*)

Input: Select from a menu (Less than Year 12 or equivalent; Year 12 or equivalent; Diploma or Vocational Certificate; Bachelor degree (including honours); Master's degree; Doctorate.)

Rationale: To adjust for confounding factors in analysis and to also see if diet and nutrition education differs across education levels.

The survey will then redirect participants to the consent page if they meet the survey requirements.

By selecting 'YES' you agree to the following:

I agree to participate in the research project: An investigation into the diets and nutritional knowledge of young men with depression (The "MENDDS" survey).

I understand that the purpose of this study to investigate the diets and nutritional education of young men with depression.

I understand that I have been asked to participate in this research because I may fit the criteria and be able to help answer these questions.

I am aware that I can contact Ms Jessica Bayes if I have any concerns about the research. I also understand that I am free to withdraw my participation from this research project at any time I wish, without consequences, and without giving a reason.

I agree that I have had an opportunity to have all of my questions answered fully and clearly.

I agree that the research data gathered from this project may be published in a form that does not identify me in any way.

I consent to being part of this survey project:

Select: yes or no

Part 2:

Depression (10 questions):

Center for Epidemiologic Studies Depression Scale Revised (CESD-R10)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week by checking the appropriate box for each question.

- I was bothered by things that usually don't bother me

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I had trouble keeping my mind on what I was doing.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I felt depressed.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I felt that everything I did was an effort.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I felt hopeful about the future.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I felt fearful.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- My sleep was restless.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I was happy.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I felt lonely.

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

- I could not "get going."

Rarely or none of the time (less than one day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of time (3-4 days)

All of the time (5-7 days)

Part 3:

Nutrition Knowledge and attitudes (10 questions):

The next set of questions are about foods and diet.

- How healthy is your overall diet on a typical day? (Healthy: high in vegetables and fresh foods, low in processed and packaged foods)

Input: Select from a likert scale (Excellent; Very good; Good; Fair; Poor)

Rationale: To compare their perceived diet quality to their FFQ results.

- How often do you read the Nutrition Facts label found on many food products which list things such as kjs, fat, cholesterol, vitamins and minerals in the product?

Input: Select from a likert scale (Most of the time; sometimes; rarely; never)

Rationale: To assess food knowledge and behaviour.

- How important is it to eat an overall healthy diet? (Healthy: high in vegetables and fresh foods, low in processed and packaged foods)

Input: Select from a likert scale (Very important; important; unsure; low importance; not at all important)

Rationale: To assess food knowledge and behaviour.

- How important is it to eat a large variety of different foods?

Input: Select from a likert scale (Very important; important; unsure; low importance; not at all important)

Rationale: To assess food knowledge and behaviour.

- How often is it ok to eat fast foods/processed foods?

Input: Select from a menu (2-3 times per day; once per day; 2-3 times per week; once a week; 2-3 times per month; less than once per month)

Rationale: To assess food knowledge and behaviour.

- What degree of impact does a healthy diet have on your physical health?

Input: Select from a likert scale (A big impact; slight impact; unsure; low impact; no impact at all)

Rationale: To assess food knowledge and behaviour.

- What degree of impact does a healthy diet have on your mental health? (Mental health is your emotional, psychological, and social well-being)

Input: Select from a likert scale (A big impact; slight impact; unsure; low impact; no impact at all)

Rationale: To assess food knowledge and behaviour.

- Do you find healthy eating to be expensive?

Input: Select yes or no

Rationale: To assess food knowledge and behaviour.

- Do you find healthy eating to be time-consuming?

Input: Select yes or no

Rationale: To assess food knowledge and behaviour.

- How likely would you be to change your diet if it improved your symptoms of depression?

Input: Select from likert scale (very likely; likely; unsure; unlikely; very unlikely)

Rationale: To assess food knowledge and behaviour.

Part 4:

Food/symptom associations (8 questions):

- When you eat **high fat** processed foods (eg. Cheese burgers/pizza/fried chicken) do you notice any **instant differences** in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you eat **high fat** processed foods (eg. Cheese burgers/pizza/fried chicken) do you notice any **delayed differences** (several hours later) in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you eat **high sugar** processed foods (eg. Chocolate/cookies/cakes) do you notice any **instant differences** in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you eat **high sugar** processed foods (eg. Chocolate/cookies/cakes) do you notice any **delayed differences** (several hours later) in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you eat **fruits and vegetables** do you notice any **instant differences** in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you eat **fruits and vegetables** do you notice any **delayed differences** (several hours later) in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you consume **alcohol** do you notice any **instant differences** in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

- When you consume **alcohol** do you notice any **delayed differences** (several hours later) in your depression symptoms?

Input: Select from likert scale (significant improvement in symptoms; improvement in symptoms; no difference; worsening of symptoms; a significant worsening of symptoms)

Rationale: To assess observed diet/symptom associations

Part5:

Diet History Questionnaire

The 26 item Dietary Screener Questionnaire (DSQ). Two questions removed as they were repeated in part 1. Questions modified for an Australian audience and some questions/answers shortened for participant ease.

- During the past month, how often did you eat hot or cold cereals? Mark one.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, what kind of cereal did you eat? Type cereal in box below. eg. weet-bix, corn flakes, rice bubbles, etc.

Input: textbox for answer

Rationale: To assess nutrient intake

- If there was another kind of cereal that you usually ate during the past month, what kind was it? Type cereal in box below, if none leave blank.

Input: textbox for answer

Rationale: To assess nutrient intake

- During the past month, how often did you have any milk (either to drink or on cereal)? Include regular milks, chocolate or other flavored milks, lactosefree milk, buttermilk. Please do not include small amounts of milk in coffee or tea. Mark one

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, what kind of milk did you usually drink? Mark one

Input: select one option (whole or regular milk; reduced or low fat; fat free or skin milk; soy milk; other plant milks (almond/coconut/oat)

Rationale: To assess nutrient intake

- During the past month, how often did you drink regular soda or pop that contains sugar? Do not include diet soda. Mark one

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you drink 100% pure fruit juices such as orange, mango, apple, grape and pineapple juices? Do not include fruitflavored drinks with added sugar or fruit juice you made at home and added sugar to. Mark one

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you drink coffee or tea that had sugar or honey added to it? Include coffee and tea you sweetened yourself and presweetened tea and coffee drinks such as Arizona Iced Tea and Frappuccino.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you drink **sweetened** fruit drinks, sports or energy drinks, such as KoolAid, lemonade, cranberry drink, Gatorade, Red Bull or Vitamin Water? Include fruit juices you made at home and added sugar to.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat fruit? Include fresh, frozen or canned fruit. Do not include juices.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat a green leafy or lettuce **salad**, with or without other vegetables?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat any kind of **fried potatoes**, including french fries, home fries, or hash brown potatoes?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat any **other kind of potatoes**, such as baked, boiled, mashed potatoes, sweet potatoes, or potato salad?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat refried beans, baked beans, beans in soup, pork and beans or any other type of cooked dried beans? Do **not** include green beans.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **brown rice** or other cooked whole grains, such as bulgur, cracked wheat, or millet? Do **not** include white rice.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, not including what you just told me about (green salads, potatoes, cooked dried beans), how often did you eat **other vegetables**?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you have Mexican type **salsa** made with tomato?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **pizza**? Include frozen pizza, fast food pizza, and homemade pizza.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you have **tomato sauces** such as with spagetti or noodles or mixed into foods such as lasagna? Do not include tomato sauce on pizza.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat any kind of **cheese**? Include cheese as a snack, cheese on burgers, sandwiches, and cheese in foods such as lasagna, quesadillas, or casseroles. Do **not** include cheese on pizza.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **red meat**, such as beef, pork, ham, or sausage? Do **not** include chicken, tu rkey or seafood. Include red meat you had in

sandwiches, lasagna, stew, and other mixtures. Red meats may also include veal, lamb, and any lunch meats made with these meats.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat any **processed meat**, such as bacon, lunch meats, or hot dogs? Include processed meats you had in sandwiches, soups, pizza, casseroles, and other mixtures. Processed meats are those preserved by smoking, curing, or salting, or by the addition of preservatives. Examples are: ham, bacon, pastrami, salami, sausages, bratwursts, frankfurters, hot dogs, and spam.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **whole grain bread** including toast, rolls and in sandwiches? Whole grain breads include whole wheat, rye, oatmeal and pumpernickel. Do **not** include white bread.

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2-3 times per day; 4 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **chocolate** or any other types of sweets/lollies?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat pastries/bakery items such as **doughnuts**, sweet rolls, danish, muffins, scrolls, or poptarts?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **cookies, cake, pie or brownies**?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat **ice cream or other frozen desserts**?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

- During the past month, how often did you eat salted or sweetened **popcorn**?

Input: Select option (Never or 1 time last month; 2-3 times last month; 1 time per week; 2-3 times per week; 4-6 times per week; 1 time per day; 2 or more times per day)

Rationale: To assess nutrient intake

Thank you for taking our survey. Your response is very important to us.

If you would like to receive the results of this research project once it has been completed sign up to our mailing list at www.mendds.com

Optional Interview Questions:

- Do you think that you could follow any specific diet for three months and why or why not?
- What time frame do you think you could stick to a **Mediterranean diet** for?
- What aspects of following a Mediterranean diet do you think would be most challenging and why?
- Would you find recipes helpful? Why/why not?
- Would you find weekly meal plans and suggestions helpful? Why/why not?
- Can you think of anything which would make the diet easier to follow?
- What number of meetings seem reasonable to you?

Appendix 11: MENDDS article Poster Presentation for the 16th World Congress on Public Health 2020

An Investigation into The Diets and Nutritional Knowledge of Young Men with Depression (The "MENDDS" survey)

Jessica Bayes[a], Dr Janet Schloss[b] and Prof David Sibbritt[a]

[a] Australian Research Centre in Complementary and Integrative Medicine, Faculty of Health, University of Technology Sydney, Ultimo, NSW, Australia
[b] National Centre for Naturopathic Medicine, Southern Cross University, Lismore, NSW, Australia

UTS:ARCCIM
CRITICAL METHODS, TRANSLATIONAL RESEARCH

Aims: To assess diet quality, nutrition knowledge and food/symptom associations.

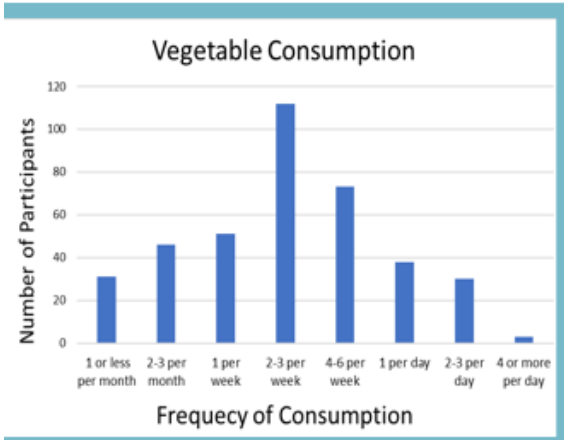
Who: In 384 young men aged 18-25 years, diagnosed with depression.

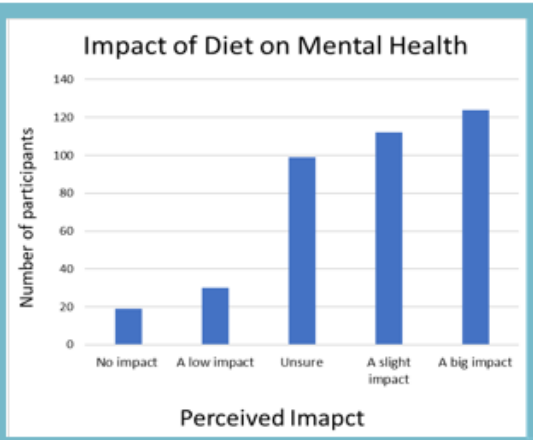
Why: Studies have shown that individual nutrients, foods and dietary patterns can have a positive impact on depressive symptoms. Gender specific research consistently shows differences in food choices and behaviours of men and women. However, studies assessing the diet quality of young men in relation to depressive symptoms is lacking.

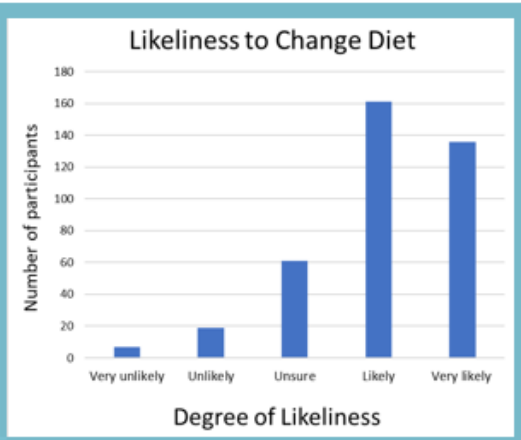
How: A cross-sectional online questionnaire.

Key Findings:

- Diet quality among young men with depression is relatively poor.
- Depressed young men perceive healthy eating to be both expensive and time consuming.
- Depressed young men feel that their diet has an impact on their mental health.
- Depressed young men will consider changing their diets if it helps their symptoms.







