

University of
South Australia

Nourishing the mind: exploring the relationship between dietary patterns, cognition, and brain volume in older adults

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Bachelor of Nutrition and Food Sciences

Submitted in fulfilment of the requirements for the degree of

Masters by Research

Allied Health and Human Performance

University of South Australia

December 2023

Table of Contents

List of Figures v

List of Tables vi

Table of Abbreviations and Symbols viii

Summary ix

Declaration xi

Acknowledgements xii

1 Introduction to thesis 1

1.1 Thesis structure 2

1.2 General Introduction 3

1.3 Research aims and hypotheses 6

2 Pathophysiology of dementia and the evidence for the Mediterranean and MIND diets 7

2.1 Chapter overview 8

2.2 Introduction 9

2.3 Dementia 9

2.3.1 Pathophysiology and disease progression 9

2.3.2 Brain atrophy and cognitive decline 12

2.3.3 Diagnosis 13

2.3.4 Modifiable risk factors 14

2.4 Mediterranean and MIND diets 18

2.4.1 Mediterranean diet 18

2.4.2 MIND diet 20

2.5 Mediterranean and MIND diets for dementia prevention 21

2.5.1 Mediterranean diet and cognitive function 21

2.5.2 MIND diet and cognitive function 24

2.5.3 Mediterranean diet and neuroimaging markers of dementia risk 25

2.5.4 MIND diet and neuroimaging markers of dementia risk 26
2.6 Current limitations with Mediterranean diet adherence scoring 27
2.7 Summary 28
3 Associations between Mediterranean diet and MIND diet adherence with cognitive function in older Australian adults 30
3.1 Chapter overview 31
3.2 Abstract 32
3.3 Introduction 33
3.4 Methods 35
3.4.1 Study population 35
3.4.2 Procedure 35
3.4.3 Dietary assessment 36
3.4.4 Mediterranean diet scores 36
3.4.5 MIND diet score 37
3.4.6 Cognitive assessment 38
3.4.7 Covariates 40
3.4.8 Statistical analysis 40
3.5 Results 41
3.6 Discussion 48
3.7 Supplementary tables 54
4 Associations between Mediterranean diet and MIND diet adherence with brain volume and cognitive performance in older Australian adults 59
4.1 Chapter overview 60
4.2 Abstract 61
4.3 Introduction 63
4.4 Methods 64
4.4.1 Study population and screening 64
4.4.2 Procedure 65

4.4.3 Dietary assessment and scoring 65
4.4.4 MRI acquisition 66
4.4.5 Brain volume assessment 66
4.4.6 Cognitive assessment 67
4.4.7 Covariates 67
4.4.8 Statistical analysis 68
4.5 Results 69
4.6 Discussion 76
5 General discussion 82
5.1 Overview 83
5.2 Main findings 84
5.2.1 Mediterranean diet 84
5.2.2 MIND diet 85
5.3 Strengths and limitations and directions for future research 87
5.4 Conclusion 89
References 90
Appendices 102

List of Figures

Chapter 2		Page
Figure 1	Pathway to diagnosis of dementia	16
Figure 2	Population attributable fraction of potentially modifiable risk factors for dementia	17
Figure 3	Mediterranean diet pyramid	19
Chapter 3		
Figure 1	Violin plots of dietary adherence scores for S-Med Score, P-Med Score and MIND diet	45
Chapter 4		
Figure 1	Association between P-Med Score and long-term memory by hippocampal volume	74
Figure 2	Association between MIND diet score and long-term memory by hippocampal volume	75

List of Tables

Chapter 2		**Page**
Table 1	The four stages of dementia progression	11
Chapter 3		
Table 1	CANTAB tests and outcome measures included within each cognitive domain	39
Table 2	Participant baseline characteristics according to tertiles of Mediterranean and MIND diet scores	43
Table 3	Statistical output of ANOVA type II F tests for cognitive outcomes among participants in the ACTIVate study, with dietary scores modelled as continuous variables	47
Supplementary Table 1	Statistical output of ANOVA type II F tests for cognitive outcomes among participants in the ACTIVate study, with dietary scores modelled as tertiles	54
Supplementary Table 2	Statistical output of ANOVA type II F tests for cognitive outcomes among female participants in the ACTIVate study	55
Supplementary Table 3	Statistical output of ANOVA type II F tests for cognitive outcomes among male participants in the ACTIVate study	56
Supplementary Table 4	Statistical output of ANOVA type II F tests for cognitive outcomes among participants aged 60-65 in the ACTIVate study	57
Supplementary Table 5	Statistical output of ANOVA type II F tests for cognitive outcomes among participants aged 66-70 in the ACTIVate study	58

Chapter 4

Table 1	MRI scan parameters and resolution for T1-weighted structural scans	66
Table 2	Participant baseline characteristics according to tertiles of Mediterranean and MIND diet scores	71
Table 3	Statistical output of ANOVA type II F tests for brain volume outcomes among participants in the ACTIVate study	73

Table of Abbreviations and Symbols

β	beta
ACE-III	Addenbrooke's Cognitive Examination III
AD	Alzheimer's disease
AES	Australian Eating Survey
ANOVA	analysis of variance
BMI	body mass index
CANTAB	Cambridge Neuropsychological Test Automated Battery
CES-D	Center for Epidemiologic Studies Depression scale
DASH	Dietary Approaches to Stop Hypertension
FA	fatty acids
FFQ	food frequency questionnaire
kJ	kilojoules
MCI	mild cognitive impairment
MedDiet	Mediterranean diet
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
mmHg	millimetres of mercury
MoCA-B	Montreal Cognitive Assessment-Blind
MRI	magnetic resonance imaging
n	sample size
NFTs	neurofibrillary tangles
P-Med Score	Mediterranean diet score developed by Panagiotakos *et al.* [1]
p-tau	hyperphosphorylated tau protein
SD	standard deviation
SE	standard error
S-Med Score	Mediterranean diet score developed by Sofi *et al.* [2]
T2 FLAIR	T2 fluid-attenuated inversion recovery
TNFR1	tumour necrosis factor receptor 1
WFR	weighed food record
WMHV	white matter hyperintensity volume

Summary

Cognitive decline commonly occurs in older adults often gradually and with subtle changes over time. This natural progression stands in contrast to dementia, a broad category of conditions marked by a significant and progressive decline in cognitive function. This abnormal cognitive decline is typically preceded by observable changes in the brain, including reduced brain volume, providing a potential target for dementia prevention. While efforts have been made to identify modifiable risk factors to slow cognitive decline and preserve brain volume, and thereby reduce dementia incidence, the exact role of diet in this context remains uncertain.

A Mediterranean-style diet (MedDiet) has been shown to provide numerous health benefits, particularly in alleviating conditions associated with chronic inflammation such as metabolic syndrome, atherosclerosis, diabetes, obesity, and pulmonary diseases. Despite this, current studies present mixed findings regarding the efficacy of this dietary pattern in preserving cognitive function and brain volume. While many studies demonstrate positive associations between MedDiet adherence and cognitive domains like memory and executive function, others have found no such links. Similarly, adherence to this dietary pattern has shown associations in a number of studies with larger total brain volume, including larger total grey and white matter volumes, while other studies have not elucidated such associations. These discrepancies may be attributed to several factors, notably the vast range of MedDiet scoring metrics currently in use, resulting in scoring inconsistencies that hinder cross-study comparisons.

The Mediterranean-DASH Intervention for Neurodegenerative Delay, or MIND diet, is a newer dietary approach that has shown encouraging evidence in dementia prevention. This dietary pattern adopts a plant-based approach akin to the MedDiet, having been modelled on both the MedDiet and the Dietary Approaches to Stop Hypertension (DASH) diet. However, research on the MIND diet is still in its early stages. Initial data suggests positive associations between the MIND diet and global cognitive function, memory, processing speed and verbal comprehension/reasoning, as well as larger total brain volume, decreased hippocampal sclerosis, and increased surface area of the inferior frontal gyrus.

This thesis aimed to address inconsistencies in prior research by exploring associations between cognitive function and both the MedDiet and MIND diet, as well as examine the associations between brain volume with adherence to each dietary pattern. Information regarding dietary intake, cognitive function, and brain volume was gathered from 426 participants enrolled in the ACTIVate study, a prospective longitudinal cohort study investigating older Australian adults. The ACTIVate study aims to explore associations between activity and diet compositions with changes in cognition and brain function for dementia prevention. To explore the associations of MedDiet with cognition and brain volume in this thesis, two of the most common MedDiet scoring systems were used. The first was developed by Panagiotakos *et al.* [1] (P-Med Score), and the second was developed by Sofi *et al.* [2] (S-Med Score). Primary cognitive outcomes included global cognition, short-term and working memory, long-term storage and retrieval, executive function, and processing speed, while primary outcomes for brain volume comprised total brain volume, total grey matter volume, total white matter volume, and hippocampal volume.

Higher adherence to the MIND diet was positively associated with executive function after adjusting for sociodemographic and cardiovascular risk factors. However, following further adjustment for depression, this association became non-significant. Additionally, higher adherence to the S-Med Score was associated with higher total brain volume, white matter volume, and hippocampal volume after adjusting for demographic and cardiovascular variables and depression. Nevertheless, results became non-significant for total brain volume in models 2 and 3 after false discovery rate adjustment, and for hippocampal volume in all models, suggesting some caution in interpreting the results. Collectively, these findings offer preliminary cross-sectional evidence suggesting that MIND diet adherence may be beneficial for executive function, while higher adherence to the MedDiet could provide protective benefits to white matter volume, based on the S-Med Score. Validation of these results should be pursued through a longitudinal study approach.

Declaration

I declare that:

This thesis presents work carried out by myself and does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Signed: Dated:



14/12/2023

Acknowledgements

I would like to express my deepest gratitude to the ACTIVate team for welcoming me as part of the team, and for allowing me the opportunity to utilise data collected for this project. A huge thank you goes to everyone who was involved in this process. I would also like to acknowledge the University of South Australia and the University of Newcastle for providing the necessary resources and facilities to carry out this research.