Scan QR Code for Full Article

UTS:ARCCIM
CRITICAL METHODS, TRANSLATIONAL RESEARCH

Appendix 12: AMMEND Protocol Consort Flow Chart

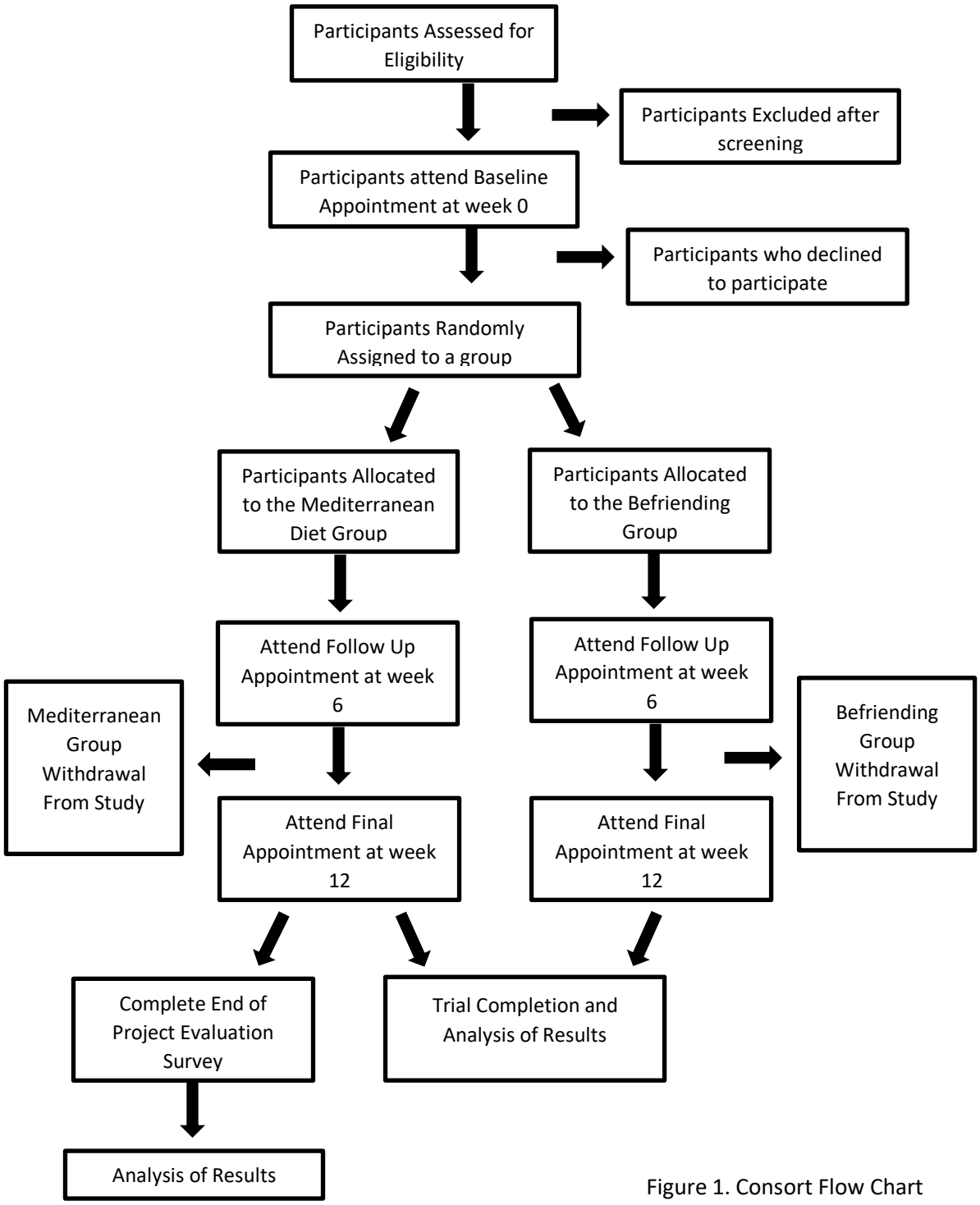


Figure 1. Consort Flow Chart

Appendix 13: AMMEND Results Consort Flow Chart

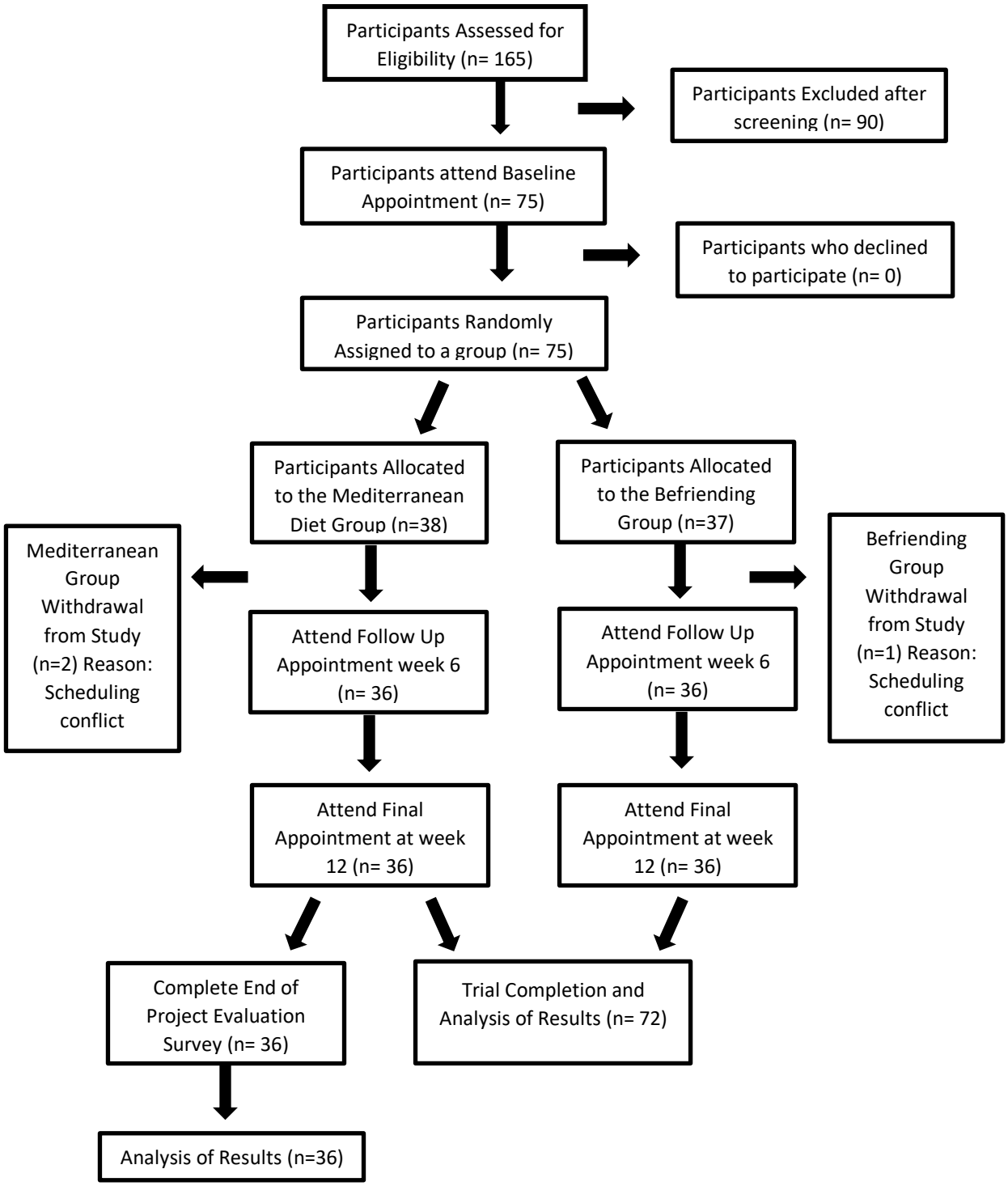
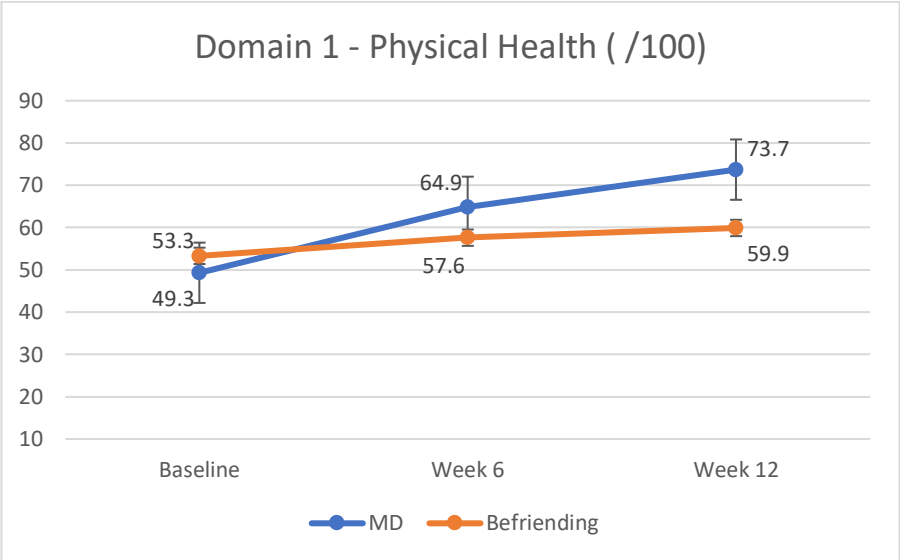
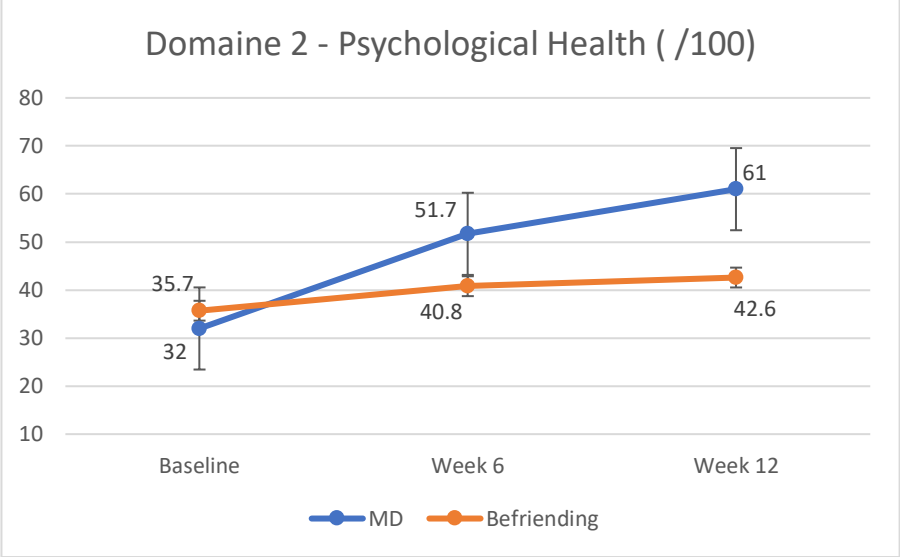
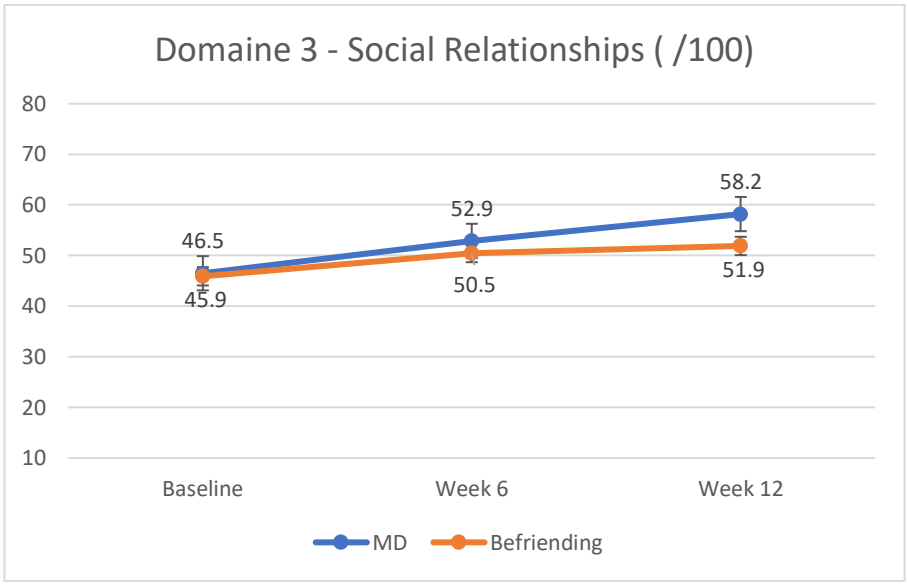


Figure 1. Consort Flow Chart

Appendix 14: AMMEND Results WHO QoL Domain Scores







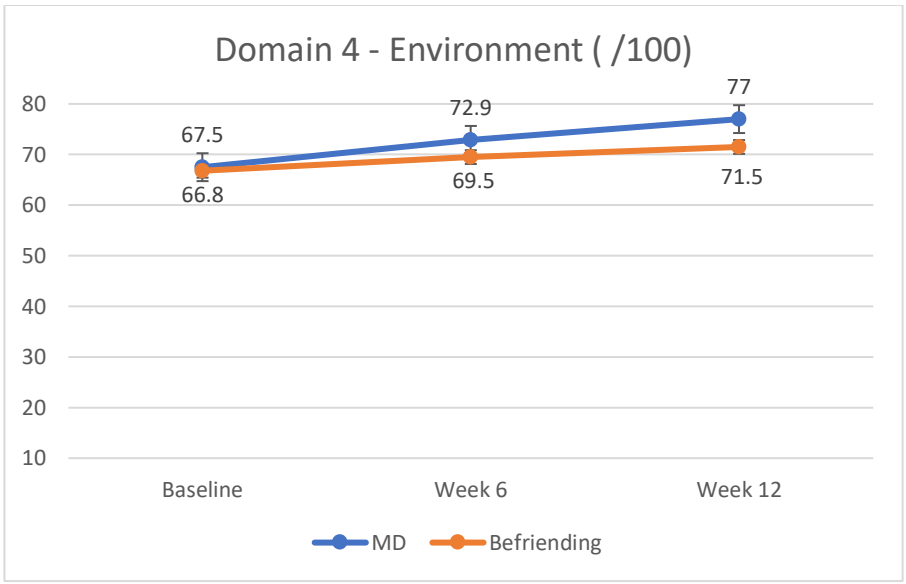


Figure 2. WHO QoL Domain Scores

Appendix 15: AMMEND Results WHO QoL Total Scores

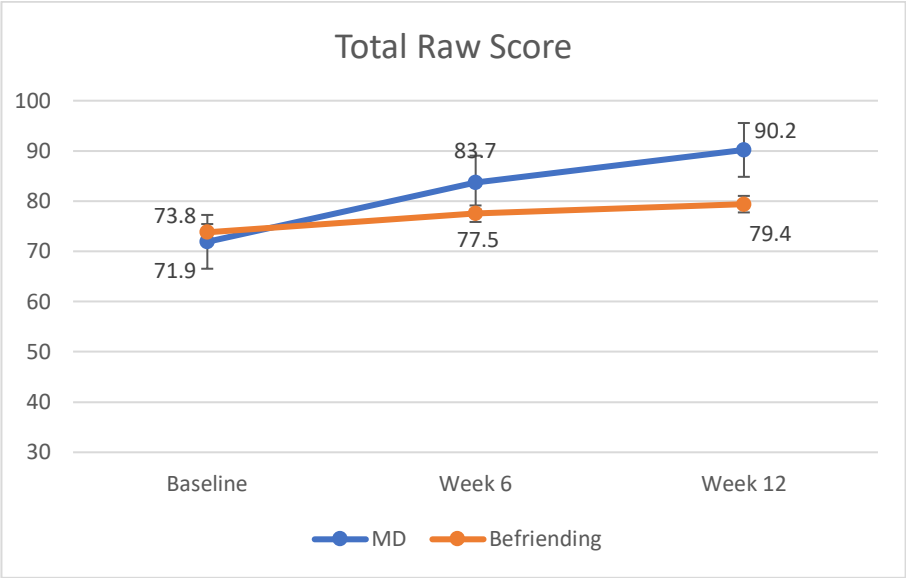


Figure 2. WHO QoL Domain Scores

Appendix 16: AMMEND Results Supplementary Material – Phone Screening Tool

Action	**Complete ✓**
"Hi, my name is (insert) and I am a researcher from the AMMEND Study, looking at the role of diet or social support on depressive symptoms in young men. I have contacted you today because you expressed interest in participating in this study, do you have a few minutes to answer some questions so I can assess your suitability?"	
If yes, proceed. If no reschedule for another time.	
"Can I confirm that you are male? *Aged between 18-25?* *And have been diagnosed with depression by your medical doctor or psychologist?"*	
(mark the table below with a tick or cross. Tick indicates yes, cross indicates no)	
If yes to all of the above, proceed to the next section. If not thank them for their time and end the screening procedure.	
"Have you been diagnosed with any other mental health condition? These include anxiety, bipolar disorder, post-traumatic stress, personality disorders, eating disorders, psychotic disorders such as schizophrenia or a substance abuse disorder such as alcoholism?" or any digestive disorders such as IBS?	
If yes mark box with a tick. All disorders (except anxiety) will be excluded at this stage.	
"Do you have any food allergies, intolerances or eversions (foods you don't like or won't eat based on religious or ethical grounds)?"	
"Are you available for the next three months to attend a baseline appointment, follow up appointment at 6 weeks and final appointment at 12 weeks?"	
"Are you happy and willing to change your diet if you are allocated to the dietary intervention group?" Are you responsible for cooking/preparing your own meals?	
"Lastly, we just need some information about your current diet. If you have access to the internet, I will direct you to a webpage with a short questionnaire or I can ask you the questions verbally over the phone?"	

The web address is: https://my.totalwellbeingdiet.com/healthy-diet-score. Here you will find the CSIRO Healthy diet score survey. It should take you less than 10 minutes to complete. Once you have finished it will give you a 'diet score'. That score is the final aspect of this screening interview. If you are eligible, we will discuss making your first appointment.	
Wait for the participant to complete the diet score survey and deliver their score. Scores are out of 100. A score less than 40 is deemed 'poor' and thus eligible for participation in this study.	

Date	Male	Aged 18-25	Depression diagnosis	Other mental disorder	Allergies, intolerances or aversions	Available	Willing	Diet Score	Eligible

Action	**Complete ✓**
Inform the participant if they have passed the screening procedure.	
"Thank you for answering those questions for me. Unfortunately, you are not eligible to participate in our study, but we thank you for your interest. *If you feel like you may be experiencing depression it's important that you seek help. There are a variety of mental health services and professionals out there that can help you with your mental health issues and prevent things from getting worse.* *We recommend:* *Lifeline Australia - 13 11 14* *Men's Line Australia - 1300 78 99 78* *Suicide Call Back Service - 1300 659 467* *If your life is in danger call emergency services on 000."*	
OR	

"Thank you for answering those questions for me. From those answers I can see that you are eligible to participate in our study. Would you like to continue?"	
If yes, collect the participants initials and email address.	
"I will be emailing you a detailed participant information form which outlines all aspects of the trial. Please read this document carefully. You will be able to ask any questions you may have your first face to face appointment. Shall we schedule that in now?"	
Schedule and record the appointment date/time and a contact number. Send the potential participant a reminder text message the evening before their appointment at 5pm.	
Dear ….. *This is a reminder of your appointment for the AMMEND study booked for …/…../…. at ……am/pm at Endeavour College of Natural Health 368 Elizabeth St, Melbourne VIC 3000. Please proceed to the reception on level 2 and inform staff you are here to see Jessica Bayes for the AMMEND trial.* *Warm regards, Jessica*	

Although this research project is not actively targeting Aboriginal or Torres Strait Islander participants, in the event of this demographic participating, ensure permission is sought from their elders before commencing trial activities.

Appendix 17: AMMEND Results Supplementary Material – Participant Information and Consent Form

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*	*UTS HREC REF NO. ETH19-4413.*

Title	*A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)*
Short Title	*The AMMEND Study*
Project Sponsor	*Endeavour College of Natural Health*
Coordinating Principal Investigator/ Principal Investigator	*Jessica Bayes*
Location	*Melbourne*

Part 1 What does my participation involve?

1. Introduction

You are invited to take part in this research project. This is because you have been diagnosed with depression. The research project is testing the effect of a Mediterranean diet or social support on the symptoms of depression in young men. We are going to be looking at the effect these interventions have on depressive symptoms.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to have the tests and treatments that are described

• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research?

The aim of this research is to explore the effect of a Mediterranean diet or social support on the symptoms of depression in young men. The research project is a 12-week study where participants are randomly allocated to either follow a Mediterranean diet or receive social support. We are going to be looking at the effect these interventions have on depressive symptoms. The Mediterranean Diet is an experimental treatment. This means that it is not an approved treatment for Depression in Australia. This research has been funded by Endeavour College of Natural Health

What is a Mediterranean Diet?

The term 'Mediterranean diet' reflects the diets of several countries in the Mediterranean Basin during the early 1960s. It is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds and legumes. The principle source of dietary lipids is in the form of olive oil. It is low in processed foods and red meat. Dairy is consumed in low to moderate amounts and no more than 4 eggs are consumed per week. The guidelines for following this diet are as follows: Include-

- Wholegrains (such as wholemeal bread, oats and brown rice) 5-8 serves per day
- Vegetables (cooked, raw or salad) 5 serves per day
- Fruit (fresh or dried) 2 serves per day
- Legumes (beans, peas, hummus ect) 1-2 severs per day
- Nuts and seeds (walnuts, almonds ect) 1 serves per day
- Extra virgin olive oil (in salads or cooking) 3 tbsp per day
- Fish/ seafood 2 serves per week
- Milk/ dairy alternatives 1-2 serves per day
- Limit – alcohol, red meat, sweets and lollies, chocolate and other confectionary.

If you are allocated to the Mediterranean diet group, you will be required to adopt this diet for a three-month period. You will also be required to fill out online diet history forms each day (which will take approximately 5 minutes per day) to be submitted to the lead researcher to check compliance. Past research has shown that participants following a Mediterranean diet spent less money on their weekly food budget compared to their previous diet. The researcher will discuss different options with you to fit these foods into your current budget.

What is Befriending?

If you are allocated to the befriending group you will not need to change your diet. The aim of befriending is to provide additional social support through the development of an affirming, emotion-focused relationship over time. You will meet with the researcher 3 times over the 3-month period to discuss topics of interest such as sports, movies, hobbies ect. Please note that this is **not** a counselling or a psychology appointment and should not replace your current psychologist or mental health support team.

3. What does participation in this research involve?

If you decide to participate, I will invite you to: read the following information carefully and contact the lead researcher if you have any questions or concerns (Jessica: 0401962947). Involvement in this study includes:

You will first be contacted via phone and asked a few questions to see if you are eligible to participate. These include questions about your health such as allergies and illnesses. If you pass the screening procedure and are willing, we will then schedule an online baseline appointment via Zoom with the lead researcher. If you decide to participate in this research project, the primary researcher will inform your local doctor.

Your involvement will require you to meet with the lead researcher via zoom for 3 appointments which will each last for 1 hour over a 12 week period (once every 6 weeks). A consent form will be signed prior to any study assessments being performed. You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). The two groups include the Mediterranean Diet group and the social support group. There is a 50% chance you will be in the diet group.

In the first session you will complete a case history form and a questionnaire about your mental health.

4. What do I have to do?

If you are in the Mediterranean diet group you will have to follow that specific diet for the 12-week duration of the study. (A Mediterranean diet is high in wholegrains, fruits and vegetables, legumes, nuts and seeds and plenty of olive oil, it is low in processed or "fast foods" and high sugar snack foods and beverages). You are required to record your daily meals on diet forms which will be collected at the two follow up appointments. You will be provided with detailed instructions and support from a qualified Nutritionist to help you transition into the diet. You will also be provided with a food voucher at the commencement of the trial. This voucher allows you to buy some staple ingredients included in a Mediterranean diet such as an assortment of vegetables, fruit, wholegrains, beans, fish, olive oil and nuts. You will also be provided with a booklet containing recipes, meal idea, serving sizes, eating out options and handy tips.

If you are allocated to the social support group you do not need to change your diet. Instead you will engage in an activity called 'befriending' which involves talking with the researcher for an hour about various topics of interest or importance to you. These may include sports, movies, work, study, hobbies or any other topic of interest. Please note that this is not a counselling or psychology appointment and you should continue with your current mental health care plan and team.

Both groups will have scheduled follow up appointments at 6 weeks and 12 weeks after beginning the study. The diet group will be given additional nutritional counselling to help them adhere to the program and the social support group will have another befriending session. Both groups will complete depression rating scales at both follow up appointments.

You will be required to continue with your usual depression treatments such as anti-depressant medications and/or psychology visits for the duration of the trial.

At the conclusion of the study at the 12 week follow up appointment the diet group will receive another food hamper and the social support group will receive a $50 movie voucher to thank you for your time. All information collected about you will be kept strictly confidential and your information will be de-identified. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study researchers or participants jumping to conclusions.

5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the University of Technology Sydney.

What Will Happen If I Say No?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason, by contacting Jessica at Jessica.c.bayes@student.uts.edu.au. If you decide to leave the research project, we will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results.

6. What are the possible risks and disadvantages of taking part?

Yes, there are some risks/inconvenience. They include possible distress from completing the depression rating scale from reflecting on your depressive symptoms. If you become upset or distressed as a result of your participation in the research, we will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

You may also feel slightly uncomfortable while answering sensitive questions about your health or from having your physical measurements taken.

For those who are allocated to the diet group you may experience some mild gastrointestinal symptom such as bloating when first transitioning to a new diet. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any

of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the researcher immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the researcher may need to stop your treatment and will discuss the best way of managing any side effects with you.

Possible side effects include abdominal bloating, constipation and diarrhoea. This should only be temporary and you will be guided by a qualified nutritionist to support you if this does occur.

Possible inconveniences during this study include making dietary changes/learning to cook new foods if you are allocated to the diet group.

12. Can I have other treatments during this research project?

Whilst you are participating in this research project, you are required to continue with your current medications or other depression treatments and not make any changes to these for the duration of the trial. We will ask you not to make any changes to your exercise habits, or commence any other complementary or alternative therapy during the trial period.

13. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the researcher and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14. Do I Get Paid for Participation?

Participants allocated to the diet group will receive a food voucher valued at $50 at the beginning of the trial. Participants allocated to the social support group will receive a $50 Hoyte's gift voucher at the end of the study to thank you for your participation.

15. Will My Information Be Kept Private?

By signing the consent form, you consent to the research team collecting and using personal information about you for the research project. All this information will be treated confidentially. Your data will be de-identified and only accessed by the research team. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

We plan to publish the results in a peer reviewed academic journal. In any publication, information will be provided in such a way that you cannot be identified.

16. What Happens When the Research Project Ends?

If you wish to be informed about the outcomes of this research you will be invited to provide a contact email. You will be emailed a summary of the results upon completion of the project (estimated for June 2021).

Part 2 How is the research project being conducted?

17. What Will Happen to Information About Me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

In accordance with relevant Australian privacy laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study

team member named at the end of this document if you would like to access your information. Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17. Complaints and compensation

If you have concerns about the research that you think I or my supervisor can help you with, please feel free to contact us. Lead researcher, Jessica at Jessica.bayes@yahoo.com or supervisor Prof David Sibbritt at David.sibbritt@uts.edu.au. You will be given a copy of this form to keep.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

NOTE:

This study has been approved by the University of Technology Sydney Human Research Ethics Committee [UTS HREC]. If you have any concerns or complaints about any aspect of the conduct of this research, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome.

18. Who Is Organising and Funding The Research?

This research project is being conducted by the University of Technology Sydney (UTS) and is being funded by Endeavour College of Natural Health. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19. Who Has Reviewed the Research Project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of UTS.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

20. Further Information and Who to Contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study researcher (Jessica Bayes) on 0401962947.

Consent Form - *Adult providing own consent UTS HREC REF NO. ETH19-4413.*

Title	*A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)*
Short Title	The AMMEND Study
Project Sponsor	*Endeavour College of Natural Health*
Coordinating Principal Investigator/ Principal Investigator	*Jessica Bayes*
Location	*Melbourne, Australia*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please _____

Signature _____ Date _____

Declaration by Study Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of

Researcher (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent UTS HREC REF NO. ETH19-4413.*

Title	*A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)*
Short Title	The AMMEND Study
Project Sponsor	*Endeavour College of Natural Health*
Coordinating Principal Investigator/ Principal Investigator	*Jessica Bayes*
Location	*Melbourne, Australia*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the University of Technology Sydney.

Name of Participant (please _____

Signature _____ Date _____

Details:

Declaration by Study Researcher

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Researcher (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

Appendix 18: AMMEND Results Supplementary Material – Case Report Form

Case Report Form - Baseline

CONFIDENTIAL

A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)

UTS HREC Approval Number: UTS HREC REF NO. ETH19-4413.

Research Officer Name: _____ Signature: _____

Participant Allocation Number: ☐ ☐ ☐

Baseline Date: ☐ ☐ ☐ ☐ ☐ ☐

D D M M Y Y

Procedure	Screening	Baseline Visit 1	Follow up Visit 2	Final Follow up Visit 3
Screening Procedure Complete	X			End of Treatment
Sent Participant Information Sheet	X		Week 2	Week 4
Scheduled Baseline visit	X			
Written Informed Consent		X		
De-identified Participant and allocated participant code		X		
Randomised into group		X		
Case Report Form		X		X
Anthropometric Measurements		X		X
Becks Depression Inventory		X	X	X
Online Diet History Forms		X	X	X
Follow up survey (diet group only)				X
Adverse events recorded			X	X

Instructions for the completion of CRF

- All CRF's must be legibly completed using a black ballpoint pen
- Any corrections must be made by striking out with a single stroke of pen
- All corrections must be dated and initialed by investigator or a nominee
- Missing values must be recorded as ND = Not Done
- All dates should be recorded in the following format dd/mm/yy
- Patients must initial questionnaires as proof of completion

Informed Consent:

Has written consent been obtained? Yes ☐ No ☐

When did the participant give informed consent? ☐☐ ☐☐ ☐☐

D D M M Y Y

Participant Allocation Number: ☐☐☐

Baseline Date: ☐☐ ☐☐ ☐☐

D D M M Y Y

Group Allocation: Mediterranean Diet ☐ Befriending Protocol ☐

By signing and dating this page of the Case Report Form for the study and subject identified above, I declare that informed consent was obtained from the subject, and that the information contained on the attached pages of this patient's Case Report Forms correspond to this patient. The information herein –

1. Has been reviewed by me or my delegate, and
2. Is accurate, and.
3. Includes the results of tests and evaluations performed on the dates specified.

Investigator's Signature	**DD / MM/ YY**

Demographics:

Date of Birth: ____/____/_____

Place/country of birth: _____

Medical History:

☐ Diabetes ☐ Asthma ☐ Cardiovascular disease ☐ Epilepsy/seizers ☐ Migraines

☐ Bone/joint problems ☐ High/low blood pressure ☐ High Cholesterol ☐ Skin disease

☐ Stomach problems ☐ Anxiety

☐ Other _____

Allergies:

☐ Peanuts ☐ shellfish ☐ Soy ☐ Dairy ☐ Eggs ☐ Wheat/gluten

☐ Other_____

☐ Bee Stings ☐ Pollen ☐ Inspect Bites ☐ Dust mites

☐ Other_____

☐ Penicillin ☐ Latex ☐ Adhesive tape

☐ **Other**_____

Habits:

Do you drink caffeinated beverages? ☐ **Yes** ☐ **No** **How much?** _____ **Daily / weekly**

Do you drink alcoholic beverages? ☐ **Yes** ☐ **No** **How much?** _____ **Daily / weekly**

Do you smoke? ☐ **Yes** ☐ **No** **How many?** _____ **Daily / weekly**

Do you take recreational drugs? ☐ **Yes** ☐ **No** **How often?** _____ **Daily / weekly**

Do you exercise? ☐ **Yes** ☐ **No** **How often?** _____ **Daily / weekly**

Depression History

Are you currently taking antidepressant Medications? **Yes** ☐ **No** ☐

Type/brand: _____ **Dose:** _____

Doctors Name: _____ **Contact number:** _____

Do you or your doctor have plans to change

your medication or dose over the next 3 months? **Yes** ☐ **No** ☐

Are you currently seeing a psychologist or counsellor? **Yes** ☐ **No** ☐

Type/speciality: (eg CBT/Psychoanalysis) _____

Frequency of visit: _____

Psychologist name: _____ Contact number: _____

Do you have plans to change your counsellor or

frequency of visit over the next 3 months? **Yes** ☐ **No** ☐

Are you currently using any complementary/natural

medicine to treat your depression? **Yes** ☐ **No** ☐

Type/speciality: (eg acupuncture/St John's Wort) _____

Frequency of visit/dose: _____

Health Practitioners name: _____ Contact Number: _____

Do you have plans to change your complementary medicine

use or frequency of visit over the next 3 months? **Yes** ☐ **No** ☐

Are you currently taking any Medications? ☐ **Yes** ☐ **No**

Name	Route	Daily Dose	Reason for use	Date:	
				Start	End

Are you currently taking any complementary medications?

Include all supplementation of vitamins, minerals or herbal remedies ☐**Yes** ☐ **No**

Name	Route	Daily Dose	Reason for use	Date:	
				Start	End

Anthropometric Measures:

Height: _____cm **Weight: _____kg**

Waist circumference: _____cm **BMI: _____**

Blood Pressure: _____

What year were you diagnosed with depression?

_____

How long have you been on your current treatment regime?

_____

Have you tried other medications/therapies in the past?

_____

If yes, what were they:

_____

Was it effective? _____

Do you live with:

- ☐ **Parents/guardians?**
- ☐ **In student accommodation?**
- ☐ **Share house/rent?**
- ☐ **Live alone?**
- ☐ **Homeless/temporary accommodation**

On a normal day do you:

- ☐ **Prepare all of your own meals?**
- ☐ **Prepare some of your meals?**
- ☐ **Have your meals prepared by someone else?**
- ☐ **Rely on takeout/fast food?**

Do you have access to the following cooking appliances and utilities?

- ☐ **Oven?**
- ☐ **Stove top?**
- ☐ **Blender/food processor?**
- ☐ **Microwave?**

Do you find healthy eating to be expensive? ☐ Yes, ☐ No, ☐ Unsure, ☐ Prefer not to say

Do you find healthy eating to be time consuming? ☐ Yes, ☐ No, ☐ Unsure, ☐ Prefer not to say

What is your usual weekly food budget?

_____

How much time per day do you spend preparing/cooking meals?

_____

Have you followed any specific diets in the past?

_____

Mental health goals/desired outcomes?

_____

_____

_____

Sleep quality? _____ Energy levels? _____/ 10 Stress levels? _____/ 10

Do you take any nutritional or herbal supplements?

_____

How often do you spend time outside/ in nature?

_____

Hobbies and community activities?

_____

(eg sports teams/ church / volunteering ect)

Do you use any social media/ online support groups or apps for:

- ☐ **Mental health**
- ☐ **Depression**
- ☐ **Sleep**
- ☐ **Mindfulness**

Family History of mental illness?

_____

The World Health Organization Quality Of Life (Whoqol) -Bref

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1

4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the	1	2	3	4	5

	opportunity for leisure activities?					

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5

22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	**Domain 1**	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 □ + □ + □ + □ + □ + □ + □	a. =	b:	c:
28.	**Domain 2**	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) □+□+□+ □ + □ + □	a. =	b:	c:
29.	**Domain 3**	Q20 + Q21 + Q22 □ + □ + □	a. =	b:	c:
30.	**Domain 4**	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 □+□+□ + □ + □ + □ + □ + □	a. =	b:	c:

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2.

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3.

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4.

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5.

0 I don't feel particularly guilty
1 I feel guilty over many things I have done or should have done
2 I feel guilty most of the time.
3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.

0 I feel the same about myself as ever.
1 I have lost confidence in myself
2 I am disappointed with myself.
3 I dislike myself.

8.

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.

0 I don't cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11.

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated, it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12.

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13.

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14.

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to others.
3 I feel utterly worthless.

15.

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16.

0 I have not experienced any change in my sleeping
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17.

0 I am not more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18.

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19.

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20.

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21.

0	I have not noticed any recent change in my interest in sex.
1	I am less interested in sex than I used to be.
2	I am much less interested in sex now.
3	I have lost interest in sex completely.

Notes:

Case Report Form – Follow Up Week 6

CONFIDENTIAL

A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)

UTS HREC Approval Number: UTS HREC REF NO. ETH19-4413.

Research Officer Name: _____Signature: _____

Participant Allocation Number: ☐☐☐

Follow Up Visit: ☐☐ ☐☐ ☐☐

D D M M Y Y

Have there been any changes to your medications, does or frequency? ☐ Yes ☐ No

If Yes, what were they? _____

Have there been any changes to your psychology appointments ☐ Yes ☐ No (practitioner or frequency)?

If yes, what were they? _____

Have there been any changes to your complementary medicine use? ☐ Yes ☐ No

If yes, what were they? _____

Sleep quality? _____ Energy levels? _____/ 10 Stress levels? _____/ 10

Have any adverse events occurred? ☐ Yes ☐ No

If yes, has the Adverse Events Log been completed? ☐ Yes ☐ No

Have any challenges or difficult life circumstances occurred in the last 6 weeks? ☐ Yes ☐ No

(eg, relationship break up, started a new job ect)

Anthropometric Measures:

Height: _____cm **Weight: _____kg**

Waist circumference: _____cm **BMI: _____**

Blood Pressure: _____

Comments:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

The World Health Organization Quality Of Life (Whoqol) -Bref

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5

6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5

25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

_____

_____

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	**Domain 1**	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 □ + □ + □ + □ + □ + □ + □	a. =	b:	c:
28.	**Domain 2**	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) □+□+□+ □ + □ + □	a. =	b:	c:
29.	**Domain 3**	Q20 + Q21 + Q22 □ + □ + □	a. =	b:	c:
30.	**Domain 4**	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 □+□+□ + □ + □ + □ + □ + □	a. =	b:	c:

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2.

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3.

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4.

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5.

0 I don't feel particularly guilty
1 I feel guilty over many things I have done or should have done
2 I feel guilty most of the time.
3 I feel guilty all of the time

6.

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.

0 I feel the same about myself as ever.
1 I have lost confidence in myself
2 I am disappointed with myself.
3 I dislike myself.

8.

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.

0 I don't cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11.

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated, it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12.

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13.

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14.

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to others.
3 I feel utterly worthless.

15.

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16.

0	I have not experienced any change in my sleeping
1a	I sleep somewhat more than usual.
1b	I sleep somewhat less than usual.
2a	I sleep a lot more than usual.
2b	I sleep a lot less than usual.
3a	I sleep most of the day.
3b	I wake up 1-2 hours early and can't get back to sleep.

17.

0	I am not more irritable than usual.
1	I am more irritable than usual.
2	I am much more irritable than usual.
3	I am irritable all the time.

18.

1	I have not experienced any change in my appetite.
1a	My appetite is somewhat less than usual.
1b	My appetite is somewhat greater than usual.
2a	My appetite is much less than before.
2b	My appetite is much greater than usual.
3a	I have no appetite at all.
3b	I crave food all the time.

19.

0	I can concentrate as well as ever.
1	I can't concentrate as well as usual.
2	It's hard to keep my mind on anything for very long.
3	I find I can't concentrate on anything.

20.

0	I am no more tired or fatigued than usual.
1	I get more tired or fatigued more easily than usual.
2	I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Case Report Form – Follow Up Week 12

CONFIDENTIAL

A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study)

UTS HREC Approval Number: UTS HREC REF NO. ETH19-4413.

Research Officer Name: _____ Signature: _____

Participant Allocation Number: ☐☐☐

Follow Up Visit: ☐☐ ☐☐ ☐☐

D D M M Y Y

Have there been any changes to your medications, does or frequency? ☐ Yes ☐ No

If Yes, what were they? _____

Have there been any changes to your psychology appointments ☐ Yes ☐ No (practitioner or frequency)?

If yes, what were they? _____

Have there been any changes to your complementary medicine use? ☐ Yes ☐ No

If yes, what were they? _____

Sleep quality? _____ Energy levels? _____/ 10 Stress levels? _____/ 10

Have any adverse events occurred? ☐ Yes ☐ No

If yes, has the Adverse Events Log been completed? ☐ Yes ☐ No

Have noticed a change in your depressive symptoms over the last 12 weeks? ☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Prefer not to say**

Do you think your depressive symptoms have?

☐ **Improved**

☐ **Stayed the same**

☐ **Worsened**

☐ **Unsure**

Anthropometric Measures:

Height: _____cm **Weight: _____kg**

Waist circumference: _____cm **BMI: _____**

Blood Pressure: _____

Have any challenges or difficult life circumstances occurred in the last 6 weeks? ☐ **Yes** ☐ **No**

(eg, relationship break up, started a new job ect)

Comments:

The World Health Organization Quality Of Life (Whoqol) -Bref

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1

5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5
20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5

25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

_____

_____

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	**Domain 1**	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18	a. =	b:	c:
28.	**Domain 2**	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26)	a. =	b:	c:
29.	**Domain 3**	Q20 + Q21 + Q22	a. =	b:	c:
30.	**Domain 4**	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25	a. =	b:	c:

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2.

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3.

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4.

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5.

0 I don't feel particularly guilty
1 I feel guilty over many things I have done or should have done
2 I feel guilty most of the time.
3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.

0 I feel the same about myself as ever.
1 I have lost confidence in myself
2 I am disappointed with myself.
3 I dislike myself.

8.

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.

0 I don't cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11.

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated, it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12.

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13.

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14.

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to others.
3 I feel utterly worthless.

15.

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16.

0	I have not experienced any change in my sleeping
1a	I sleep somewhat more than usual.
1b	I sleep somewhat less than usual.
2a	I sleep a lot more than usual.
2b	I sleep a lot less than usual.
3a	I sleep most of the day.
3b	I wake up 1-2 hours early and can't get back to sleep.

17.

0	I am not more irritable than usual.
1	I am more irritable than usual.
2	I am much more irritable than usual.
3	I am irritable all the time.

18.

0	I have not experienced any change in my appetite.
1a	My appetite is somewhat less than usual.
1b	My appetite is somewhat greater than usual.
2a	My appetite is much less than before.
2b	My appetite is much greater than usual.
3a	I have no appetite at all.
3b	I crave food all the time.

19.

0	I can concentrate as well as ever.
1	I can't concentrate as well as usual.
2	It's hard to keep my mind on anything for very long.
3	I find I can't concentrate on anything.

20.

0	I am no more tired or fatigued than usual.
1	I get more tired or fatigued more easily than usual.
2	I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Adverse Events Log

Participant Allocation Number	Description of Adverse Event	Severity 1 = Mild 2 = Moderate 3 = Severe	Serious Adverse Event? Yes/No	Relationship to Study Intervention 0 = Unrelated 1 = Unlikely 2 = Possible 3 = Probable 4 = Definitely	Action Taken

Withdrawal from study form

Date of withdrawal: ____/____/____
Participant Allocation number: _____
Reason: ☐ Lack of efficacy ☐ Lost to Follow up ☐ Adverse Event ☐ Serious Adverse Event ☐ Other
Details/comments:
In the event of withdrawal due to a serious adverse event, did the participant get appropriate medical assistance? ☐ Yes ☐ No

Details:

Notes:

Appendix 19: AMMEND Results Supplementary Material – Participant Documents

Mediterranean Diet Overview

What does a Mediterranean Diet involve?

The term 'Mediterranean diet' reflects the diets of several countries in the Mediterranean Basin during the early 1960s. It is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds and legumes. The principle source of dietary lipids is in the form of olive oil. It is low in processed foods and red meat. Dairy is consumed in low to moderate amounts and no more than 4 eggs are consumed per week. The guidelines for following this diet are as follows:

Include:

- Wholegrains (such as wholemeal bread, oats and brown rice) 5-8 serves per day
- Vegetables (cooked, raw or salad) 5 serves per day
- Fruit (fresh or dried) 2 serves per day
- Legumes (beans, peas, hummus etc) 1-2 severs per day
- Nuts and seeds (walnuts, almonds etc) 1 serves per day
- Extra virgin olive oil (in salads or cooking) 3 tbsp per day
- Fish/ seafood 2 serves per week
- Milk/ dairy alternatives 1-2 serves per day

Limit – alcohol, red meat, sweets and lollies, chocolate and other confectionary.

If you are allocated to the Mediterranean diet group, you will be required to adopt this diet for a three-month period. You will also be required to fill out diet history forms each day to be submitted to the lead researcher to check compliance.

Mediterranean Diet Serving Sizes

The **bulk** of the Mediterranean diet is made up of the following foods:

Wholes Grains 5-8 serves per day	
Examples:	1 serve:
Wholemeal bread	1 slice
Rolled oats	½ cup
Whole bran muesli	½ cup
Wholemeal pasta	½ cup
Brown rice	½ cup
Other cooked grain (quinoa/barley/millet)	½ cup

Vegetables 5+ serves per day	
Examples:	1 serve:
Cooked vegetables (carrots/broccoli/mushrooms/capsicums etc)	½ cup
Salad vegetables (spinach/kale/silverbeet/rocket etc)	1 cup
Starchy vegetables (potatoes/sweet potatoes/pumpkin etc)	1 medium item
Tomatoes (large whole/small cherry/pureed in sauce or soup)	1 medium tomato or ½ cup

Fruit 2 serves per day	
Examples:	1 serve:
Medium sized fresh fruit (apple/banana/nectarine/mandarin)	1 whole fruit item
Small sized fresh fruit (plum/grapes/cherries)	2 whole fruit item
Large fruit (pineapple/melon	1 cup diced
Dried fruit (apricots/raisons/ figs/dates)	30 grams

Legumes and pulses 1-2 serves per day	
Examples:	1 serve:
Beans (chickpeas/lentils/kidney beans/baked beans)	½ cup
Other legumes (peas/ split peas/tofu/edamame/tempeh)	½ cup
Hummus	60 grams
Falafel	½ cup

Fish 2 serves per week	
Examples:	1 serve:
Canned fish (tuna/sardines/maceral)	1 small can
Fresh fillet (salmon/	100 grams
Shellfish (scallops/crab/muscles/oysters)	100 grams

Nuts and Seeds 1-2 serves per day	
Examples:	1 serve:

Whole, raw nuts (almonds/cashews/walnuts etc)	30 grams
Whole raw seeds (pumpkin seeds/sunflower seeds/chia seeds)	30 grams
Nut spread (peanut butter/almond spread etc)	30 grams

Extra Virgin Olive Oil (EVOO) 3 serves per day	
Examples:	1 serve
Extra virgin olive oil	1tbsp of oil

Water 8 glasses per day	
Examples:	1 serve
Water	1 glass
Herbal tea (green/lemon/ginger/peppermint/camomile etc)	1 mug

Moderate amounts of the following foods:

Milk and alternatives 1-2 serves per day	
Examples:	1 serve:
Low fat dairy milk or soy/almond/coconut milk	1 cup (250 ml)
Greek yogurt or coconut yogurt	¾ cup (300 grams)
Feta or goats cheese	½ cup (120 grams)

Eggs no more than 6 per week	
Example:	1 serve
Free range omega 3 egg	1 medium sized egg 60g

Poultry no more than 4 per week	
Examples:	1 serve:
Free range chicken/turkey	80 g (palm size)

Red meat no more than 1 per week	
Examples:	1 serve:
Grass fed beef steak	65 g
Mince	½ cup

Limit the following foods:

One serve of discretionary “extra” food or drinks is roughly 600kJ

Extras no more than 2 per week	
Examples:	1 serve:
Ice cream	75 grams (2 scoops)
Chocolate	½ small bar (25 grams)

Processed meats eg salami, bacon	2 slices
Fried hot chips	12 chips (60 grams)
Sugary/fizzy drinks	1 can
Donut	1 donut

Alcohol	
Examples:	1 serve:
Wine	150 ml glass
Beer	285 ml (middy)
Spirits	30 ml

Meal Ideas

Breakfast Options:

Mushroom omelette

With red onion, tomatoes, 1 egg, evoo, and goats cheese

Oats

with walnuts, berries and Greek yoghurt

Wholemeal toast

With hummus, spinach and tomatoes

Beans on toast

Low salt baked beans, spinach and tomatoes

Eggs on toast

Salmon and a poached egg with spinach and tomatoes

Avocado on toast

Avocado and feta with spinach and tomatoes

Whole bran muesli

With nuts, fruit and milk

Lunch Options:

Tuna salad bowl

With brown rice, zucchini, salad vegetables and tomatoes

Baked sweet potato

With sweet corn, peas, grated carrot and beetroot, walnuts and feta, evoo

Falafel wrap

With hummus, tahini, salad, tomatoes

Mediterranean veggie sandwich

Roast capsicum, eggplant, spinach, red onion, tomato, cucumber and avocado

Lemon herb chicken salad

With avocado and tomatoes

Mediterranean couscous with tuna

With cherry tomatoes, olives and capers

Stuffed eggplant

With rice lentils and feta

Salmon flat bread crackers

With goats cheese and red onion

Lemon chicken and white bean soup

With kale, garlic and carrots

Lemon potato salad with tabouli

With tomatoes, feta and olives

Dinner Options:

Egyptian Lentils with Rice

With onion, herbs and spices

Eggplant, Lentils, and Peppers cooked in Olive Oil

Served with rice

Harissa chickpea stew

With eggplant and millet

Homemade Mediterranean pizza

Pita bread topped with olives, tomatoes, eggplant, capsicum, rocket, feta

Lentil and barley soup

Served with wholemeal bread

Spanish Moroccan fish

With potatoes and chickpeas

Herb Lamb meat balls pita pockets

With salad and tzatziki

Cupboard Swaps

Canola/palm or other cooking oils	**SWAP**	for Extra virgin olive oil
White bread/rolls/wraps	**SWAP**	for wholemeal or multigrain
Processed sandwich meats	**SWAP**	for cans of fish, falafel or feta
Sugary or soft drinks	**SWAP**	for mineral/plain water or herbal tea
High sugar cereal	**SWAP**	for whole bran muesli
Chocolate snacks	**SWAP**	for a piece of fruit or handful of nuts

Pantry Staples Shopping List

- Wholemeal multigrain bread
- Brown rice or other grains eg quinoa
- Whole grain crackers
- Whole bran muesli
- Extra virgin olive oil
- Herbs and spices (onions, garlic, rosemary etc)
- Fresh fruit (apples, bananas, oranges etc)
- Fresh salad (spinach, rocket, silver beet, kale etc)
- Fresh vegetables (mushrooms, sweet potatoes, broccoli, carrots etc)
- Nut and seed mix
- Tins of fish
- Hummus
- Cans of legumes (chickpeas, lentils, kidney beans)
- Greek Yogurt or dairy free alternative
- Meat or alternative (lean chicken fillets, beef mince, tofu, falafel)
- Dairy or alternatives (milk, cheese etc)
- Eggs
- Tomatoes (either whole, pureed or sauce)

Eating on a Budget

Healthy eating doesn't have to be expensive! When you take out all of the "extra" items such as chocolates, sweets, biscuits, soft drink etc you will have plenty of room in your budget for fresh food. The clever spending tips below will help you stick to a tight budget.