Furthermore, I extend my appreciation to A/Prof Karen Murphy for her invaluable advice regarding dietary scoring and analysis, and to Dr Ty Stanford for his assistance with data analysis. Finally, I extend my thanks to my supervisory team, A/Prof Ashleigh Smith, Dr Alexandra Wade, Dr Anson Chau, and Dr Maddison Mellow, for their constant support, advice, and encouragement throughout my candidature.

Candidature support was provided by the Australian Federal Government (Department of Education & Training) through a Research Training Program Scholarship.

This thesis is dedicated to my grandma, Rose, and her best friend, Max.

1 Introduction to thesis

1.1 Thesis structure

This thesis is structured into five chapters, with the main body of research contained in chapters three and four. The present chapter outlines the structure of the thesis, followed by a general introduction and research aims and hypotheses.

Chapter 2 provides a literature review of dementia, the Mediterranean diet (MedDiet) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, as well as cognitive and neuroimaging markers of dementia risk. Current evidence for the role of the MedDiet and MIND diet for dementia prevention is presented and discussed.

Chapters 3 and 4 are the primary research studies investigating the associations between cognition and brain volume with MedDiet and MIND diet adherence. Chapter 3 presents a cross-sectional study exploring the associations between adherence to the MedDiet and MIND diet and cognitive performance in older Australian adults. Greater adherence to the MedDiet or MIND diet was not associated with higher cognitive function among a healthy older population in Australia.

Chapter 4 is a cross-sectional study investigating whether increased adherence to the MedDiet and MIND diet in older Australians was associated with higher total brain volume, total grey matter volume, total white matter volume, and hippocampal volume. The findings of this study offer initial cross-sectional evidence that adherence to the MedDiet is linked to greater white matter volume.

Chapter 5 collates and discusses the main findings of the thesis and how it contributes to the current body of research. Limitations of the study and recommendations for future research are presented.

1.2 General Introduction

While cognitive decline and brain atrophy can be considered a common feature of ageing, significant and progressive decreases in cognitive function and brain volume are considered abnormal and often indicate the potential presence of dementia. In Australia alone, 472,000 people are estimated to be currently living with dementia and, without a significant health or medical advancement, this number is expected to increase to over 1 million by 2058 [3]. Dementia is the second leading cause of death for all Australians, the leading cause of death for Australian women [3], and has recently been declared the leading cause of disease burden in Australians aged 65 and over [4]. Dementia has widespread impacts, affecting not only the cognitive domain, but also behavioural, psychological, and physical domains [5, 6].

Previous findings have shown that cognitive decline and brain atrophy are more pronounced in those with dementia compared to that observed in normal ageing [7]. In Alzheimer's disease (AD), the predominant form of dementia, reduced volume has been observed in brain regions affected by AD neuropathology prior to any signs of cognitive decline and before a clinical diagnosis of AD has been made [8]. This long preclinical period provides an opportunity for early identification and preventive strategies to be employed [9], with around 40% of dementia risk thought to be potentially modifiable [10]. With minimal effective pharmacological options available to treat or slow dementia progression [11], research efforts have now shifted to the prevention during preclinical stages through addressing modifiable risk factors such as diet [9].

In recent years, mounting evidence supports the potential for diet to play a role in dementia prevention by slowing cognitive decline [9, 12, 13] and affecting several other neuroimaging indices of dementia risk such as brain volume, structural and functional connectivity [14], and white matter hyperintensity volume (WMHV) [15]. Diet is also directly linked with cardiometabolic health, and has implications for the presence of obesity, type 2 diabetes, and hypertension [16, 17, 18]. Each of these conditions are known risk factors for dementia [10, 14, 19] and are associated with cerebral small vessel disease and markers of compromised cerebrovascular integrity, which may accelerate the ageing process of the brain and contribute to cognitive decline [20]. One dietary pattern that is gaining popularity in dementia prevention research is the MedDiet [21]. The MedDiet reflects the typical dietary

pattern consumed in countries of the Mediterranean region such as Greece, Spain and Italy. Emerging research indicates the MedDiet is associated with reduced mortality and incidence of AD [22, 23], improved cognition [21], less brain atrophy [24] and WHMV [25], as well as preserved white matter integrity [26]. It is believed these benefits are due to high intake of mono- and poly-unsaturated fatty acids, and micronutrients such as vitamins C, E, and B12, folate, flavonoids, and carotenes, which have been shown to reduce biomarkers of oxidative stress and positively influence cognitive performance [21]. There is also some evidence that the MedDiet can reduce low-grade systemic inflammation, a known risk factor for cognitive decline [21].

The MIND diet is another dietary pattern that has demonstrated protective effects on the brain. It was developed by Morris *et al.* [27] and was modelled on a combination of the MedDiet and the Dietary Approaches to Stop Hypertension (DASH) diet. Evidence suggests that moderate to high adherence to the MIND diet (according to dietary adherence scores) may decrease the risk of AD [28, 29], with associations between higher adherence and greater cognitive function and total brain volume also demonstrated [30]. Notably, current research suggests that the MIND diet may be superior to other plant-rich diets such as the MedDiet in improving cognitive function [31].