Clever spending

- Plan your healthy weekly menu ahead including meals and snacks for the week and then write your shopping list
- Shop around locally to find the best prices, and look for the lowest cost per kg or unit
- Look out for specials and buy everyday foods in bulk as they are usually cheaper
- Cook in bulk and freeze for later use
- Go for fresh fruit and vegies that are in season as they are often less expensive and better in quality and taste
- Try legumes such as tinned kidney beans, chick peas, soya beans or lentils for a tasty and cheaper alternative to meats in salads or casseroles
- Spend the least on 'occasional' foods such as soft drinks, lollies, chocolates, cakes, biscuits, potato crisps and takeaway foods, which are not recommended for everyday healthy eating and are often expensive.
- Frozen and canned fruit and vegetables can be a cheap and healthy alternative to fresh items. Choose canned vegies with no added salt (or reduced salt), and canned fruit in natural juice or water
- Buy from local food co-ops or farmers markets in your area.
- Buy generic brands ("no name" or "home brand") where possible
- Don't shop when you are hungry as you are more likely to buy things you don't need

Example 7 day Meal Plan

Monday (06/05/19)
Breakfast ½ cup of rolled oats ½ cup of walnuts ½ cup mixed berries ½ cup of Greek yoghurt 1 glass of water
Lunch ½ cup of brown rice 2 large tomatoes 1 cup of salad vegetables ½ cup of grated zucchini 95 grams of tuna 2 tbsp of extra virgin olive oil Juice from 1 lemon 1 tbsp balsamic vinegar 1 glass of water
Dinner Soup: ½ cup of barley ½ cup of lentils ½ cup of mushrooms 1 cup of mixed veg (carrots/broccoli/pumpkin) Garlic/onion/herbs/spices 2 slices of wholemeal bread 1 glass of water
Snack 1 chopped carrot ¼ cup of hummus 1 cup of green tea 1 litre bottle of water
Total

Tuesday (07/05/19)
Breakfast 2 slices of wholemeal bread toasted 2 tbsp of hummus ½ cup spinach 1 tomato sliced Red apple 1 glass of water
Lunch 1 large baked sweet potato ½ cup sweetcorn and peas ½ cup grated carrot and beetroot 30 g feta 30 g walnuts 2 tbsp extra virgin olive oil 1 glass of water
Dinner ½ cup couscous Chicken grilled 300 g tomatoes 1 cup broccoli/eggplant/carrots Garlic/onion/herbs/spices 1 glass of water
Snack 2 wholegrain flatbread crackers 2 tbsp peanut butter 1 cup of black tea 1 litre bottle of water
Total

Wednesday (08/05/19)
Breakfast Mushroom omelette: ½ cup mushrooms 1 egg ½ red onion 1 tomato 30 g goats cheese 2 tbsp extra virgin olive oil 2 slices of wholemeal bread toasted 1 glass of water
Lunch 2 pieces of wholemeal wrap bread 30 g falafel 30 g hummus 1 cup of salad leaves (spinach/rocket/silver beet) 1 tomato sliced 1 banana 1 glass of water
Dinner Red lentil dahl: ½ cup of lentils ½ cup of brown rice 1 cup of mixed veg (carrots/broccoli/pumpkin) Garlic/onion/herbs/spices 1 cup coconut milk 2 tbsp extra virgin olive oil 1 glass of water
Snack ½ cup almonds 1 cup of green tea 1 litre bottle of water

Total
Thursday (09/05/19)
Breakfast 2 slices of wholemeal bread toasted ½ can of salt free backed beans ½ cup spinach 1 tomato sliced Red apple 1 glass of water
Lunch 2 whole grain flat bread crackers 95 g salmon 1 cup salad vegetables 30 g walnuts 2 tbsp extra virgin olive oil 1 glass of water
Dinner ½ cup couscous Chicken grilled 300 g tomatoes 1 cup broccoli/eggplant/carrots Garlic/onion/herbs/spices 1 glass of water
Snack ½ cup Greek yoghurt ½ cup mixed berries 1 cup of black tea 1 litre bottle of water
Total

Friday (10/05/19)
Breakfast Mushroom omelette: ½ cup mushrooms 1 egg ½ red onion 1 tomato 30 g goats cheese 2 tbsp extra virgin olive oil 2 slices of wholemeal bread toasted 1 glass of water
Lunch 2 pieces of wholemeal wrap bread 30 g falafel 30 g hummus 1 cup of salad leaves (spinach/rocket/silver beet) 1 tomato sliced 1 banana 1 glass of water
Dinner Red lentil dahl: ½ cup of lentils ½ cup of brown rice 1 cup of mixed veg (carrots/broccoli/pumpkin) Garlic/onion/herbs/spices 1 cup coconut milk 2 tbsp extra virgin olive oil 1 glass of water
Snack ½ cup almonds 1 cup of green tea

1 litre bottle of water

Total

Saturday (11/05/19)

Breakfast

½ cup of rolled oats
½ cup of almonds
½ cup mixed berries
½ cup of Greek yoghurt
1 glass of water

Lunch

1 large baked sweet potato
½ cup sweetcorn and peas
½ cup grated carrot and beetroot
30 g feta
30 g walnuts
2 tbsp extra virgin olive oil
1 glass of water

Dinner

Soup: ½ cup of barley
½ cup of lentils
½ cup of mushrooms
1 cup of mixed veg (carrots/broccoli/pumpkin)
Garlic/onion/herbs/spices
2 slices of wholemeal bread
1 glass of water

Snack

Wholegrain sugar free muesli bar
Banana
1 cup of black tea
1 litre bottle of water

Total

Sunday (12/05/19)

Breakfast

Mushroom omelette:
½ cup mushrooms
1 egg
½ red onion
1 tomato
30 g goats cheese
2 tbsp extra virgin olive oil
2 slices of wholemeal bread toasted
1 glass of water

Lunch

2 pieces of wholemeal wrap bread
30 g falafel
30 g hummus
1 cup of salad leaves (spinach/rocket/silver beet)
1 tomato sliced
1 banana
1 glass of water

Dinner

Red lentil dahl:
½ cup of lentils
½ cup of brown rice
1 cup of mixed veg (carrots/broccoli/pumpkin)
Garlic/onion/herbs/spices
1 cup coconut milk
2 tbsp extra virgin olive oil
1 glass of water

Snack ½ cup almonds 1 cup of green tea 1 litre bottle of water
Total

Weekly checklist	
Whole grains 5-8 serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Vegetables 6+ serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Fruit 1-2 serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Nuts 1-2 serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Extra virgin olive oil 3 serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Legumes at least 4+ serves per week	☐ ☐ ☐ ☐
Fish at least 2 serves per week	☐ ☐
Dairy or alternative 1-2 serves per day	☐ ☐ ☐ ☐ ☐ ☐ ☐
Eggs no more than 5 per week	Number of eggs consumed:
Poultry	Number of poultry portions consumed:

Red Meat	Number of red meat portions consumed:
Extras no more than 2 per week	Number of extras consumed:
Alcohol	Number of drinks consumed:

Food Allergy

Food allergy occurs in around 10% of infants, 4-8% of children, and about 2% of adults in Australia and New Zealand. The most common triggers are egg, cow's milk, peanut, tree nuts, sesame, soy, fish, shellfish, and wheat. Some food allergies can be severe, causing life-threatening reactions known as anaphylaxis.

What is allergy?

An allergy is when the immune system reacts to a substance (allergen), in the environment which is usually harmless (such as food, pollen, animal dander, and dust mite), or bites, stings and medications. This results in the production of allergy antibodies which are proteins in the immune system that identify and react with foreign substances.

An allergic reaction happens when a person develops symptoms following exposure to an allergen. Symptoms may include hives, swelling of the lips, eyes or face, vomiting, or wheeze. It is important to note that only some people with allergy antibodies will develop symptoms following exposure to the allergen. Confirmation of allergy by a clinical immunology/allergy specialist is required.

Symptoms of food allergy

Mild to moderate symptoms of food allergy include:

- Swelling of the face, lips and/or eyes.
- Hives or welts on the skin.
- Abdominal pain and/or vomiting.

Signs of a severe allergic reaction (anaphylaxis) to foods include:

- Difficult/noisy breathing.
- Swelling of the tongue.
- Swelling/tightness in the throat.
- Difficulty talking and/or hoarse voice.
- Wheeze or persistent cough.

- Persistent dizziness and/or collapse.
- Pale and floppy (in young children).

Sometimes food allergy isn't obvious

Less common symptoms of food allergy include infantile colic, reflux of stomach contents, eczema, chronic diarrhea and failure to thrive in infants.

Food allergy can be dangerous

Although mild, moderate and severe allergic reactions (anaphylaxis), to foods are common in Australia and New Zealand, deaths from anaphylaxis due to food allergy are rare. Most deaths can be prevented by careful allergen avoidance measures, and immediate administration of an adrenaline (epinephrine) autoinjector.

Not all adverse reactions to foods are due to allergy

The term allergy is often misused to describe any adverse reaction to foods. Adverse reactions to foods that are not allergy include food intolerances, toxic reactions, food poisoning, enzyme deficiencies, food aversion, or irritation from skin contact with certain foods. Symptoms include headaches after having chocolate or red wine, or bloating after drinking a milkshake or eating pasta.

How common is food allergy and is it increasing?

Studies have shown that food allergy affects 10% of children up to one year of age, 8% of children up to five years of age, and approximately 2% of adults. Hospital admissions for severe allergic reactions (anaphylaxis), have doubled over the last decade in Australia, USA and UK. In Australia, admissions for anaphylaxis due to food allergy in children aged zero to four years are even higher, having increased five-fold over the same period.

What is causing the rise in food allergy?

We currently don't have clear information as to why food allergy has increased so rapidly in recent years, particularly in young children. This area requires additional research, several of which are already underway.

Possible explanations include:

- Hygiene hypothesis which proposes that less exposure to infections in early childhood is associated with an increased risk of allergy. The make-up and type of the micro-organisms to which the mother and infant are exposed and colonised with may alter allergic risk.
- Delayed introduction of allergenic foods such as egg, peanut or tree nuts.
- Methods of food processing, such as roasted versus boiled peanuts.
- Development of allergy to food by skin exposure such as the use of unrefined nut oil based moisturisers.

Allergies to cow's milk, eggs and peanuts are the most common in children

Nine foods cause 90% of food allergic reactions, including cow's milk, egg, peanut, tree nuts, sesame, soy, fish, shellfish and wheat.

Peanut, tree nuts, shellfish, fish, sesame and egg are the most common food allergens in older children and adults.

Other triggers such as herbal medicines, fruits and vegetables have been described, and almost any food can cause an allergic reaction.

When does food allergy develop?

Food allergy can develop at any age, but is most common in children less than five years old. Even young babies can develop symptoms of food allergy.

Reliable diagnosis of food allergy is important

Your doctor will ask a series of questions that may help narrow down the list of likely causes, such as foods or medications consumed that day, or exposure to stinging insects.

Skin tests or blood tests for allergen specific IgE antibodies help to confirm or exclude potential triggers.

Sometimes a temporary elimination diet under close medical supervision will be needed, followed by food challenges to identify the cause. Long term unsupervised restricted diets should not be undertaken, as this can lead to malnutrition.

While the results of allergy testing are a useful guide in determining whether a person is allergic, they do not provide a reliable guide to whether the reaction will be mild or severe.

Food allergy is not hereditary

Most of the time children with food allergy do not have parents with food allergy. However, if a family has one child with food allergy, their brothers and sisters are at a slightly higher chance of having food allergy.

A positive allergy test is not the same as being food allergic

A positive skin test or blood test for allergen specific IgE antibodies means that the body's immune system has produced a response to a food. Sometimes these are false positives and the person can eat the food without allergy symptoms. Therefore it is important to confirm the test with a supervised food challenge.

Unorthodox allergy tests are unproven

There are several unorthodox tests for food allergy that have no scientific basis. These include cytotoxic food testing, Vega testing, kinesiology, allergy elimination techniques, iridology, pulse testing, alcat testing, Rinkel's intradermal skin testing, reflexology, hair

analysis and IgG food antibody testing. There is no Medicare rebate available in Australia for these tests, and their use is not supported in New Zealand.

ASCIA INFORMATION FOR PATIENTS, CONSUMERS AND CARERS

Treatment based on non-scientific tests may lead to ineffective, and expensive treatments, and delay more effective therapy. Harmful therapy such as unnecessary dietary avoidance may risk malnutrition.

Food allergy can be outgrown

Most children allergic to cow's milk, soy, wheat or egg will outgrow their food allergy. By contrast, allergic reactions to peanut, tree nuts, sesame and seafood persist in approximately 75% of children affected. When food allergy develops for the first time in adults, it usually persists.

Allergic reactions may be mild, moderate or severe, and can be influenced by many factors

These factors include:

- The severity of the allergy.
- The amount of food eaten.
- The form of the food; liquid may be absorbed faster, and cooked food is sometimes better tolerated.
- Whether it is eaten on its own or mixed in with other foods.
- Intake of alcohol.
- Exercise around the same time as the meal, as this may worsen severity.
- The presence or absence of asthma.
- Menstrual cycle.

Research into food allergy is ongoing

The increase of food allergy is driving research into areas such as prevention, treatment, and why it has become more common. Areas of research include allergen immunotherapy (AIT), also known as desensitisation, to switch off the allergy once it has developed.

ASCIA Action Plans

Many people with food allergies will have an exposure every few years, even when they are very careful to avoid the foods they are allergic to. People with allergy should have an ASCIA Action Plan for Anaphylaxis and an adrenaline autoinjector if it has been prescribed.

Living with food allergy

Strict avoidance is essential in the management of food allergy.

It is important for people with food allergy to:

- Carry their adrenaline autoinjector and ASCIA Action Plan for Anaphylaxis with them at all times.
- Know the signs and symptoms of allergic reactions, and know what to do when a reaction occurs.
- Read and understand food labels for food allergy.
- Tell wait staff that they have a food allergy when eating out.
- Be aware of cross contamination of food allergens when preparing food.

Food allergy can be effectively managed

People with food allergy can learn to manage their condition with the guidance of their clinical immunology/allergy specialist. Having an ASCIA Action Plan for Anaphylaxis and adrenaline autoinjector offers reassurance, but this is not a substitute for strategies to minimise the risk of exposure.

ascia
australasian society of clinical immunology and allergy
www.allergy.org.au

ACTION PLAN FOR Allergic Reactions

Name: _____

Date of birth: _____

Confirmed allergens:

Family/emergency contact name(s):

_____

_____

Work Ph: _____

Home Ph: _____

Mobile Ph: _____

Plan prepared by medical or nurse practitioner:

_____

I hereby authorise medications specified on this plan to be administered according to the plan

Signed:

_____

Date: _____

Action Plan due for review – date:

_____

Note: This ASCIA Action Plan for Allergic Reactions is for people with mild to moderate allergies, who need to avoid certain allergens.

For people with severe allergies (and at risk of anaphylaxis) there are red ASCIA Action Plans for Anaphylaxis (brand specific or generic versions) for use with adrenaline (epinephrine) autoinjectors.

Instructions are on the device label.

Adrenaline autoinjectors (300 mcg) are prescribed for children over 20kg and adults. Adrenaline autoinjectors (150 mcg) are prescribed for children 10-20kg.

SIGNS OF MILD TO MODERATE ALLERGIC REACTION

- Swelling of lips, face, eyes
- Hives or welts
- Tingling mouth
- Abdominal pain, vomiting (these are signs of anaphylaxis for insect allergy)

ACTION FOR MILD TO MODERATE ALLERGIC REACTION

- For insect allergy - flick out sting if visible
- For tick allergy ☐ seek medical help or ☐ freeze tick and let it drop off
- Stay with person and call for help
- Give other medications (if prescribed).....
- Phone family/emergency contact

Mild to moderate allergic reactions (such as hives or swelling) may not always occur before anaphylaxis

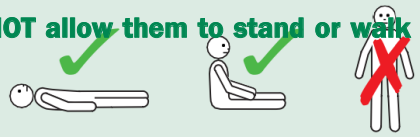
WATCH FOR ANY ONE OF THE FOLLOWING SIGNS OF ANAPHYLAXIS (SEVERE ALLERGIC REACTION)

- **Difficult/noisy breathing**
- **Swelling of tongue**
- **Swelling/tightness in throat**
- **Wheeze or persistent cough**
- **Difficulty talking and/or hoarse voice**
- **Persistent dizziness or collapse**
- **Pale and floppy (young children)**

ACTION FOR ANAPHYLAXIS

1 Lay person flat - do NOT allow them to stand or walk

- **If unconscious, place in recovery position**
- **If breathing is difficult allow them to sit**



2 Give adrenaline (epinephrine) autoinjector if available

3 Phone ambulance - 000 (AU) or 111 (NZ)

4 Phone family/emergency contact

5 Transfer person to hospital for at least 4 hours of observation

If in doubt give adrenaline autoinjector

Commence CPR at any time if person is unresponsive and not breathing normally

ALWAYS give adrenaline autoinjector FIRST if available, and then asthma reliever puffer if someone with known asthma and allergy to food, insects or medication has SUDDEN BREATHING DIFFICULTY (including wheeze, persistent cough or hoarse voice) even if there are no skin symptoms

Asthma reliever medication prescribed: ☐ Y ☐ N

- *If adrenaline is accidentally injected (e.g. into a thumb) phone your local poisons information centre.*
- *Continue to follow this action plan for the person with the allergic reaction.*

Participant Assistance Sheet

Seeking Help for Depression

You don't have to struggle alone in silence. If you feel like you may be experiencing depression it's important that you seek help. There are a variety of mental health services and professionals out there that can help you with your mental health issues and prevent things from getting worse.

Counselling (24 /7):

Lifeline Australia - 13 11 14

Men's Line Australia - 1300 78 99 78

Suicide Call Back Service - 1300 659 467

You can also:

Talk to someone you trust

Visit a hospital emergency department

Contact your GP, a counsellor, psychologist or psychiatrist.

Emergency help:

Some people may have suicidal thoughts when they are very worried and things are too hard and painful. If you feel that life is not worth living, it's really important to seek immediate help. With help, you can overcome these thoughts and stay safe.

Help is available:

If your life is in danger call emergency services:

Emergency Australia - 000

You are not alone. There is always someone to hear your pain and problems, and to help you keep safe.

Appendix 20: AMMEND Results Supplementary Material – Adapted 15 item MEDAS

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? (1 serving : 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving : 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, orcustard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes

Questions	Criteria for 1 point
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥2
Added Questions 15. How many serves of whole grains (wholemeal bread, brown rice, oats etc) do you consume per day?	>3

Appendix 21: AMMEND Results Table 1. Demographic Characteristics of Study Participants (Including p-values)

Item	MD Group	Control Group	p-values[2]
Number of Participants	**36**	**36**	
Age (Mean ± SD)	21.5 (2.9)	22.5 (2.5)	0.121
Born in Australia (%)	n=27 (75%)	n=27 (75%)	1.000
Habits:			
Baseline CSIRO diet score /100	35.1(4.9)	35.3 (4.7)	0.860
Caffeine intake, drinks/week (Mean ± SD)	11 (8.2)	9 (7.9)	0.296
Alcohol intake, drinks/week (Mean ± SD)	6.6 (7.3)	5.4 (5.3)	0.428
Exercise sessions/week (Mean ± SD)	2.3 (2.1)	2.5 (2.7)	0.727
Cigarette smokers (%)	n=5 (13.8%)	n=7 (19.4%)	0.527
Recreational drug use (%)	n=12 (33.1%)	n=13 (36.1%)	0.824
Depression:			
Baseline BDI-II Score	34.8 (8.1)	33.5 (9.0)	0.522
Taking anti-depressant medication (%)	n=11 (31%)	n=15 (41%)	0.326
Undergoing psychotherapy (%)	n=16 (44%)	n=17 (47%)	0.813
Using phone apps[1] focused on mental health (%)	n=11 (31%)	n=11 (31%)	1.000
Home:			
Living at home with parents (%)	n=14 (39%)	n=15 (42%)	0.810
Living in student accommodation (%)	n=4 (11%)	n=1 (3%)	0.164
Share housing (%)	n=13 (36%)	n=14 (39%)	0.808
Living alone (%)	n=5 (14%)	n=6 (17%)	0.743
Money spent on food/week ($AUD) (Mean ± SD)	$110 (54.1)	$104 (56.7)	0.647
Time spent cooking/day (minutes) (Mean ± SD)	44 (29.2)	37 (30.7)	0.325
Other Factors:			
Energy/10 (Mean ± SD)	4.2 (1.5)	4.0 (1.9)	0.622
Stress/10 (Mean ± SD)	6.5 (1.8)	6.4 (1.8)	0.814
Family History of Mental Illness (%)	n=26 (72%)	n=28 (77%)	0.586

[1]Phone applications such as Calm, Headspace, Smiling Mind etc. which have a focus on mental health,

[2]p-values for X^2 and t-tests

12. BIBLIOGRAPHY

1. Greden JF. The burden of recurrent depression: causes, consequences, and future prospects. *Journal of Clinical Psychiatry.* 2001;62:5-9.

2. Marcus M, Yasamy MT, van Ommeren Mv, Chisholm D, Saxena S. Depression: A global public health concern. 2012.

3. Australian Bureau of Statistics, . *National Survey of Mental Health and Wellbeing: Summary of Results 2007.* Canberra ABS;2008.

4. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS medicine.* 2013;10(11).

5. Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. *Archives of General Psychiatry.* 2004;61(11):1097-1103.

6. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PloS one.* 2015;10(2):e0116820.

7. McTernan WP, Dollard MF, LaMontagne AD. Depression in the workplace: An economic cost analysis of depression-related productivity loss attributable to job strain and bullying. *Work & Stress.* 2013/10/01 2013;27(4):321-338.

8. Whiteford H. The Productivity Commission inquiry into mental health. *Australian & New Zealand Journal of Psychiatry.* 2021:00048674211031159.

9. Australian Institute of Health and Welfare. Mental health services in Australia. 2020; https://www.aihw.gov.au/reports/mental-health-services/mental-health-services-in-australia. Accessed 26/-8/, 2020.

10. Lopert R. Evidence-based decision-making within Australia's pharmaceutical benefits scheme. 2009.

11. Parliament of Australia. A national approach to mental health – from crisis to community

First Report, Chapter 4 - Resourcing 2006; https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Former_Committees/mentalhealth/report/c04. Accessed 26/08 2020.

12. Steel Z, Momartin S, Bateman C, et al. Psychiatric status of asylum seeker families held for a protracted period in a remote detention centre in Australia. *Australian and New Zealand journal of public health.* 2004;28(6):527-536.

13. Butler T, Indig D, Allnutt S, Mamoon H. Co-occurring mental illness and substance use disorder among Australian prisoners. *Drug and alcohol review.* 2011;30(2):188-194.

14. McGorry PD, Purcell R, Hickie IB, Jorm AF. Investing in youth mental health is a best buy. *Medical Journal of Australia.* 2007;187(S7):S5-S7.

15. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bulletin of the World health Organization.* 2004;82:858-866.

16. Shepherd CC, Li J, Mitrou F, Zubrick SR. Socioeconomic disparities in the mental health of Indigenous children in Western Australia. *BMC Public Health.* 2012;12(1):756.

17. Jorm AF, Bourchier SJ, Cvetkovski S, Stewart G. Mental health of Indigenous Australians: a review of findings from community surveys. *Medical Journal of Australia.* 2012;196(2):118-121.
18. Spicer B, Smith DI, Conroy E, Flatau PR, Burns L. Mental illness and housing outcomes among a sample of homeless men in an Australian urban centre. *Australian & New Zealand Journal of Psychiatry.* 2015;49(5):471-480.
19. Memmott P, Birdsall-Jones C, Greenop K. *Why are special services needed to address Indigenous homelessness?*: University of Queensland; 2012.
20. Reynolds EH, Wilson JVK. Depression and anxiety in Babylon. *Journal of the Royal Society of Medicine.* 2013;106(12):478-481.
21. Wallace ER. *History of Psychiatry and Medical Psychology With an Epilogue on Psychiatry and the Mind-Body Relation*: Springer; 2008.
22. Tipton CM. The history of "Exercise Is Medicine" in ancient civilizations. *Advances in physiology education.* 2014;38(2):109-117.
23. Matews M. How did Pre-twentieth century theories of the etiology of depression develop. *Psychiatry On-line.* 2004.
24. Al-Jadiry A-M. Evolution of Concept and Treatment of Depression and the Use of Antipsychotic Agents as Adjuvants to Antidepressants. *Arab Journal of Psychiatry.* 2016;27(1).
25. De Saussure R. A History of Medical Pyschology. By Gregory Zilboorg, MD, in collaboration with George W. Henry. New York: WW Norton & Co., Inc., 1941. 606 pp: Taylor & Francis; 1942.
26. Lund MA. *Melancholy, Medicine and Religion in Early Modern England: Reading'The Anatomy of Melancholy'*: Cambridge University Press; 2010.
27. Farreras IG. History of mental illness. *General Psychology: Required Reading.* 2019:244.
28. Mendes ED, Viana TdC, Bara O. Melancolia e depressão: um estudo psicanalítico. *Psicologia: Teoria e Pesquisa.* 2014;30(4):423-431.
29. Taylor MA, Fink M. *Melancholia: the diagnosis, pathophysiology and treatment of depressive illness*: Cambridge University Press; 2006.
30. Joshi C, Marszalek JM, Berkel LA, Hinshaw AB. An empirical investigation of Viktor Frankl's logotherapeutic model. *Journal of Humanistic Psychology.* 2014;54(2):227-253.
31. Beck AT. *Cognitive therapy of depression*: Guilford press; 1979.
32. David D, Cristea I, Hofmann SG. Why cognitive behavioral therapy is the current gold standard of psychotherapy. *Frontiers in psychiatry.* 2018;9:4.
33. López-Muñoz F, Alamo C. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Current pharmaceutical design.* 2009;15(14):1563-1586.
34. Praag Hv. Neuroendocrine disorders in depressions and their significance for the monoamine hypothesis of depression. *Acta Psychiatrica Scandinavica.* 1978;57(5):389-404.
35. Jesulola E, Micalos P, Baguley IJ. Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model-are we there yet? *Behavioural brain research.* 2018;341:79-90.
36. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. *BMC psychiatry.* 2014;14(1):1-13.
37. Garcia-Toro M, Aguirre I. Biopsychosocial model in depression revisited. *Medical hypotheses.* 2007;68(3):683-691.

38. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology.* 2011;36(12):2375.
39. Association AP. *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub; 2013.
40. Tolentino JC, Schmidt SL. DSM-5 criteria and depression severity: implications for clinical practice. *Frontiers in psychiatry.* 2018;9:450.
41. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology.* 2004;29(10):1765.
42. Goldstein B, Rosselli F. Etiological paradigms of depression: The relationship between perceived causes, empowerment, treatment preferences, and stigma. *Journal of Mental Health.* 2003;12(6):551-563.
43. Perlis RH. Betting on biomarkers: Am Psychiatric Assoc; 2011.
44. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2011;35(3):676-692.
45. Maletic V, Robinson M, Oakes T, Iyengar S, Ball S, Russell J. Neurobiology of depression: an integrated view of key findings. *International journal of clinical practice.* 2007;61(12):2030-2040.
46. Benjamin J, Klein E. The biology of tryptophan depletion and mood disorders. *The Israel journal of psychiatry and related sciences.* 2010;47(1):46.
47. Meyer JH, Ginovart N, Boovariwala A, et al. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. *Archives of general psychiatry.* 2006;63(11):1209-1216.
48. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. *Journal of affective disorders.* 2013;148(1):12-27.
49. Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. *Journal of affective disorders.* 2012;140(3):205-214.
50. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Archives of internal medicine.* 2003;163(20):2433-2445.
51. Mimura M. Comorbidity of Depression and Other Diseases. *JAPAN MEDICAL ASSOCIATION JOURNAL.* 2001;44(5):225-229.
52. Cameron OG. Understanding comorbid depression and anxiety. *Psychiatric Times.* 2007;24(14):51-51.
53. Nettle D. Evolutionary origins of depression: a review and reformulation. *Journal of affective disorders.* 2004;81(2):91-102.
54. Hendrie C, Pickles A. Depression as an evolutionary adaptation: Implications for the development of preclinical models. *Medical hypotheses.* 2009;72(3):342-347.
55. Raison CL, Miller A. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Molecular psychiatry.* 2013;18(1):15-37.
56. Kinney DK, Tanaka M. An evolutionary hypothesis of depression and its symptoms, adaptive value, and risk factors. *The Journal of nervous and mental disease.* 2009;197(8):561-567.
57. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin.* 2014;140(3):774.

58. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* 2016;16(1):22.
59. Gurven M, Kaplan H. Longevity among hunter-gatherers: a cross-cultural examination. *Population and Development review.* 2007;33(2):321-365.
60. ABS. *National Survey of Mental Health and Wellbeing: Summary of Results*: Australian Bureau of Statistics;2008.
61. Möller-Leimkühler AM. Barriers to help-seeking by men: a review of sociocultural and clinical literature with particular reference to depression. *Journal of affective disorders.* 2002;71(1-3):1-9.
62. Brownhill S, Wilhelm K, Barclay L, Schmied V. 'Big build': hidden depression in men. *Australian & New Zealand Journal of Psychiatry.* 2005;39(10):921-931.
63. Funabiki D, Bologna NC, Pepping M, FitzGerald KC. Revisiting sex differences in the expression of depression. *Journal of Abnormal Psychology.* 1980;89(2):194.
64. Oliffe JL, Phillips MJ. Men, depression and masculinities: A review and recommendations. *Journal of Men's Health.* 2008;5(3):194-202.
65. Winkler D, Pjrek E, Kasper S. Gender-specific symptoms of depression and anger attacks. *Journal of Men's Health and Gender.* 2005;3(1):19-24.
66. Blair-West GW, Mellsop GW. Major depression: does a gender-based down-rating of suicide risk challenge its diagnostic validity? *Australian & New Zealand Journal of Psychiatry.* 2001;35(3):322-328.
67. Kilmartin C. Depression in men: Communication, diagnosis and therapy. *Journal of Men's Health and Gender.* 2005;2(1):95-99.
68. Zierau F, Bille A, Rutz W, Bech P. The Gotland Male Depression Scale: A validity study in patients with alcohol use disorder. *Nordic journal of psychiatry.* 2002;56(4):265-271.
69. Rice SM, Aucote HM, Möller-Leimkühler AM, Amminger GP. Confirmatory factor analysis of the Gotland Male Depression Scale in an Australian community sample. *European Journal of Psychological Assessment.* 2015.
70. Sharpe MJ, Heppner PP. Gender role, gender-role conflict, and psychological well-being in men. *Journal of Counseling Psychology.* 1991;38(3):323.
71. Heifner C. The male experience of depression. *Perspectives in psychiatric care.* 1997;33(2):10-18.
72. Angst J, Gamma A, Gastpar M, Lépine J-P, Mendlewicz J, Tylee A. Gender differences in depression. *European archives of psychiatry and clinical neuroscience.* 2002;252(5):201-209.
73. Möller-Leimkühler AM. The gender gap in suicide and premature death or: why are men so vulnerable? *European archives of psychiatry and clinical neuroscience.* 2003;253(1):1-8.
74. ABS. Causes of Death Australia 2014, preliminary data., Cat. no. (3303.0). Canberra: ABS2016.
75. Link BG, Struening EL, Rahav M, Phelan JC, Nuttbrock L. On stigma and its consequences: evidence from a longitudinal study of men with dual diagnoses of mental illness and substance abuse. *Journal of health and social behavior.* 1997:177-190.
76. DeRoo RL. I Don't Want to Talk About It: Overcoming the Secret Legacy of Male Depression. *Journal of Marital and Family Therapy.* 1999;25(1):131.
77. Weissman MM. Treatment of depression: men and women are different?: Am Psychiatric Assoc; 2014.

78. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *American Journal of Psychiatry.* 2000;157(9):1445-1452.
79. Arnett JJ. *Emerging adulthood: The winding road from the late teens through the twenties*: Oxford University Press; 2014.
80. Aalto-Setälä T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lönnqvist J. One-month prevalence of depression and other DSM-IV disorders among young adults. *Psychological medicine.* 2001;31(5):791-801.
81. Byrne ML, O'Brien-Simpson NM, Mitchell SA, Allen NB. Adolescent-onset depression: are obesity and inflammation developmental mechanisms or outcomes? *Child Psychiatry & Human Development.* 2015;46(6):839-850.
82. Matthews T, Danese A, Wertz J, et al. Social isolation, loneliness and depression in young adulthood: a behavioural genetic analysis. *Social psychiatry and psychiatric epidemiology.* 2016;51(3):339-348.
83. Lin LY, Sidani JE, Shensa A, et al. Association between social media use and depression among US young adults. *Depression and anxiety.* 2016;33(4):323-331.
84. Ostovar S, Allahyar N, Aminpoor H, Moafian F, Nor MBM, Griffiths MD. Internet addiction and its psychosocial risks (depression, anxiety, stress and loneliness) among Iranian adolescents and young adults: A structural equation model in a cross-sectional study. *International Journal of Mental Health and Addiction.* 2016;14(3):257-267.
85. Boumosleh JM, Jaalouk D. Depression, anxiety, and smartphone addiction in university students-A cross sectional study. *PloS one.* 2017;12(8):e0182239.
86. Friis RH, Wittchen H-U, Pfister H, Lieb R. Life events and changes in the course of depression in young adults. *European Psychiatry.* 2002;17(5):241-253.
87. Keles B, McCrae N, Grealish A. A systematic review: the influence of social media on depression, anxiety and psychological distress in adolescents. *International Journal of Adolescence and Youth.* 2020;25(1):79-93.
88. Rosenthal SR, Buka SL, Marshall BD, Carey KB, Clark MA. Negative experiences on Facebook and depressive symptoms among young adults. *Journal of Adolescent Health.* 2016;59(5):510-516.
89. Chen W, Lee K-H. Sharing, liking, commenting, and distressed? The pathway between Facebook interaction and psychological distress. *Cyberpsychology, behavior, and social networking.* 2013;16(10):728-734.
90. Kasteenpohja T, Marttunen M, Aalto-Setälä T, Perälä J, Saarni SI, Suvisaari J. Treatment received and treatment adequacy of depressive disorders among young adults in Finland. *BMC psychiatry.* 2015;15(1):47.
91. Jorm AF, Morgan AJ, Wright A. Interventions that are helpful for depression and anxiety in young people: a comparison of clinicians' beliefs with those of youth and their parents. *Journal of Affective Disorders.* 2008;111(2-3):227-234.
92. Hetrick SE, Simmons M, Thompson A, Parker AG. What are specialist mental health clinician attitudes to guideline recommendations for the treatment of depression in young people? *Australian & New Zealand Journal of Psychiatry.* 2011;45(11):993-1001.
93. Hickie IB, Luscombe GM, Davenport TA, Burns JM, Highet NJ. Perspectives of young people on depression: awareness, experiences, attitudes and treatment preferences. *Early intervention in psychiatry.* 2007;1(4):333-339.

94. Jorm AF, Wright A. Influences on young people's stigmatising attitudes towards peers with mental disorders: national survey of young Australians and their parents. *The British journal of psychiatry.* 2008;192(2):144-149.
95. Bradbury A. Mental health stigma: the impact of age and gender on attitudes. *Community mental health journal.* 2020;56(5):933-938.
96. Yap MBH, Reavley N, Jorm AF. Where would young people seek help for mental disorders and what stops them? Findings from an Australian national survey. *Journal of affective disorders.* 2013;147(1-3):255-261.
97. Lubman DI, Hides L, Jorm AF. Beliefs of young people and their parents about the harmfulness of alcohol, cannabis and tobacco for mental disorders. *Medical journal of Australia.* 2007;187(5):266-269.
98. Huda AS. The medical model and its application in mental health. *Int. Rev. Psychiatry.* 2021;33(5):463-470.
99. Wiese M, Oster C, Pincombe J. Understanding the emerging relationship between complementary medicine and mainstream health care: A review of the literature. *Health:.* 2010;14(3):326-342.
100. Crocker RL, Grizzle AJ, Hurwitz JT, et al. Integrative medicine primary care: assessing the practice model through patients' experiences. *BMC complementary and alternative medicine.* 2017;17(1):1-8.
101. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry.* 2005;62(6):617-627.
102. Lépine J-P, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *Int. Clin. Psychopharmacol.* 1997.
103. Goldberg D, Privett M, Ustun B, Simon G, Linden M. The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities. *Br J Gen Pract.* 1998;48(437):1840-1844.
104. Lecrubier Y, Hergueta T. Differences between prescription and consumption of antidepressants and anxiolytics. *Int. Clin. Psychopharmacol.* 1998;13:S7-11.
105. Mulrow CD, Williams Jr JW, Chiquette E, et al. Efficacy of newer medications for treating depression in primary care patients. *The American journal of medicine.* 2000;108(1):54-64.
106. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of clinical psychiatry.* 2001;3(1):22.
107. Taylor C, Fricker AD, Devi LA, Gomes I. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. *Cellular signalling.* 2005;17(5):549-557.
108. Daws LC. Unfaithful neurotransmitter transporters: focus on serotonin uptake and implications for antidepressant efficacy. *Pharmacology & therapeutics.* 2009;121(1):89-99.
109. Dale E, Bang-Andersen B, Sanchez C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochemical pharmacology.* 2015;95(2):81-97.
110. Hindmarch I. Beyond the monoamine hypothesis: mechanisms, molecules and methods. *European Psychiatry.* 2002;17:294-299.
111. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular psychiatry.* 2007;12(4):331-359.

112. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular psychiatry.* 2022:1-14.
113. Hendrie C, Pickles A. Depression as an evolutionary adaptation: anatomical organisation around the third ventricle. *Medical hypotheses.* 2010;74(4):735-740.
114. Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. "Broad spectrum" antidepressants: is more better for the treatment of depression? *Life sciences.* 2003;73(25):3175-3179.
115. Bschor T, Kilarski LL. Are antidepressants effective? A debate on their efficacy for the treatment of major depression in adults. *Expert review of neurotherapeutics.* 2016;16(4):367-374.
116. Cape J, Whittington C, Buszewicz M, Wallace P, Underwood L. Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. *BMC medicine.* 2010;8(1):38.
117. Driessen E, Hollon SD. Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. *Psychiatric Clinics.* 2010;33(3):537-555.
118. Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. *Journal of consulting and clinical psychology.* 2007;75(3):475.
119. Sudak DM. Cognitive behavioral therapy for depression. *Psychiatric Clinics.* 2012;35(1):99-110.
120. Johansson R, Andersson G, Ebmeier, et al. Internet-based psychological treatments for depression. *Expert review of neurotherapeutics.* 2012;12(7):861-870.
121. Andersson G. Using the Internet to provide cognitive behaviour therapy. *Behaviour research and therapy.* 2009;47(3):175-180.
122. Clarke G, Kelleher C, Hornbrook M, DeBar L, Dickerson J, Gullion C. Randomized effectiveness trial of an Internet, pure self-help, cognitive behavioral intervention for depressive symptoms in young adults. *Cognitive behaviour therapy.* 2009;38(4):222-234.
123. Reid R, Steel A, Wardle J, Trubody A, Adams J. Complementary medicine use by the Australian population: a critical mixed studies systematic review of utilisation, perceptions and factors associated with use. *BMC complementary and alternative medicine.* 2016;16(1):176.
124. Steel A, McIntyre E, Harnett J, et al. Complementary medicine use in the Australian population: Results of a nationally-representative cross-sectional survey. *Scientific reports.* 2018;8(1):1-7.
125. Solomon D, Adams J. The use of complementary and alternative medicine in adults with depressive disorders. A critical integrative review. *Journal of affective disorders.* 2015;179:101-113.
126. Ashraf H, Salehi A, Sousani M, Sharifi MH. Use of complementary alternative medicine and the associated factors among patients with depression. *Evidence-Based Complementary and Alternative Medicine.* 2021;2021.
127. van der Watt G, Laugharne J, Janca A. Complementary and alternative medicine in the treatment of anxiety and depression. *Current opinion in psychiatry.* 2008;21(1):37-42.
128. Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorder. *Canadian Family Physician.* 2011;57(6):659-663.
129. Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. *Journal of Clinical Psychiatry.* 2009;70(5):18-22.