In summary, an emerging body of evidence suggests that the MedDiet and MIND diet may play an important role in protecting the brain against dementia. Despite this, several studies have demonstrated no associations between these dietary patterns and dementia prevalence. Further studies are needed to investigate this relationship to determine the efficacy of these diets in slowing the progression of dementia in its preclinical stages. Randomised controlled trials (RCTs) are the gold standard study design and allow causality to be inferred from study findings, however there are many methodological challenges involved in conducting such a study within this area of research. These limitations include the inability to blind study participants to the intervention (participants will be aware of the foods they are consuming), difficulties establishing a good control given the large variation in diet in many populations, and the high burden placed on study participants which may introduce adherence issues. Therefore, observational cohort studies are used most often in analysing the associations between dietary patterns and dementia prevention.

A notable challenge in research on the MedDiet is the difficulty in comparing results across studies, primarily because there is a wide variation in how adherence is scored, with numerous different scoring systems in use. Even when the same scoring metric has been employed, often results are still not comparable due to the use of sex-specific median food intake values of the population to guide calculation of adherence scores. For example, participants may be scored a 1 for consuming higher than the within-population median intake for that particular food category for their sex, and 0 for consuming below this value [32]. This method is appropriate within a Mediterranean population such as Greece, in which the score was originally developed. However, in non-Mediterranean populations such as Australia and the United States, this method creates variable scoring of adherence to dietary components, which is not comparable across studies [33]. Notably, in studies that have adopted the traditional number of Greek servings used in the original scoring metric, which are typically higher than the median intakes observed in Western populations, associations between higher adherence and lesser cognitive decline and AD incidence have been demonstrated [33]. This thesis proposed the use of pre-determined cut-off values of food intake to determine MedDiet adherence rather than utilising sex-specific within-population medians. A scoring metric developed by Panagiotakos *et al.* [1] was used which includes 11 food groups and assigns scoring values based on suggested intake according to the MedDiet pattern. An additional scoring metric, developed by Sofi *et al.* [2], was also used. This includes nine food categories and bases cut-off values on prospective cohort studies investigating MedDiet and health outcomes. Possible total scores for these methods range from 0 to 55 and 0 to 18, respectively. Two scoring systems were chosen instead of one as many different scoring systems currently exist, with no one score identified as superior to the others. Chapter 3 discusses these scoring metrics in further detail.

Few studies have considered the association between MedDiet and MIND diet adherence and both cognition and neuroimaging markers of dementia within the same cohort. To the best of our knowledge, no studies have analysed MIND diet adherence with both cognition and brain volume within an Australian population. Additionally, the older age of participants within the population used in this thesis allows a greater possibility of identifying significant associations, given that this demographic may exhibit a greater prevalence of dementia neuropathologies compared to recruitment of a younger sample. Such a study may provide

important information regarding the associations between dietary patterns, cognition, and brain volume that have not been elucidated in previous studies.

1.3 Research aims and hypotheses

The aim of this thesis was to investigate whether adherence to different dietary patterns (MedDiet and MIND diet) is associated with cognitive outcomes and brain volume. These variables were assessed using baseline results from the ACTIVate study [34], a three-year prospective longitudinal cohort study focusing on older adults. The study was conducted across two study sites in Adelaide, South Australia and Newcastle, New South Wales in Australia.

The research questions explored in this thesis are:

1 What is the association between MedDiet adherence and cognitive function in an older Australian population?

2 What is the association between MIND diet adherence and cognitive function in an older Australian population?

3 What is the association between MedDiet adherence and brain volume in an older Australian population?

4 What is the association between MIND diet adherence and brain volume in an older Australian population?

5 Does brain volume moderate the relationship between MedDiet and MIND diet adherence, and cognitive function?

It was hypothesised that higher adherence to these dietary patterns would be associated with:

1 Higher global cognition and memory performance

2 Higher total brain volume, total grey matter volume, total white matter volume, and hippocampal volume

2 Pathophysiology of dementia and the evidence for the Mediterranean and MIND diets

2.1 Chapter overview

In this chapter, a narrative literature review is presented in which the pathophysiology of dementia is explored in depth, including observable symptoms and diagnosis. An overview of the Mediterranean diet (MedDiet), including adherence in Australia and current evidence for the protective effects of the MedDiet on cognitive function and brain structure, is then discussed. An overview of the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is also presented along with current evidence for its neuroprotective effects.

2.2 Introduction

Dementia prevalence is on the rise due to ageing populations in many developed countries around the world. Early detection and prevention strategies are currently a focus for much of the research within this field, with a number of modifiable risk factors already identified. While diet has not been formally identified as a modifiable risk factor for dementia in key papers such as the Lancet Commission's '*Dementia prevention, intervention and care'* report [10], the MedDiet and MIND diets have emerged as potential dietary patterns that may offer protective benefits to cognition and brain volume, both of which are known to be impacted in individuals with dementia.