130. Fusar-Poli L, Vozza L, Gabbiadini A, et al. Curcumin for depression: a meta-analysis. *Critical reviews in food science and nutrition.* 2020;60(15):2643-2653.
131. Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Human Psychopharmacology: Clinical and Experimental.* 2014;29(6):517-527.
132. Kious BM, Sabic H, Sung Y-H, Kondo DG, Renshaw P. An open-label pilot study of combined augmentation with creatine monohydrate and 5-hydroxytryptophan for SSRI-or SNRI-resistant depression in adult women. *J. Clin. Psychopharmacol.* 2017;37(5):578.
133. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients.* 2014;6(4):1501-1518.
134. Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression: the research evidence. *Journal of affective disorders.* 2005;89(1-3):13-24.
135. Jorm AF, Christensen H, Griffiths KM, Rodgers B. Effectiveness of complementary and self-help treatments for depression. *Medical Journal of Australia.* 2002;176(10):S84-S84.
136. Haller H, Anheyer D, Cramer H, Dobos G. Complementary therapies for clinical depression: an overview of systematic reviews. *BMJ open.* 2019;9(8):e028527.
137. Jacka FN. Nutritional psychiatry: where to next? *EBioMedicine.* 2017;17:24-29.
138. Fardet A, Rock E. Toward a new philosophy of preventive nutrition: from a reductionist to a holistic paradigm to improve nutritional recommendations. *Adv. Nutr.* 2014;5(4):430-446.
139. Marx W, Lane M, Hockey M, et al. Diet and depression: exploring the biological mechanisms of action. *Molecular psychiatry.* 2021;26(1):134-150.
140. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES'trial). *BMC medicine.* 2017;15(1):1-13.
141. Lichtenstein AH, Russell RM. Essential nutrients: Food or supplements?: where should the emphasis be? *Jama.* 2005;294(3):351-358.
142. Sarris J, Schoendorfer N, Kavanagh DJ. Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments. *Nutrition reviews.* 2009;67(3):125-131.
143. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: A systematic review and meta-analysis. *Clinical Nutrition.* 2018.
144. Sanchez-Villegas A, Henriquez P, Bes-Rastrollo M, Doreste J. Mediterranean diet and depression. *Public health nutrition.* 2006;9(8A):1104-1109.
145. Serra-Majem L, Trichopoulou A, de la Cruz JN, et al. Does the definition of the Mediterranean diet need to be updated? *Public health nutrition.* 2004;7(7):927-929.
146. Willett WC, Sacks F, Trichopoulou A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *The American journal of clinical nutrition.* 1995;61(6):1402S-1406S.
147. Nestle M. Mediterranean diets: science and policy implications. 1995.
148. Sánchez-Villegas A, Delgado-Rodríguez M, Alonso A, et al. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento

Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Archives of General Psychiatry.* 2009;66(10):1090-1098.
149. Sandhu KV, Sherwin E, Schellekens H, Stanton C, Dinan TG, Cryan JF. Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Translational Research.* 2017;179:223-244.
150. Evrensel A, Ceylan ME. The gut-brain axis: the missing link in depression. *Clinical Psychopharmacology and Neuroscience.* 2015;13(3):239.
151. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *Bmj.* 2008;337:a1344.
152. Lucas M, Chocano-Bedoya P, Shulze MB, et al. Inflammatory dietary pattern and risk of depression among women. *Brain, behavior, and immunity.* 2014;36:46-53.
153. Jacka FN, Pasco JA, Mykletun A, et al. Association of Western and traditional diets with depression and anxiety in women. *American Journal of Psychiatry.* 2010;167(3):305-311.
154. Shelton RC, Miller AH. Inflammation in depression: is adiposity a cause? *Dialogues in clinical neuroscience.* 2022.
155. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine.* 2009;71(2):171-186.
156. Sanchez-Villegas A, Martínez-González MA. Diet, a new target to prevent depression? *BMC medicine.* 2013;11(1):3.
157. Maes M, Yirmyia R, Noraberg J, et al. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metabolic brain disease.* 2009;24(1):27-53.
158. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological psychiatry.* 2009;65(9):732-741.
159. Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. *Psychosomatic medicine.* 2005;67:S37-S41.
160. Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain, behavior, and immunity.* 2001;15(1):7-24.
161. van den Biggelaar AH, Gussekloo J, de Craen AJ, et al. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Experimental gerontology.* 2007;42(7):693-701.
162. Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. *Neuro endocrinology letters.* 2008;29(3):287-291.
163. Halassa MM, Haydon PG. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annual review of physiology.* 2010;72:335-355.
164. Yirmiya R, Rimmerman N, Reshef R. Depression as a microglial disease. *Trends in neurosciences.* 2015;38(10):637-658.
165. Steiner J, Walter M, Gos T, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *Journal of neuroinflammation.* 2011;8(1):94.
166. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA psychiatry.* 2013;70(1):31-41.

167. Zhu C-B, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology.* 2006;31(10):2121.
168. Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D. Neopterin production, tryptophan degradation, and mental depression—what is the link? *Brain, behavior, and immunity.* 2002;16(5):590-595.
169. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Archives of general psychiatry.* 2001;58(5):445-452.
170. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. *Biological psychiatry.* 2008;63(11):1022-1029.
171. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews neuroscience.* 2008;9(1):46.
172. Coelho R, Viola T, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatrica Scandinavica.* 2014;129(3):180-192.
173. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation.* 2003;108(12):e81-e85.
174. Bilici M, Efe H, Köroğlu MA, Uydu HA, Bekaroğlu M, Değer O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *Journal of affective disorders.* 2001;64(1):43-51.
175. Rybka J, Kędziora-Kornatowska K, Banaś-Leżańska P, et al. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. *Free Radical Biology and Medicine.* 2013;63:187-194.
176. Lopresti AL, Maker GL, Hood SD, Drummond PD. A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2014;48:102-111.
177. Catena-Dell'Osso M, Bellantuono C, Consoli G, Baroni S, Rotella F, Marazziti D. Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development? *Current medicinal chemistry.* 2011;18(2):245-255.
178. Galland L. Diet and inflammation. *Nutr. Clin. Prac.* 2010;25(6):634-640.
179. Griffith JA, Ma Y, Chasan-Taber L, et al. Association between dietary glycemic index, glycemic load, and high-sensitivity C-reactive protein. *Nutrition (Burbank, Los Angeles County, Calif.).* 2008;24(5):401-406.
180. North C, Venter C, Jerling J. The effects of dietary fibre on C-reactive protein, an inflammation marker predicting cardiovascular disease. *European journal of clinical nutrition.* 2009;63(8):921-933.
181. Ma Y, Hébert JR, Li W, et al. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition (Burbank, Los Angeles County, Calif.).* 2008;24(10):941-949.
182. Petersson H, Lind L, Hulthe J, Elmgren A, Cederholm T, Risérus U. Relationships between serum fatty acid composition and multiple markers of inflammation and endothelial function in an elderly population. *Atherosclerosis.* 2009;203(1):298-303.
183. Kennedy A, Martinez K, Chuang C-C, LaPoint K, McIntosh M. Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. *The Journal of nutrition.* 2009;139(1):1-4.

184. He K, Liu K, Daviglus ML, et al. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *The American journal of cardiology.* 2009;103(9):1238-1243.
185. Chacko SA, Song Y, Nathan L, et al. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. *Diabetes care.* 2010;33(2):304-310.
186. Watzl B, Kulling SE, Möseneder J, Barth SW, Bub A. A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. *The American journal of clinical nutrition.* 2005;82(5):1052-1058.
187. González-Gallego J, García-Mediavilla MV, Sánchez-Campos S, Tuñón MJ. Anti-inflammatory and immunomodulatory properties of dietary flavonoids. *Polyphenols in human health and disease*: Elsevier; 2014:435-452.
188. Chun OK, Chung S-J, Claycombe KJ, Song WO. Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in US adults. *The Journal of nutrition.* 2008;138(4):753-760.
189. Foster JA, Neufeld K-AM. Gut–brain axis: how the microbiome influences anxiety and depression. *Trends in neurosciences.* 2013;36(5):305-312.
190. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain research.* 2018;1693:128-133.
191. Rogers G, Keating DJ, Young RL, Wong M-L, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Molecular psychiatry.* 2016;21(6):738-748.
192. Gill SR, Pop M, DeBoy RT, et al. Metagenomic analysis of the human distal gut microbiome. *science.* 2006;312(5778):1355-1359.
193. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: focus on depression. *Current opinion in psychiatry.* 2015;28(1):1-6.
194. Jacka FN, Mykletun A, Berk M. Moving towards a population health approach to the primary prevention of common mental disorders. *BMC medicine.* 2012;10(1):149.
195. Lach G, Schellekens H, Dinan TG, Cryan JF. Anxiety, depression, and the microbiome: a role for gut peptides. *Neurotherapeutics.* 2018;15(1):36-59.
196. Okano-Matsumoto S, McRoberts JA, Taché Y, Adelson DW. Electrophysiological evidence for distinct vagal pathways mediating CCK-evoked motor effects in the proximal versus distal stomach. *The Journal of physiology.* 2011;589(2):371-393.
197. Prinz M, Priller J. The role of peripheral immune cells in the CNS in steady state and disease. *Nature neuroscience.* 2017;20(2):136.
198. Dinan TG, Cryan JF. Melancholic microbes: a link between gut microbiota and depression? *Neurogastroenterology & Motility.* 2013;25(9):713-719.
199. Wong M-L, Licinio J. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nature Reviews Drug Discovery.* 2004;3(2):136.
200. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell host & microbe.* 2015;17(5):565-576.
201. O'mahony S, Clarke G, Borre Y, Dinan T, Cryan J. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural brain research.* 2015;277:32-48.
202. Matsumoto M, Kibe R, Ooga T, et al. Impact of intestinal microbiota on intestinal luminal metabolome. *Scientific reports.* 2012;2:233.

203. Kaplan BJ, Rucklidge JJ, Romijn A, McLeod K. The emerging field of nutritional mental health: inflammation, the microbiome, oxidative stress, and mitochondrial function. *Clinical Psychological Science.* 2015;3(6):964-980.
204. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC medicine.* 2013;11(1):200.
205. Maes M, Kubera M, Leunis J-C, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. *Journal of affective disorders.* 2012;141(1):55-62.
206. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infection and immunity.* 1979;23(2):403-411.
207. Mass M, Kubera M, Leunis J-C. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuroendocrinology Letters.* 2008;29(1):117-124.
208. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in cellular neuroscience.* 2015;9:392.
209. Singh RK, Chang H-W, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *Journal of translational medicine.* 2017;15(1):73.
210. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484):559-563.
211. Sánchez-Villegas A, Toledo E, de Irala J, Ruiz-Canela M, Pla-Vidal J, Martínez-González MA. Fast-food and commercial baked goods consumption and the risk of depression. *Public health nutrition.* 2012;15(3):424-432.
212. Moreira APB, Texeira TFS, Ferreira AB, Peluzio MdCG, Alfenas RdCG. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. *British Journal of Nutrition.* 2012;108(5):801-809.
213. Ghanim H, Abuaysheh S, Sia CL, et al. Increase in plasma endotoxin concentrations and the expression of toll like receptors and suppressor of cytokine signaling-3 in mononuclear cells following a high fat high carbohydrate meal: implications for insulin resistance. *Diabetes care.* 2009.
214. Selhub EM, Logan AC, Bested AC. Fermented foods, microbiota, and mental health: ancient practice meets nutritional psychiatry. *Journal of physiological anthropology.* 2014;33(1):2.
215. Goffin D, Delzenne N, Blecker C, Hanon E, Deroanne C, Paquot M. Will isomalto-oligosaccharides, a well-established functional food in Asia, break through the European and American market? The status of knowledge on these prebiotics. *Critical reviews in food science and nutrition.* 2011;51(5):394-409.
216. Hotel ACP, Cordoba A. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. *Prevention.* 2001;5(1):1-10.
217. Silva SD, Robbe-Masselot C, Ait-Belgnaoui A, et al. Stress disrupts intestinal mucus barrier in rats via mucin O-glycosylation shift: prevention by a probiotic treatment. *American Journal of Physiology-Gastrointestinal and Liver Physiology.* 2014;307(4):G420-G429.
218. Ait-Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology.* 2012;37(11):1885-1895.

219. Cepeda MS, Katz EG, Blacketer C. Microbiome-gut-brain axis: probiotics and their association with depression. *The Journal of neuropsychiatry and clinical neurosciences.* 2017;29(1):39-44.
220. Huang R, Wang K, Hu J. Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. *Nutrients.* 2016;8(8):483.
221. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. *Biological psychiatry.* 2013;74(10):720-726.
222. Chao L, Liu C, Sutthawongwadee S, et al. Effects of probiotics on depressive or anxiety variables in healthy participants under stress conditions or with a depressive or anxiety diagnosis: a meta-analysis of randomized controlled trials. *Front. Neurol.* 2020;11:421.
223. Dinan TG, Stanton C, Long-Smith C, et al. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. *Clinical Nutrition.* 2019;38(5):1995-2001.
224. Bastiaanssen TF, Cussotto S, Claesson MJ, Clarke G, Dinan TG, Cryan JF. Gutted! Unraveling the role of the microbiome in major depressive disorder. *Harv. Rev. Psychiatry.* 2020;28(1):26.
225. Nagpal R, Shively CA, Register TC, Craft S, Yadav H. Gut microbiome-Mediterranean diet interactions in improving host health. *F1000Research.* 2019;8.
226. Khalid S, Williams CM, Reynolds SA. Is there an association between diet and depression in children and adolescents? A systematic review. *British journal of nutrition.* 2016;116(12):2097-2108.
227. Wu P-Y, Chen K-M, Belcastro F. Dietary patterns and depression risk in older adults: Systematic review and meta-analysis. *Nutrition reviews.* 2021;79(9):976-987.
228. Sparling TM, Henschke N, Nesbitt RC, Gabrysch S. The role of diet and nutritional supplementation in perinatal depression: a systematic review. *Maternal & child nutrition.* 2017;13(1).
229. Li Y, Lv M-R, Wei Y-J, et al. Dietary patterns and depression risk: a meta-analysis. *Psychiatry research.* 2017;253:373-382.
230. Quirk SE, Williams LJ, O'Neil A, et al. The association between diet quality, dietary patterns and depression in adults: a systematic review. *BMC psychiatry.* 2013;13(1):175.
231. Acharya R, Saha S, Ray S, Hazra S, Mitra MK, Chakraborty J. siRNA-nanoparticle conjugate in gene silencing: A future cure to deadly diseases? *Materials Science and Engineering: C.*
232. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *The American journal of clinical nutrition.* 2014;99(1):181-197.
233. Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public health nutrition.* 2015;18(11):2074-2093.
234. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: A systematic review and meta-analysis. *Clinical Nutrition.* 2019;38(5):2045-2052.
235. Patsalos O, Keeler J, Schmidt U, Penninx BW, Young AH, Himmerich H. Diet, obesity, and depression: a systematic review. *Journal of personalized medicine.* 2021;11(3):176.

236. Altun A, Brown H, Szoeke C, Goodwill AM. The Mediterranean dietary pattern and depression risk: A systematic review. *Neurology, Psychiatry and Brain Research.* 2019;33:1-10.
237. Ibarra O, Gili M, Roca M, et al. The Mediterranean diet and micronutrient levels in depressive patients. *Nutrición Hospitalaria, 2014, vol. 31, num. 3, p. 1171-1175.* 2020.
238. Wade AT, Davis CR, Dyer KA, et al. A Mediterranean diet supplemented with dairy foods improves mood and processing speed in an Australian sample: Results from the MedDairy randomized controlled trial. *Nutritional neuroscience.* 2020;23(8):646-658.
239. Sánchez-Villegas A, Martínez-González MA, Estruch R, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC medicine.* 2013;11(1):208.
240. Parletta N, Zarnowiecki D, Cho J, et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). *Nutritional neuroscience.* 2019;22(7):474-487.
241. Jacka FN, Pasco JA, Williams LJ, et al. Red meat consumption and mood and anxiety disorders. *Psychotherapy and psychosomatics.* 2012;81(3):196-198.
242. Hariton E, Locascio JJ. Randomised controlled trials—the gold standard for effectiveness research. *BJOG: an international journal of obstetrics and gynaecology.* 2018;125(13):1716.
243. Johnson JL, Oliffe JL, Kelly MT, Galdas P, Ogrodniczuk JS. Men's discourses of help-seeking in the context of depression. *Sociology of health & illness.* 2012;34(3):345-361.
244. Curtin SC, Warner M, Hedegaard H. *Increase in suicide in the United States, 1999-2014*: US Department of Health and Human Services, Centers for Disease Control and …; 2016.
245. Seidler ZE, Rice SM, Oliffe JL, Fogarty AS, Dhillon HM. Men in and out of treatment for depression: Strategies for improved engagement. *Australian Psychologist.* 2018;53(5):405-415.
246. Broom A, Willis E. Competing paradigms and health research. *Researching health: qualitative, quantitative and mixed methods.* 2007:16-30.
247. Rehman AA, Alharthi K. An introduction to research paradigms. *International Journal of Educational Investigations.* 2016;3(8):51-59.
248. Tuli F. The basis of distinction between qualitative and quantitative research in social science: reflection on ontological, epistemological and methodological perspectives. *Ethiopian Journal of Education and Sciences.* 2011;6(1).
249. Olivan-Blázquez B, Montero-Marin J, García-Toro M, et al. Facilitators and barriers to modifying dietary and hygiene behaviours as adjuvant treatment in patients with depression in primary care: a qualitative study. *BMC psychiatry.* 2018;18(1):205.
250. Gunasekare DU. Mixed research method as the third research paradigm: a literature review. *International Journal of Science and Research (IJSR).* 2015.
251. Abusabha R, Woelfel ML. Qualitative vs quantitative methods: Two opposites that make a perfect match. *Journal of the Academy of Nutrition and Dietetics.* 2003;103(5):566.
252. Walker W. The strengths and weaknesses of research designs involving quantitative measures. *Journal of research in nursing.* 2005;10(5):571-582.

253. Lovegrove JA, Hodson L, Sharma S, Lanham-New SA. *Nutrition research methodologies*: John Wiley & Sons; 2015.
254. Sanson-Fisher RW, Bonevski B, Green LW, D'Este C. Limitations of the randomized controlled trial in evaluating population-based health interventions. *American journal of preventive medicine.* 2007;33(2):155-161.
255. Verhoef MJ, Lewith G, Ritenbaugh C, Boon H, Fleishman S, Leis A. Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. *Complementary therapies in medicine.* 2005;13(3):206-212.
256. Ventriglio A, Sancassiani F, Contu MP, et al. Mediterranean diet and its benefits on health and mental health: a literature review. *Clinical practice and epidemiology in mental health: CP & EMH.* 2020;16(Suppl-1):156.
257. Marcus M, Yasamy MT, van Ommeren M, Chisholm D, Saxena S. Depression: A global public health concern. 2012.
258. McCall WV, Kintziger KW. Late life depression: a global problem with few resources. *Psychiatric Clinics.* 2013;36(4):475-481.
259. Angelino D, Godos J, Ghelfi F, et al. Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. *International journal of food sciences and nutrition.* 2019:1-16.
260. Suzuki T, Miyaki K, Tsutsumi A, et al. Japanese dietary pattern consistently relates to low depressive symptoms and it is modified by job strain and worksite supports. *Journal of Affective Disorders.* 2013;150(2):490-498.
261. Opie R, Itsiopoulos C, Parletta N, et al. Dietary recommendations for the prevention of depression. *Nutritional neuroscience.* 2017;20(3):161-171.
262. Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. *Nutritional neuroscience.* 2018:1-14.
263. Pathak L, Agrawal Y, Dhir A. Natural polyphenols in the management of major depression. *Expert opinion on investigational drugs.* July 2013

2018-01-17 2013;22(7):863-880.
264. Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. *Nutritional neuroscience.* 2012;15(3):127-133.
265. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. *The Journal of nutrition.* 2000;130(8):2073S-2085S.
266. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews.* 2015;4(1):1.
267. The Joanna Brigs Institute. Checklist for Quasi-Experimental Studies (non-randomized experimental studies). 2016. Retrieved from http://joannabriggs.org/research/critical-appraisal-tools.html.
268. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *International journal of surgery.* 2014;12(12):1500-1524.
269. Bergman J, Miodownik C, Bersudsky Y, et al. Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. *Clinical neuropharmacology.* 2013;36(3):73-77.
270. Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. *Journal of affective disorders.* 2014;167:368-375.