2.3 Dementia

2.3.1 Pathophysiology and disease progression

Dementia describes over 100 diseases affecting the brain, with the most common causes being Alzheimer's disease (AD) (accounting for around 50% to 75% of cases globally) and vascular dementia (20% to 30%), followed by frontotemporal dementia (5% to 10%) and dementia with Lewy bodies (up to 5%) [35, 36]. Many people with dementia are believed to have 'mixed dementia', meaning that they have dementia pathologies characteristic of more than one disease [36]. A case series by Jellinger [37] found that, in over 1000 autopsies of individuals with late-life dementia, 22.6% were found to have AD with cerebrovascular lesions as seen in vascular dementia, and 10.8% were found to have AD with Lewy body pathology. This highlights the complexity of dementia and its pathophysiology.

Broadly, dementia occurs as a result of damage to the brain. However, this can occur via several pathways. This allows classification of the different causes of dementia based on specific neuropathologic features. Being among the most extensively researched types of dementia, AD can be characterised by two hallmark features: neurofibrillary tangles (NFTs) and senile plaques. Neurofibrillary tangles are formed when tau protein, usually found in nerve cell axons, misfolds and aggregates inside the cell body of the neuron [38]. While neurofibrillary tangles have been observed in the brains of people without dementia [39], they are more abundant in those with AD and increase in density and distribution as the

disease progresses in severity and duration [40, 41]. Senile plaques, also known as amyloid plaques, contain the protein amyloid β as their major constituent [42, 43]. Like NFTs, senile plaques are also found in the brains of cognitively normal older adults, as well as those with AD [43]. However, in the brains of those with AD, the presence of senile plaques is accompanied by neuritic degeneration, which is not observed in the brains of people without dementia [44]. It is believed this may be due to elements other than amyloid that are present in the plaques seen in AD but not in aged individuals without dementia, such as abnormal neurites [43, 44]. Understanding the pathophysiology of AD and other types of dementia is critical as it offers focal points for investigating potential preventive strategies, which may ultimately lead to the development of effective treatments and interventions.

Regardless of the underlying cause, dementia can be described as a terminal, progressive condition. It typically presents in four stages, including the preclinical stage (Table 1), although the progression of the disease varies among individuals [36]. Given that the preclinical phase of this condition may last from 2 to 15 years before symptoms become apparent [45], it is vital to prolong the duration in which individuals remain in this stage for as long as possible. This elongation is necessary to slow the progression into subsequent stages of the disease, where adverse effects on the individual become more pronounced. One potential focus for this objective may be tumour necrosis factor receptor 1 (TNFR1), a marker associated with chronic inflammation. Studies suggest that elevated TNFR1 levels are linked to more rapid cognitive decline and an increased likelihood of progressing from the preclinical to the early stage of dementia [46]. This underscores the potential for intervention strategies to prolong the preclinical phase by targeting this receptor. Dietary patterns, such as the MedDiet, are emerging as promising candidates due to their recognised anti-inflammatory properties [47].

Table 1 The four stages of dementia progression

	Timeframe	Description
Preclinical stage	2-15 years prior to early stage	Normal cognitive ability with no observable symptoms. During this stage, amyloid accumulation and reductions in brain volume may be detected.
Early stage	Years 1-2	Often dismissed as a normal part of the ageing process. This stage can be difficult to define as onset is gradual (though it can be sudden in the case of vascular dementia). Symptoms can include memory loss, disorientation in familiar places, changes in mood and personality, and loss of interest in hobbies and activities.
Middle stage	Years 2-5	Daily activities become difficult and limitations more obvious, and the person is no longer able to live at home without issues. They often need assistance with cooking, cleaning, and personal hygiene. They may become very forgetful, have increased difficulties with speech, and may also experience hallucinations.
Late stage	Years 5+	Independence is lost, with physical symptoms more obvious. At this stage the person may have difficulty eating and walking, may experience incontinence, may not recognise friends and relatives, may be unable to communicate, and often have difficulty understanding what is going on around them. Many people will be confined to a bed or wheelchair at this stage.

Sources: Alzheimer's Disease International [36], Vermunt *et al.* [45]

2.3.2 Brain atrophy and cognitive decline

The varying underlying neuropathologic features seen in dementia typically present as accelerated brain atrophy and cognitive decline, with studies demonstrating that these characteristics are more pronounced in those with AD compared to normal ageing [7]. Diminished brain volume is frequently observed in areas impacted by AD pathology before any indications of cognitive decline manifest and prior to an official diagnosis of dementia [8]. Accelerated atrophy of the whole brain and regions of the medial temporal lobe, including the hippocampus, have been observed [48]. Hippocampal atrophy is widely used in research to map the progression of AD, with clinical AD patients presenting with 15-40% smaller hippocampal volume than healthy participants [49]. Reduction in total grey matter volume has also been reported [50], with grey matter loss identified in the hippocampus and entorhinal cortex in early stages. This is followed by atrophy in the middle and inferior temporal gyri, inferior parietal lobe, and posterior cingulate cortex, before spreading to further areas of the parietal lobe, frontal brain regions, and anterior parts of the cingulate cortex [51]. While grey matter atrophy is more prominent in AD, white matter volume is also affected. Typically, volumes decline in mediotemporal structures such as the hippocampus and entorhinal cortex [52], often involving partial loss of myelin, axons, and oligodendroglial cells in affected regions [53]. In addition to the observed declines in mediotemporal structures, atrophy of white matter has been noted in the inferior parietal, temporal, and anterior frontal brain regions, as well as the posterior cingulate cortex, posterior corpus callosum, and cerebellum [54, 55].

Atrophy in regions of the brain described previously is thought to contribute to changes in cognitive function. Cognitive functioning is typically classified into domains and subdomains based on the general cognitive process involved such as memory, attention, language, or executive functioning [56]. Cognitive decline in one or more of these domains often emerges as one of the first clinical symptoms of dementia, with episodic memory deficits typically the earliest to become evident [57]. This often manifests as difficulties learning new information, which can be attributed to an encoding dysfunction that affects the consolidation of new information into long-term memory [7]. Decline in episodic memory has previously been linked to atrophy of the hippocampus. This association is not unexpected, considering the widespread occurrence of hippocampal atrophy in individuals with AD [58]. Semantic

memory is also affected in early AD and is often reflected in difficulty finding words [59]. Additionally, there is an impact on visuospatial ability, including difficulties with orientation [60], while deficits in attention and processing speed have also been identified towards the later stages of the disease [7, 61]. A decline in executive function has also been observed in individuals with dementia, affecting higher-order processes such as inhibition, abstract thinking, and cognitive flexibility [62]. Executive function has been long associated with the integrity of the frontal lobes, and research indicates that decreased frontal lobe volume is correlated with a more pronounced longitudinal decline in executive functioning [63].

2.3.3 Diagnosis

Diagnosing dementia can be challenging due to its myriad causes, diverse pathologies, and symptoms that may overlap or not always be readily apparent [64]. Often, a firm diagnosis is not made until an average of 3.1 years after the onset of symptoms [65]. Figure 1 illustrates the typical pathway to diagnosis, which was derived from a 2007 survey conducted in New South Wales, Australia [65].

Dementia diagnosis is typically made following an evaluation of cognitive impairment, particularly in the memory domain [36]. It is important that any cognitive impairment observed is identified as a decline from a previous level of functioning [36]. This can be done using many different tests such as the commonly used Mini-Mental State Examination, the Montreal Cognitive Assessment [66, 67], or Addenbrooke's Cognitive Examination III (ACE-III) [68]. In addition to cognitive testing, it is important to conduct other forms of assessment to eliminate other potential causes of cognitive impairment and obtain an accurate diagnosis. According to Dementia Australia [69], a standard assessment to diagnose dementia may include a detailed medical history, physical and neurological examinations, laboratory tests including blood and urine tests, neuropsychological testing, and medical imaging. Typically, medical imaging techniques such as structural magnetic resonance imaging (MRI) are used to exclude non-degenerative or surgical causes of cognitive impairment, rather than to provide a definitive diagnosis of dementia[70]. However, MRI scans can be useful in identifying the presence of brain atrophy which can aid in the diagnostic process[71].

Given the delay between onset of dementia symptoms and diagnosis, therapeutic interventions often commence after significant neurodegeneration has already occurred.

Individuals at the point of diagnosis are typically experiencing challenges in performing their everyday activities and are no longer capable of driving (Figure 1). Earlier diagnosis of dementia, particularly in the preclinical stage, is essential to enhance the likelihood of success in preventing or slowing the progression of the disease in an effort to minimise these impacts. Medical imaging techniques, such as MRI, can be utilised to identify neuroimaging biomarkers of AD, such as atrophy and disruptions to neural networks [72]. Advanced MRI-based neuroimaging methods can also be applied to identify biomarkers of preclinical AD, such as reduced functional connectivity, lower fractional anisotropy, and decreased cerebral blood flow. While not currently able to be used as a standalone diagnostic tool, efforts are underway among researchers to standardise the scanning and analysis techniques employed in MRI, alongside the establishment of a database containing scans from individuals with dementia. This initiative aims to enable comparisons between an individual's scan and the database, facilitating the determination of whether the scan indicates normal ageing or the presence of dementia[71]. The ability to detect brain changes during the preclinical or early stages of dementia through diagnostic tools like medical imaging creates an opportunity to implement interventions sooner, whether through the development of medications or by addressing modifiable risk factors.

2.3.4 Modifiable risk factors

Twelve modifiable risk factors have been identified which may impact the likelihood of developing dementia. These include less education in early life; hypertension, hearing loss, obesity, excessive alcohol consumption, and traumatic brain injury in midlife; and smoking, depression, physical inactivity, diabetes, social isolation, and air pollution in late life (Figure 2) [10, 73]. It is believed that these factors account for around 40% of dementia risk, with hearing loss and less education considered the highest contributors.