271. Sanmukhani J, Satodia V, Trivedi J, et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytotherapy research.* 2014;28(4):579-585.
272. Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. *Phytotherapy Research.* 2015;29(1):17-21.
273. Yu J-J, Pei L-B, Zhang Y, Wen Z-Y, Yang J-L. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J. Clin. Psychopharmacol.* 2015;35(4):406-410.
274. Sathyapalan T, Beckett S, Rigby AS, Mellor DD, Atkin SL. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. *Nutrition Journal.* 2010

2015-09-02 2010;9:55.
275. Atteritano M, Mazzaferro S, Bitto A, et al. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. *Osteoporosis International.* Mar 2014

2014-08-30 2014;25(3):1123-1129.
276. Ibero-Baraibar I, Perez-Cornago A, Ramirez MJ, Martínez JA, Zulet MA. An increase in plasma homovanillic acid with cocoa extract consumption is associated with the alleviation of depressive symptoms in overweight or obese adults on an energy restricted diet in a randomized controlled trial. *J. Nutr.* 2016;146(4):897S-904S.
277. Esmaily H, Sahebkar A, Iranshahi M, et al. An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. *Chin. J. Integr. Med.* 2015;21(5):332-338.
278. Chen X, Lu W, Zheng Y, et al. Exercise, tea consumption, and depression among breast cancer survivors. *J. Clin. Oncol.* 2010;28(6):991.
279. Omagari K, Sakaki M, Tsujimoto Y, et al. Coffee consumption is inversely associated with depressive status in Japanese patients with type 2 diabetes. *Journal of clinical biochemistry and nutrition.* 2014:14-30.
280. Kazemian A, Toghiani A, Shafiei K, et al. Evaluating the efficacy of mixture of Boswellia carterii, Zingiber officinale, and Achillea millefolium on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients. *Journal of Research in Medical Sciences.* 2017;22(11).
281. Li Y, Dai Q, Tedders SH, Arroyo C, Zhang J. Legume consumption and severe depressed mood, the modifying roles of gender and menopausal status. *Public health nutrition.* Aug 2010

2015-08-15 2010;13(8):1198-1206.
282. Chang S-C, Cassidy A, Willett WC, Rimm EB, O'Reilly EJ, Okereke OI. Dietary flavonoid intake and risk of incident depression in midlife and older women. *The American journal of clinical nutrition.* September 2016

2018-08-15 2016;104(3):704-714.
283. Godos J, Castellano S, Ray S, Grosso G, Galvano F. Dietary Polyphenol Intake and Depression: Results from the Mediterranean Healthy Eating, Lifestyle and Aging (MEAL) Study. *Molecules (Basel, Switzerland).* 2018;23(5).
284. Miyake Y, Tanaka K, Okubo H, Sasaki S, Furukawa S, Arakawa M. Soy isoflavone intake and prevalence of depressive symptoms during pregnancy in Japan: baseline

data from the Kyushu Okinawa Maternal and Child Health Study. *European journal of nutrition.* 2018;57(2):441-450.

285. Herge WM, Landoll RR, La Greca AM. Center for Epidemiologic Studies Depression Scale (CES-D). *Encyclopedia of Behavioral Medicine.* 2013:366-367.

286. Nina Estrella RE, Landa AI, Lafuente JV, Gargiulo PA. Effects of antidepressants and soybean association in depressive menopausal women. *Acta Pol. Pharm. Drug Res.* 2014;71(2):323-327.

287. Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. *Maturitas.* 2017;96:77-83.

288. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Low-dose isoflavone aglycone alleviates psychological symptoms of menopause in Japanese women: a randomized, double-blind, placebo-controlled study. *Archives of Gynecology and Obstetrics.* 2016;293(3):609-615.

289. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research.* 2002;52(2):69-77.

290. Su Q, Yu B, He H, et al. Nut consumption is associated with depressive symptoms among Chinese adults. *Depression and anxiety.* 2016;33(11):1065-1072.

291. Yu B, Yu F, Su Q, et al. A J-shaped association between soy food intake and depressive symptoms in Chinese adults. *Clinical Nutrition.* 2018;37(3):1013-1018.

292. Zung WW, Richards CB, Short MJ. Self-rating depression scale in an outpatient clinic: further validation of the SDS. *Archives of general psychiatry.* 1965;13(6):508-515.

293. Kamalifard M, Khalili AF, Namadian M, Herizchi S, Ranjbar Y. Comparison of the effect of lavender and bitter orange on depression in menopausal women: A triple-blind randomized controlled trial. *Int. J. Women's Health Reproduction Sci.* 2017;5(3):224-230.

294. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. *Journal of advanced nursing.* 2016;72(2):306-315.

295. Mirghafourvand M, Charandabi SMA, Hakimi S, Khodaie L, Galeshi M. The effect of orange peel essential oil on postpartum depression and anxiety: A randomized controlled clinical trial. *Iranian Red Crescent Medical Journal.* 2017;19(2).

296. Pribis P. Effects of walnut consumption on mood in young adults—A randomized controlled trial. *Nutrients.* 2016;8(11).

297. Mofrad MD, Siassi F, Gilani B, Bellissimo N, Azadbakht L. The association of dietary phytochemical index and mental health in women: A cross-sectional study. *British Journal of Nutrition.* 2019.

298. Chan S-P, Yong P, Sun Y, et al. Associations of long-term tea consumption with depressive and anxiety symptoms in community-living elderly: findings from the diet and healthy aging study. *The journal of prevention of Alzheimer's disease.* 2018;5(1):21-25.

299. Hintikka J, Tolmunen T, Honkalampi K, et al. Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. *European journal of epidemiology.* 2005;20(4):359-363.

300. Niu K, Hozawa A, Kuriyama S, et al. Green tea consumption is associated with depressive symptoms in the elderly. *The American journal of clinical nutrition.* 2009;90(6):1615-1622.
301. Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public health nutrition.* 2010;13(8):1215-1220.
302. Lucas M, Mirzaei F, Pan A, et al. Coffee, caffeine, and risk of depression among women. *Archives of internal medicine.* 2011;171(17):1571-1578.
303. Feng L, Li J, Kua EH, et al. Association between tea consumption and depressive symptoms in older Chinese adults. *J. Am. Geriatr. Soc.* 2012;60(12):2358-2360.
304. Feng L, Yan Z, Sun B, et al. Tea Consumption and Depressive Symptoms in Older People in Rural C hina. *J. Am. Geriatr. Soc.* 2013;61(11):1943-1947.
305. Pham NM, Nanri A, Kurotani K, et al. Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. *Public health nutrition.* 2014;17(3):625-633.
306. Yu S, Guo X, Yang H, Zheng L, Sun Y. Soybeans or soybean products consumption and depressive symptoms in older residents in rural Northeast China: a cross-sectional study. *The journal of nutrition, health & aging.* 2015;19(9):884-893.
307. Li F-D, He F, Ye X-J, et al. Tea consumption is inversely associated with depressive symptoms in the elderly: A cross-sectional study in eastern China. *Journal of affective disorders.* 2016;199:157-162.
308. Navarro A, Abasheva D, Martínez-González M, et al. Coffee consumption and the risk of depression in a middle-aged cohort: The sun project. *Nutrients.* 2018;10(9):1333.
309. Brown D. Do food frequency questionnaires have too many limitations? *Journal of the American Dietetic Association.* 2006;106(10):1541-1542.
310. Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Molecular psychiatry.* 2018:1.
311. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. *Annals of neurology.* 2013;74(4):580-591.
312. Dias GP, Cavegn N, Nix A, et al. The role of dietary polyphenols on adult hippocampal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety. *Oxidative medicine and cellular longevity.* 2012;2012.
313. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *The American journal of clinical nutrition.* 2004;79(5):727-747.
314. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American journal of clinical nutrition.* 2005;81(1):230S-242S.
315. Akram M, Shahab-Uddin AA, Usmanghani K, Hannan A, Mohiuddin E, Asif M. Curcuma longa and curcumin: a review article. *Rom J Biol Plant Biol.* 2010;55(2):65-70.
316. Nagpal M, Sood S. Role of curcumin in systemic and oral health: An overview. *Journal of natural science, biology, and medicine.* 2013;4(1):3.
317. Chauhan M, Saha S, Roy A. Curcumin: a review. *Journal of Applied Pharmaceutical Research.* 2014;2(1):18-28.

318. Ferruzzi MG. The influence of beverage composition on delivery of phenolic compounds from coffee and tea. *Physiology & behavior.* 2010;100(1):33-41.
319. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry.* 2005;62(6):593-602.
320. Slade T, Johnston A, Oakley Browne MA, Andrews G, Whiteford H. 2007 National Survey of Mental Health and Wellbeing: methods and key findings. *Australian and New Zealand Journal of Psychiatry.* 2009;43(7):594-605.
321. Ivancic L, Perrens, B., Fildes, J., Perry, Y. and Christensen, H *Youth Mental Health Report, June 2014.* Sydney: Mission Australia and Black Dog Institute;2014.
322. Slade J, Teesson W, Burgess P. The mental health of Australians 2: report on the 2007 National Survey of Mental Health and Wellbeing. 2009.
323. Mathews RR, Hall WD, Vos T, Patton GC, Degenhardt L. What are the major drivers of prevalent disability burden in young Australians? *Medical journal of Australia.* 2011;194(5):232-235.
324. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of consulting and clinical psychology.* 2006;74(4):658.
325. Fava M. Diagnosis and definition of treatment-resistant depression. *Biological psychiatry.* 2003;53(8):649-659.
326. Cascade E, Kalali AH, Kennedy SH. Real-world data on SSRI antidepressant side effects. *Psychiatry (Edgmont).* 2009;6(2):16.
327. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES'trial). *BMC medicine.* 2017;15(1):23.
328. Opie RS, O'Neil A, Jacka FN, Pizzinga J, Itsiopoulos C. A modified Mediterranean dietary intervention for adults with major depression: Dietary protocol and feasibility data from the SMILES trial. *Nutritional neuroscience.* 2017:1-15.
329. Swardfager W, Herrmann N, Mazereeuw G, Goldberger K, Harimoto T, Lanctôt KL. Zinc in depression: a meta-analysis. *Biological psychiatry.* 2013;74(12):872-878.
330. Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *The American journal of clinical nutrition.* 2002;76(5):1158S-1161S.
331. Almeida OP, Ford AH, Flicker L. Systematic review and meta-analysis of randomized placebo-controlled trials of folate and vitamin B12 for depression. *International psychogeriatrics.* 2015;27(5):727-737.
332. Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M. N-Acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis2016.
333. Derom M-L, Sayón-Orea C, Martínez-Ortega JM, Martínez-González MA. Magnesium and depression: a systematic review. *Nutritional neuroscience.* 2013;16(5):191-206.
334. Saghafian F, Malmir H, Saneei P, Milajerdi A, Larijani B, Esmaillzadeh A. Fruit and vegetable consumption and risk of depression: accumulative evidence from an updated systematic review and meta-analysis of epidemiological studies. *British Journal of Nutrition.* 2018;119(10):1087-1101.

335. Liu X, Yan Y, Li F, Zhang D. Fruit and vegetable consumption and the risk of depression: a meta-analysis. *Nutrition (Burbank, Los Angeles County, Calif.).* 2016;32(3):296-302.
336. Bayes J, Schloss J, Sibbritt D. Effects of Polyphenols in a Mediterranean Diet on Symptoms of Depression: A Systematic Literature Review. *Adv. Nutr.* 2019.
337. Sanhueza C, Ryan L, Foxcroft D. Diet and the risk of unipolar depression in adults: systematic review of cohort studies. *Journal of Human Nutrition and Dietetics.* 2013;26(1):56-70.
338. Beer-Borst S, Hercberg S, Morabia A, et al. Dietary patterns in six european populations: results from EURALIM, a collaborative European data harmonization and information campaign. *Eur J Clin Nutr.* Mar 2000;54(3):253-262.
339. Serdula MK, Gillespie C, Kettel-Khan L, Farris R, Seymour J, Denny C. Trends in fruit and vegetable consumption among adults in the United States: behavioral risk factor surveillance system, 1994–2000. *American Journal of Public Health.* 2004;94(6):1014-1018.
340. Davy SR, Benes BA, Driskell JA. Sex differences in dieting trends, eating habits, and nutrition beliefs of a group of midwestern college students. *Journal of the American Dietetic Association.* 2006;106(10):1673-1677.
341. Wardle J, Haase AM, Steptoe A, Nillapun M, Jonwutiwes K, Bellisie F. Gender differences in food choice: the contribution of health beliefs and dieting. *Annals of behavioral medicine.* 2004;27(2):107-116.
342. Smith KJ, McNaughton SA, Gall SL, Blizzard L, Dwyer T, Venn AJ. Takeaway food consumption and its associations with diet quality and abdominal obesity: a cross-sectional study of young adults. *International Journal of Behavioral Nutrition and Physical Activity.* 2009;6(1):29.
343. Larson NI, Perry CL, Story M, Neumark-Sztainer D. Food preparation by young adults is associated with better diet quality. *Journal of the American dietetic association.* 2006;106(12):2001-2007.
344. National Cancer Institute. Dietary Screener Questionnaires (DSQ) in the NHANES 2009-10: DSQ. https://epi.grants.cancer.gov/nhanes/dietscreen/questionnaires.html. Accessed 01/05/2019.
345. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck depression Inventory-II (BDI-II), center for epidemiologic studies depression scale (CES-D), geriatric depression scale (GDS), hospital anxiety and depression scale (HADS), and patient health Questionnaire-9 (PHQ-9). *Arthritis care & research.* 2011;63(S11):S454-S466.
346. Knüppel A, Shipley MJ, Llewellyn CH, Brunner EJ. Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study. *Scientific reports.* 2017;7(1):6287.
347. Piasecki TM, Trela CJ, Mermelstein RJ. Hangover symptoms, heavy episodic drinking, and depression in young adults: a cross-lagged analysis. *Journal of studies on alcohol and drugs.* 2017;78(4):580-587.
348. Bolton JM, Robinson J, Sareen J. Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of affective disorders.* 2009;115(3):367-375.
349. Whittle EL, Fogarty AS, Tugendrajch S, et al. Men, depression, and coping: Are we on the right path? *Psychology of Men & Masculinity.* 2015;16(4):426.

350. Darvishi N, Farhadi M, Haghtalab T, Poorolajal J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. *PloS one.* 2015;10(5):e0126870.
351. Brug J. Determinants of healthy eating: motivation, abilities and environmental opportunities. *Family practice.* 2008;25(suppl_1):i50-i55.
352. Caperchione CM, Vandelanotte C, Kolt GS, et al. What a man wants: understanding the challenges and motivations to physical activity participation and healthy eating in middle-aged Australian men. *American journal of men's health.* 2012;6(6):453-461.
353. Health N, Council MR. Australian Dietary Guidelines Providing the Scientific Evidence for Healthier Australian Diets: National Health and Medical Research Council Canberra, Australia; 2013.
354. Barosh L, Friel S, Engelhardt K, Chan L. The cost of a healthy and sustainable diet–who can afford it? *Australian and New Zealand journal of public health.* 2014;38(1):7-12.
355. Ward PR, Verity F, Carter P, Tsourtos G, Coveney J, Wong KC. Food stress in Adelaide: the relationship between low income and the affordability of healthy food. *Journal of environmental and public health.* 2013;2013.
356. Kettings C, Sinclair AJ, Voevodin M. A healthy diet consistent with Australian health recommendations is too expensive for welfare-dependent families. *Australian and New Zealand journal of public health.* 2009;33(6):566-572.
357. Lee AJ, Kane S, Ramsey R, Good E, Dick M. Testing the price and affordability of healthy and current (unhealthy) diets and the potential impacts of policy change in Australia. *BMC Public Health.* 2016;16(1):315.
358. Rahe C, Unrath M, Berger K. Dietary patterns and the risk of depression in adults: a systematic review of observational studies. *European journal of nutrition.* 2014;53(4):997-1013.
359. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj.* 2013;346:e7586.
360. Collins S, Dash S, Allender S, Jacka F, Hoare E. Diet and Mental Health During Emerging

Adulthood: A Systematic Review. *Emerging Adulthood, Sage Journals.* 2020.
361. Bayes J, Schloss J, Sibbritt D. An Investigation into The Diets and Nutritional Knowledge of Young Men with Depression (The “MENDDS” survey). *Nutrition (Burbank, Los Angeles County, Calif.).* 2020:110946.
362. Dozois DJ, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory–II. *Psychological assessment.* 1998;10(2):83.
363. Masson SC, Tejani AM. Minimum clinically important differences identified for commonly used depression rating scales. *Journal of clinical epidemiology.* 2013;66(7):805-807.
364. Tayama J, Ogawa S, Nakaya N, et al. Omega-3 polyunsaturated fatty acids and psychological intervention for workers with mild to moderate depression: A double-blind randomized controlled trial. *Journal of affective disorders.* 2019;245:364-370.
365. Sepehrmanesh Z, Kolahdooz F, Abedi F, et al. Vitamin D supplementation affects the beck depression inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: a randomized, controlled clinical trial. *The Journal of nutrition.* 2015;146(2):243-248.
366. Hendrie G, Baird D, Golley S, Noakes M. CSIRO Healthy Diet Score 2016. *Retrieved September.* 2016;10:2016.

367. Bendall S, Jackson HJ, Killackey E, et al. The credibility and acceptability of befriending as a control therapy in a randomized controlled trial of cognitive behaviour therapy for acute first episode psychosis. *Behavioural and Cognitive Psychotherapy.* 2006;34(3):277.
368. Wang Y-P, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Brazilian Journal of Psychiatry.* 2013;35(4):416-431.
369. Wang Y-P, Gorenstein C. Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II. *Clinics.* 2013;68(9):1274-1287.
370. Lasa L, Ayuso-Mateos J, Vazquez-Barquero J, Dıez-Manrique F, Dowrick C. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. *Journal of affective disorders.* 2000;57(1-3):261-265.
371. Skevington SM, Lotfy M, O'Connell K. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of life Research.* 2004;13(2):299-310.
372. Berlim MT, Pavanello DP, Caldieraro MA, Fleck MP. Reliability and validity of the WHOQOL BREF in a sample of Brazilian outpatients with major depression. *Quality of life research.* 2005;14(2):561-564.
373. Papadaki A, Johnson L, Toumpakari Z, et al. Validation of the English version of the 14-item Mediterranean Diet Adherence Screener of the PREDIMED study, in people at high cardiovascular risk in the UK. *Nutrients.* 2018;10(2):138.
374. García-Toro M, Vicens-Pons E, Gili M, et al. Obesity, metabolic syndrome and Mediterranean diet: Impact on depression outcome. *Journal of affective disorders.* 2016;194:105-108.
375. Middleton G, Keegan R, Smith MF, Alkhatib A, Klonizakis M. Implementing a Mediterranean diet intervention into a RCT: lessons learned from a non-Mediterranean based country. *The journal of nutrition, health & aging.* 2015;19(10):1019-1022.
376. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. *Bmj.* 2015;351.
377. Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *American Journal of Psychiatry.* 2010;167(3):281-288.
378. LaChance LR, Ramsey D. Antidepressant foods: An evidence-based nutrient profiling system for depression. *World journal of psychiatry.* 2018;8(3):97.
379. Marx W, Moseley G, Berk M, Jacka F. Nutritional psychiatry: the present state of the evidence. *Proc. Nutr. Soc.* 2017;76(4):427-436.
380. Martínez-González MÁ, Hershey MS, Zazpe I, Trichopoulou A. Transferability of the Mediterranean diet to non-Mediterranean countries. What is and what is not the Mediterranean diet. *Nutrients.* 2017;9(11):1226.
381. Masana MF, Haro JM, Mariolis A, et al. Mediterranean diet and depression among older individuals: The multinational MEDIS study. *Experimental gerontology.* 2018;110:67-72.