Various mechanisms have been proposed to explain how these risk factors affect the likelihood of developing dementia, including their influences on cognitive function. For example, education during childhood is believed to enhance overall cognitive capacity, although the cognitive benefits tend to plateau after approximately 20 years of age. This underscores the significance of early-life education in promoting cognitive health and, consequently, guarding against dementia [10]. Numerous risk factors have also been linked to

brain atrophy, including conditions like hearing loss, which has been correlated with more pronounced volume reduction in the temporal lobe, including the hippocampus and entorhinal cortex. Additionally, hypertension in midlife has been linked to diminished brain volume [10]. Excessive alcohol consumption is also recognised for its association with alterations in brain structure, as well as cognitive impairment, with research indicating that consumption of more than 112 grams of alcohol per week is associated with right sided hippocampal atrophy [74]. Australian guidelines recommend no more than 100 grams of alcohol per week.

Other risk factors have been associated with a higher presence of dementia-related neuropathologies. For instance, air pollution, according to animal models, may expedite neurodegenerative processes through impacts on cerebrovascular and cardiovascular health, amyloid β deposition, and amyloid precursor protein processing [10]. Hypertension has also been tied to an increase in the volume of white matter hyperintensities. Additionally, severe traumatic brain injuries, including skull fractures, oedema, and brain injury or bleeding, are associated with widespread hyperphosphorylated tau pathology in both human and mouse models [10].

Given that diet has been associated with many of these modifiable risk factors including hypertension, obesity, diabetes, and depression [16, 17, 18, 75], it is worthwhile to explore the potential role that diet might have in mitigating the risk of dementia.

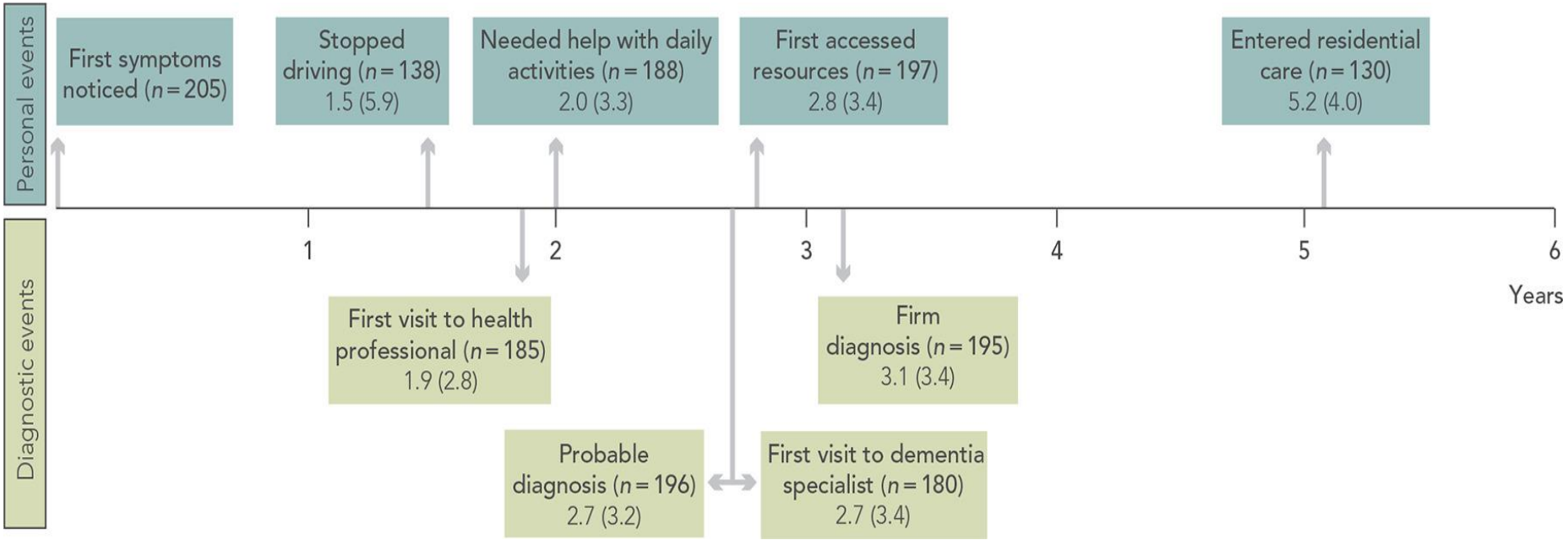

Figure 1 Pathway to diagnosis of dementia

Sourced from Speechly *et al.* [65]