382. Skarupski KA, Tangney C, Li H, Evans D, Morris M. Mediterranean diet and depressive symptoms among older adults over time. *The journal of nutrition, health & aging.* 2013;17(5):441-445.
383. Yin W, Löf M, Chen R, Hultman CM, Fang F, Sandin S. Mediterranean diet and depression: a population-based cohort study. *International Journal of Behavioral Nutrition and Physical Activity.* 2021;18(1):1-10.
384. Fresán U, Bes-Rastrollo M, Segovia-Siapco G, et al. Does the MIND diet decrease depression risk? A comparison with Mediterranean diet in the SUN cohort. *European journal of nutrition.* 2019;58(3):1271-1282.
385. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *Bmj.* 2002;324(7351):1417.
386. Bayes J, Schloss J, Sibbritt D. A randomised control trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the "AMMEND" study): A study protocol. *British Journal of Nutrition.* 2020:1-25.
387. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine.* 2013;158(3):200-207.
388. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials.* 2010;11(1):1-8.
389. Bach-Faig A, Berry EM, Lairon D, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public health nutrition.* 2011;14(12A):2274-2284.
390. The Food and Agricultural Organisation of the United Nations. National Nutrition Guide for Greek Adults. 2021; https://www.fao.org/nutrition/education/food-dietary-guidelines/regions/countries/greece/en/. Accessed 10/06/2019.
391. The Food and Agricultural Organisation of the United Nations. Food-based dietary guidelines - Spain. 2021; https://www.fao.org/nutrition/education/food-dietary-guidelines/regions/countries/spain/en/. Accessed 10/06/2019.
392. Jackson-Koku G. Beck depression inventory. *Occupational Medicine.* 2016;66(2):174-175.
393. Kim S. World Health Organization quality of life (WHOQOL) assessment. *Encyclopedia of quality of life and well-being research.* 2020:1-2.
394. Crichton GE, Howe PR, Buckley JD, Coates AM, Murphy KJ, Bryan J. Long-term dietary intervention trials: critical issues and challenges. *Trials.* 2012;13(1):1-10.
395. Gough B. 'Real men don't diet': An analysis of contemporary newspaper representations of men, food and health. *Social science & medicine.* 2007;64(2):326-337.
396. Francis HM, Stevenson RJ, Chambers JR, Gupta D, Newey B, Lim CK. A brief diet intervention can reduce symptoms of depression in young adults–A randomised controlled trial. *PloS one.* 2019;14(10):e0222768.
397. Chung C-F, Agapie E, Schroeder J, Mishra S, Fogarty J, Munson SA. When personal tracking becomes social: Examining the use of Instagram for healthy eating. Paper presented at: Proceedings of the 2017 CHI Conference on human factors in computing systems2017.
398. Keller HH, Gibbs A, Wong S, Vanderkooy P, Hedley M. Men can cook! Development, implementation, and evaluation of a senior men's cooking group. *Journal of Nutrition for the Elderly.* 2004;24(1):71-87.
399. Kumar KS, Srivastava S, Paswan S, Dutta AS. Depression-symptoms, causes, medications and therapies. *The Pharma Innovation.* 2012;1(3, Part A):37.

400. Castelli V, Grassi D, Bocale R, et al. Diet and brain health: which role for polyphenols? *Current pharmaceutical design.* 2018;24(2):227-238.
401. Bauer I, Hughes M, Rowsell R, et al. Omega-3 supplementation improves cognition and modifies brain activation in young adults. *Human Psychopharmacology: Clinical and Experimental.* 2014;29(2):133-144.
402. Narendran R, Frankle WG, Mason NS, Muldoon MF, Moghaddam B. Improved working memory but no effect on striatal vesicular monoamine transporter type 2 after omega-3 polyunsaturated fatty acid supplementation. 2012.
403. St-Onge M-P, Roberts A, Shechter A, Choudhury AR. Fiber and saturated fat are associated with sleep arousals and slow wave sleep. *Journal of Clinical Sleep Medicine.* 2016;12(1):19-24.
404. Mead N, Lester H, Chew-Graham C, Gask L, Bower P. Effects of befriending on depressive symptoms and distress: systematic review and meta-analysis. *The British Journal of Psychiatry.* 2010;196(2):96-101.
405. Perez-Cornago A, Sanchez-Villegas A, Bes-Rastrollo M, et al. Relationship between adherence to Dietary Approaches to Stop Hypertension (DASH) diet indices and incidence of depression during up to 8 years of follow-up. *Public health nutrition.* 2017;20(13):2383-2392.
406. Salari-Moghaddam A, Keshteli AH, Mousavi SM, Afshar H, Esmaillzadeh A, Adibi P. Adherence to the MIND diet and prevalence of psychological disorders in adults. *Journal of affective disorders.* 2019;256:96-102.
407. Hiza HA, Casavale KO, Guenther PM, Davis CA. Diet quality of Americans differs by age, sex, race/ethnicity, income, and education level. *Journal of the Academy of Nutrition and Dietetics.* 2013;113(2):297-306.
408. Imamura F, Micha R, Khatibzadeh S, et al. Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. *The lancet global health.* 2015;3(3):e132-e142.
409. Bayes J, Schloss J, Sibbritt D. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study): A Randomized Control Trial. *The American Journal of Clinical Nutrition.* 2022.
410. Bestwick C, Douglas F, Allan J, Macdiarmid J, Ludbrook A, Carlisle S. A perspective on the strategic approach to the complexity and challenges of behaviour change in relation to dietary health. *Nutrition Bulletin.* 2013;38(1):50-56.
411. Middleton KR, Anton SD, Perri MG. Long-term adherence to health behavior change. *Am. J. Lifestyle Med.* 2013;7(6):395-404.
412. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *Jama.* 2005;293(1):43-53.
413. Mann T, Tomiyama AJ, Westling E, Lew A-M, Samuels B, Chatman J. Medicare's search for effective obesity treatments: diets are not the answer. *American Psychologist.* 2007;62(3):220.
414. Barolia R, Petrucka P, Higginbottom GA, Khan FFS, Clark AM. Motivators and deterrents to diet change in low socio-economic Pakistani patients with cardiovascular disease. *Global qualitative nursing research.* 2019;6:2333393619883605.
415. Sprinkle SD, Lurie D, Insko SL, et al. Criterion validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a university counseling center sample. *Journal of counseling psychology.* 2002;49(3):381.

416. Bayes J, Schloss, J, Sibbritt, D. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study): A Randomized Control Trial. *The american journal of clinical nutrition.* 2022.
417. Marx W, Manger SH, Blencowe M, et al. Clinical guidelines for the use of lifestyle-based mental health care in major depressive disorder: World Federation of Societies for Biological Psychiatry (WFSBP) and Australasian Society of Lifestyle Medicine (ASLM) taskforce. *The World Journal of Biological Psychiatry.* 2022:1-54.
418. Ashton LM, Hutchesson MJ, Rollo ME, Morgan PJ, Collins CE. Motivators and barriers to engaging in healthy eating and physical activity: A cross-sectional survey in young adult men. *American journal of men's health.* 2017;11(2):330-343.
419. Gordon LM. The Differential Effects Of Peer Influence And Advertisement On Healthy Food Choices. 2015.
420. Salvy S-J, Nitecki LA, Epstein LH. Do social activities substitute for food in youth? *Annals of Behavioral Medicine.* 2009;38(3):205-212.
421. Stead M, McDermott L, MacKintosh AM, Adamson A. Why healthy eating is bad for young people's health: Identity, belonging and food. *Social science & medicine.* 2011;72(7):1131-1139.
422. National Library of Mediccine. Media coverage of health and science topics. https://www.ncbi.nlm.nih.gov/search/research-news/13453/?utm_source=gquery&utm_medium=referral&utm_campaign=gquery-home. Accessed 25/01/2022.
423. Australian Institute of Health and Welfare (AIHW). *Young Australians: Their health and wellbeing 2007.* Canberra, Australia: AIHW;2007.
424. Wright A, Harris MG, Jorm AF, et al. Recognition of depression and psychosis by young Australians and their beliefs about treatment. *Medical Journal of Australia.* 2005;183(1):18-23.
425. Jorm AF, Wright A, Morgan AJ. Beliefs about appropriate first aid for young people with mental disorders: findings from an Australian national survey of youth and parents. *Early Intervention in Psychiatry.* 2007;1(1):61-70.
426. Australian Bureau of Statistics. *Causes of Death Australia 2014, preliminary data* Canberra: ABS;2016.
427. Rechenberg K, Humphries D. Nutritional interventions in depression and perinatal depression. *The Yale journal of biology and medicine.* 2013;86(2):127.
428. Lindseth G, Helland B, Caspers J. The effects of dietary tryptophan on affective disorders. *Archives of psychiatric nursing.* 2015;29(2):102-107.
429. Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *American Journal of Psychiatry.* 2010;167(8):942-948.
430. Liao Y, Xie B, Zhang H, et al. Efficacy of omega-3 PUFAs in depression: a meta-analysis. *Translational psychiatry.* 2019;9(1):1-9.
431. Gao K, Mu C-l, Farzi A, Zhu W-y. Tryptophan metabolism: a link between the gut microbiota and brain. *Adv. Nutr.* 2020;11(3):709-723.
432. Yuly Bersudsky M, Benjamin J, Klein E. The biology of tryptophan depletion and mood disorders. *Israel Journal of Psychiatry.* 2010;47(1):46.
433. Murphy SE, Longhitano C, Ayres RE, Cowen PJ, Harmer CJ. Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers. *Psychopharmacology.* 2006;187(1):121-130.

434. Jovanovic H, Kocoska-Maras L, Rådestad AF, et al. Effects of estrogen and testosterone treatment on serotonin transporter binding in the brain of surgically postmenopausal women–a PET study. *Neuroimage.* 2015;106:47-54.
435. Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Association of dietary amino acids with low mood. *Depression and anxiety.* 2003;18(2):89-94.
436. Ullah H, Khan A, Rengasamy KR, Di Minno A, Sacchi R, Daglia M. The Efficacy of S-Adenosyl Methionine and Probiotic Supplementation on Depression: A Synergistic Approach. *Nutrients.* 2022;14(13):2751.
437. Sarris J, Price LH, Carpenter LL, et al. Is S-adenosyl methionine (SAMe) for depression only effective in males? A re-analysis of data from a randomized clinical trial. *Pharmacopsychiatry.* 2015;48(04/05):141-144.
438. Altaf R, Gonzalez I, Rubino K, Nemec II EC. Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: Systematic review & meta-analysis. *Complementary Therapies in Medicine.* 2021;61:102770.
439. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *Journal of affective disorders.* 2000;60(2):121-130.
440. Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *The Journal of clinical psychiatry.* 2009;70(suppl 5):7377.
441. Belščak-Cvitanović A, Durgo K, Huđek A, Bačun-Družina V, Komes D. Overview of polyphenols and their properties. *Polyphenols: Properties, recovery, and applications*: Elsevier; 2018:3-44.
442. Colangelo LA, He K, Whooley MA, Daviglus ML, Liu K. Higher dietary intake of long-chain ω-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition (Burbank, Los Angeles County, Calif.).* 2009;25(10):1011-1019.
443. Tanskanen A, Hibbeln JR, Tuomilehto J, et al. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatric Services.* 2001;52(4):529-531.
444. Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: the Northern Finland 1966 birth cohort study. *Journal of affective disorders.* 2004;82(3):447-452.
445. Giles GE, Mahoney CR, Kanarek RB. Omega-3 fatty acids influence mood in healthy and depressed individuals. *Nutrition reviews.* 2013;71(11):727-741.
446. Giltay EJ, Gooren LJ, Toorians AW, Katan MB, Zock PL. Docosahexaenoic acid concentrations are higher in women than in men because of estrogenic effects. *The American journal of clinical nutrition.* 2004;80(5):1167-1174.
447. Firth J, Marx W, Dash S, et al. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. *Psychosomatic medicine.* 2019;81(3):265.
448. Yoshikawa E, Nishi D, Matsuoka YJ. Association between frequency of fried food consumption and resilience to depression in Japanese company workers: a cross-sectional study. *Lipids in health and disease.* 2016;15(1):1-5.
449. Zhang Y, Yang Y, Xie M-s, et al. Is meat consumption associated with depression? A meta-analysis of observational studies. *BMC psychiatry.* 2017;17(1):1-7.
450. Nucci D, Fatigoni C, Amerio A, Odone A, Gianfredi V. Red and processed meat consumption and risk of depression: A systematic review and meta-analysis.

International journal of environmental research and public health. 2020;17(18):6686.

451. Gal D, Wilkie J. Real men don't eat quiche: Regulation of gender-expressive choices by men. *Social Psychological and Personality Science.* 2010;1(4):291-301.

452. Timeo S, Suitner C. Eating meat makes you sexy: Conformity to dietary gender norms and attractiveness. *Psychology of Men & Masculinity.* 2018;19(3):418.

453. Roos G, Prättälä R, Koski K. Men, masculinity and food: interviews with Finnish carpenters and engineers. *Appetite.* 2001;37(1):47-56.

454. Kretowicz H, Hundley V, Tsofliou F. Exploring the perceived barriers to following a Mediterranean style diet in women of childbearing age in the United Kingdom: a qualitative study. *Proc. Nutr. Soc.* 2018;77(OCE4).

455. De Souza P, Ciclitira KE. Men and dieting: a qualitative analysis. *Journal of health psychology.* 2005;10(6):793-804.

456. Tsofliou F, Theodoridis X, Arvanitidou E-I. Toward a Mediterranean-style diet beyond the Mediterranean countries: Evidence of implementation and adherence. *The Mediterranean Diet*: Elsevier; 2020:129-138.

457. Menu A. Australian Health Survey: Nutrition First Results—Foods and Nutrients. *Australian Bureau of Statistics: Canberra, Australia.* 2011.

458. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry.* 2006;163(11):1905-1917.

459. Page IS, Sparti C, Santomauro D, Harris MG. Service demand for psychological interventions among Australian adults: a population perspective. *BMC Health Services Research.* 2021;21(1):1-10.

460. Senés-Guerrero C, Gradilla-Hernández MS, García-Gamboa R, García-Cayuela T. Dietary fiber and gut microbiota. *Science and technology of fibers in food systems.* 2020:277-298.

461. Winter G, Hart RA, Charlesworth RP, Sharpley CF. Gut microbiome and depression: what we know and what we need to know. *Reviews in the Neurosciences.* 2018;29(6):629-643.

462. Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic review of the Mediterranean diet for long-term weight loss. *The American journal of medicine.* 2016;129(4):407-415. e404.

463. Khalid HA, Ab Manan SK, Saidon R, Yahaya AM, Wahab MHA. Maqasid Approach In Measuring Quality Of Life (QoL). *Journal of Fatwa Management and Research.* 2021;26(2):35-49.

464. Kołtowska-Häggström M. Measuring quality of life–theoretical background. *Medical Writing.* 2018;27:8-13.

465. WHO. WHOQOL: Measuring Quality of Life. 2021; https://www.who.int/tools/whoqol. Accessed 06/12/2021.

466. Sánchez PH, Ruano C, De Irala J, Ruiz-Canela M, Martínez-González M, Sánchez-Villegas A. Adherence to the Mediterranean diet and quality of life in the SUN Project. *European Journal of Clinical Nutrition.* 2012;66(3):360-368.

467. Alam K, Mahumud RA, Alam F, Keramat SA, Erdiaw-Kwasie MO, Sarker AR. Determinants of access to eHealth services in regional Australia. *International journal of medical informatics.* 2019;131:103960.

468. Isautier JM, Copp T, Ayre J, et al. People's experiences and satisfaction with telehealth during the COVID-19 pandemic in Australia: cross-sectional survey study. *Journal of medical Internet research.* 2020;22(12):e24531.

469. Weiss D, Rydland HT, Øversveen E, Jensen MR, Solhaug S, Krokstad S. Innovative technologies and social inequalities in health: a scoping review of the literature. *PloS one.* 2018;13(4):e0195447.
470. Dixit N, Van Sebille Y, Crawford GB, Ginex PK, Ortega PF, Chan RJ. Disparities in telehealth use: How should the supportive care community respond? *Supportive Care in Cancer.* 2022;30(2):1007-1010.
471. Debb SM, Schaffer DR, Colson DG. A reverse digital divide: comparing information security behaviors of generation Y and generation Z adults. *International Journal of Cybersecurity Intelligence & Cybercrime.* 2020;3(1):42-55.
472. The Australian Institute of Health and Welfare. Mental health services in Australia, COVID-19 impact on mental health. 2021; https://www.aihw.gov.au/reports/mental-health-services/mental-health-services-in-australia/report-contents/mental-health-impact-of-covid-19. Accessed 15/02/2022.
473. Czeisler MÉ, Wiley JF, Facer-Childs ER, et al. Mental health, substance use, and suicidal ideation during a prolonged COVID-19-related lockdown in a region with low SARS-CoV-2 prevalence. *Journal of psychiatric research.* 2021;140:533-544.
474. Churchill B. COVID-19 and the immediate impact on young people and employment in Australia: A gendered analysis. *Gender, Work & Organization.* 2021;28(2):783-794.
475. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. *Journal of clinical nursing.* 2010;19(1-2):227-233.
476. Sathian B, Asim M, Banerjee I, et al. Impact of COVID-19 on clinical trials and clinical research: a systematic review. *Nepal journal of epidemiology.* 2020;10(3):878.
477. Ronto R, Nanayakkara J, Worsley A, Rathi N. COVID-19 & culinary behaviours of Australian household food gatekeepers: A qualitative study. *Appetite.* 2021;167:105598.
478. Wright CJ, Livingston M, Dwyer R, Callinan S. Second, third, fourth COVID-19 waves and the 'pancession': We need studies that account for the complexities of how the pandemic is affecting alcohol consumption in Australia. *Drug and alcohol review.* 2021.
479. Neill E, Meyer D, Toh WL, et al. Alcohol use in Australia during the early days of the COVID-19 pandemic: initial results from the COLLATE project. *Psychiatry Clin. Neurosci.* 2020;74(10):542-549.
480. O'Kane G. COVID-19 puts the spotlight on food insecurity in rural and remote Australia. *The Australian Journal of Rural Health.* 2020;28(3):319.
481. Agnoli C, Sieri S, Ricceri F, et al. Adherence to a Mediterranean diet and long-term changes in weight and waist circumference in the EPIC-Italy cohort. *Nutrition & diabetes.* 2018;8(1):1-10.
482. Caradonna F, Consiglio O, Luparello C, Gentile C. Science and healthy meals in the world: Nutritional epigenomics and nutrigenetics of the mediterranean diet. *Nutrients.* 2020;12(6):1748.
483. Faw MH, Davidson K, Hogan L, Thomas K. Corumination, diet culture, intuitive eating, and body dissatisfaction among young adult women. *Personal Relationships.* 2021;28(2):406-426.
484. Zheng Z, Han W, Li Y, Wang D, Gu S, Wang F. The mediating effect of coping style in the relationship between depression and disordered eating among Chinese female undergraduates. *Front. Psychol.* 2020:3011.

485. Koven NS, Abry AW. The clinical basis of orthorexia nervosa: emerging perspectives. *Neuropsychiatr. Dis. Treat.* 2015;11:385.
486. Bratman S, Knight D. Orthorexia nervosa: Overcoming the obsession with healthful eating. Health Food Junkies: New York: Broadway Books; 2000.
487. Vandereycken W. Media hype, diagnostic fad or genuine disorder? Professionals' opinions about night eating syndrome, orthorexia, muscle dysmorphia, and emetophobia. *Eating disorders.* 2011;19(2):145-155.
488. Hutchins-Wiese HL, Bales CW, Starr KNP. Mediterranean diet scoring systems: Understanding the evolution and applications for Mediterranean and non-Mediterranean countries. *British Journal of Nutrition.* 2021:1-22.
489. Bertoli S, Spadafranca A, Bes-Rastrollo M, et al. Adherence to the Mediterranean diet is inversely related to binge eating disorder in patients seeking a weight loss program. *Clinical Nutrition.* 2015;34(1):107-114.
490. Miller TM, Abdel-Maksoud MF, Crane LA, Marcus AC, Byers TE. Effects of social approval bias on self-reported fruit and vegetable consumption: a randomized controlled trial. *Nutrition Journal.* 2008;7(1):1-7.
491. Beasley JM, Riley WT, Davis A, Singh J. Evaluation of a PDA-based dietary assessment and intervention program: a randomized controlled trial. *Journal of the American College of Nutrition.* 2008;27(2):280-286.
492. Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM. Dietary biomarkers: advances, limitations and future directions. *Nutrition journal.* 2012;11(1):1-14.
493. Baxter D, Lovell GP. Australian mental health practitioners' reported practice, beliefs, and barriers to the prescription of dietary change for mental health conditions. *Australian Psychologist.* 2021;56(3):245-255.
494. Nayda C, Gould J, Roberts RM. Psychologist attitudes, self-reported competence and practices associated with the use of dietary interventions for children presenting for psychological treatment. *Australian Psychologist.* 2021;56(5):394-405.
495. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry.* 2021;55(1):7-117.
496. Batterham PJ, Calear AL, McCallum SM, et al. Trajectories of depression and anxiety symptoms during the COVID-19 pandemic in a representative Australian adult cohort. *Medical Journal of Australia.* 2021;214(10):462-468.
497. Headspace. Insights: youth mental health and wellbeing over time: National Youth Mental Health Foundation, ; 2020.
498. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme Version.* 2006;1(1):b92.