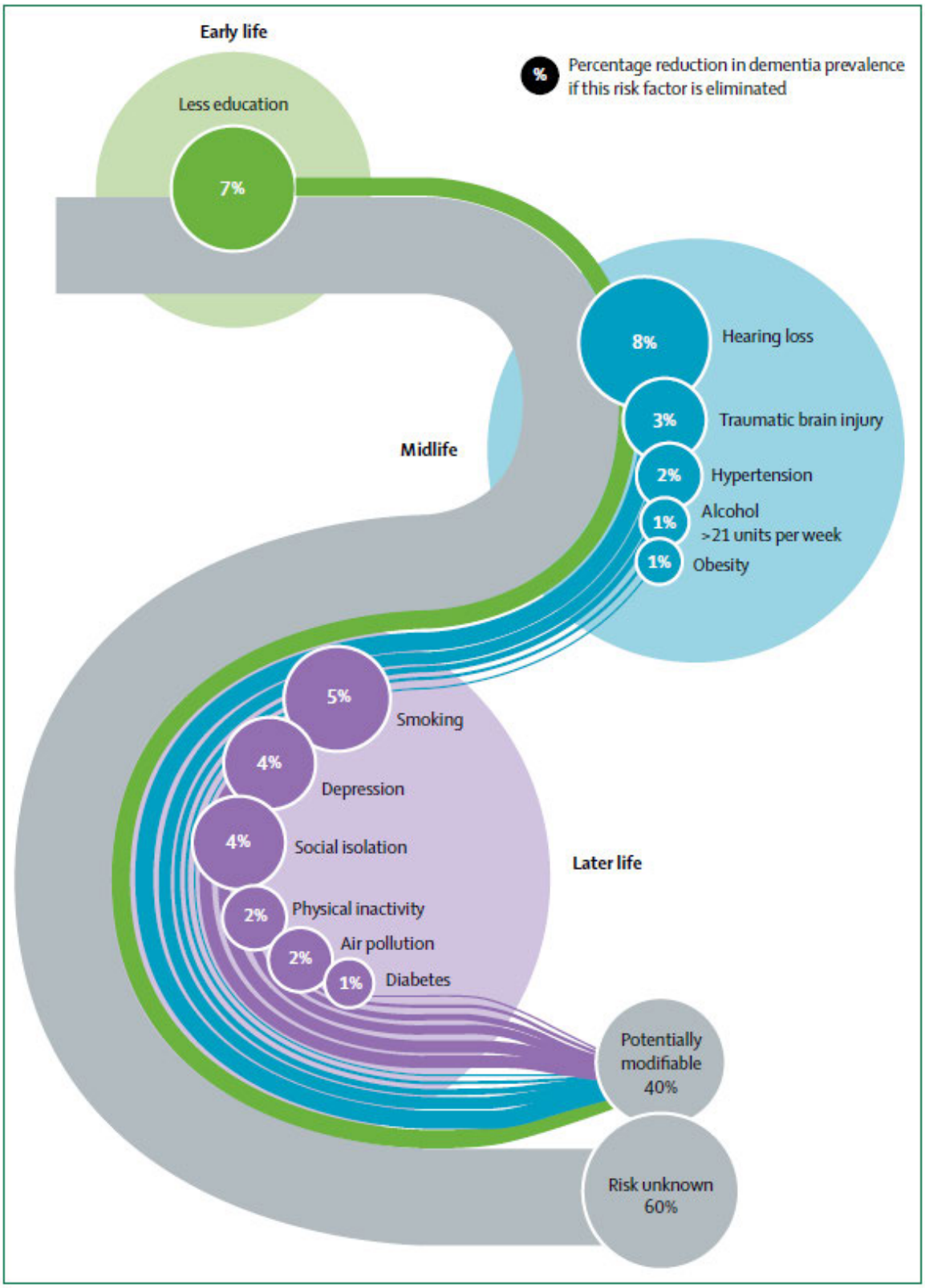

Figure 2 Population attributable fraction of potentially modifiable risk factors for dementia

Sourced from Livingston *et al.* [10]

2.4 Mediterranean and MIND diets

2.4.1 Mediterranean diet

The MedDiet, prevalent in countries within the Mediterranean like Greece, Spain, and Italy, mirrors the customary eating habits of this region. The MedDiet is characterised by several dietary components, including high intake of plant-based foods such as fruits and vegetables (particularly leafy greens), legumes, nuts, seeds, and grains; a high to moderate intake of fish; a moderate intake of dairy products, eggs, and poultry; and low intake of red meat and discretionary choices, such as sweet desserts [76, 77]. This diet also utilises olive oil as the main source of added fat and includes a moderate intake of alcohol, mainly consumed as red wine with meals [76, 77]. The recommended number of servings for each food group is typically represented as a diet pyramid, wherein the foods consumed in the greatest quantities appear in the largest section of the pyramid (Figure 3). While there are several different MedDiet pyramids in existence, each provides similar recommendations with some minor differences between them.

The mean energy content of the MedDiet, based on results from eight research articles, is approximately 9,316 kJ, with around 36.6% of this energy derived from total fat (18.8% from monounsaturated fatty acids (FA), 4.8% from polyunsaturated FA, and 4.8% from saturated FA), 42.8% derived from carbohydrate, and 14.9% from protein [78]. Polyphenols are abundant in the MedDiet, with olive oil and red wine providing a major source of these compounds.

Considering the anti-inflammatory properties of the MedDiet, a growing body of evidence indicates that following this dietary pattern may help mitigate conditions linked to chronic inflammation including metabolic syndrome, atherosclerosis, cancer, diabetes, obesity, and pulmonary diseases [47].

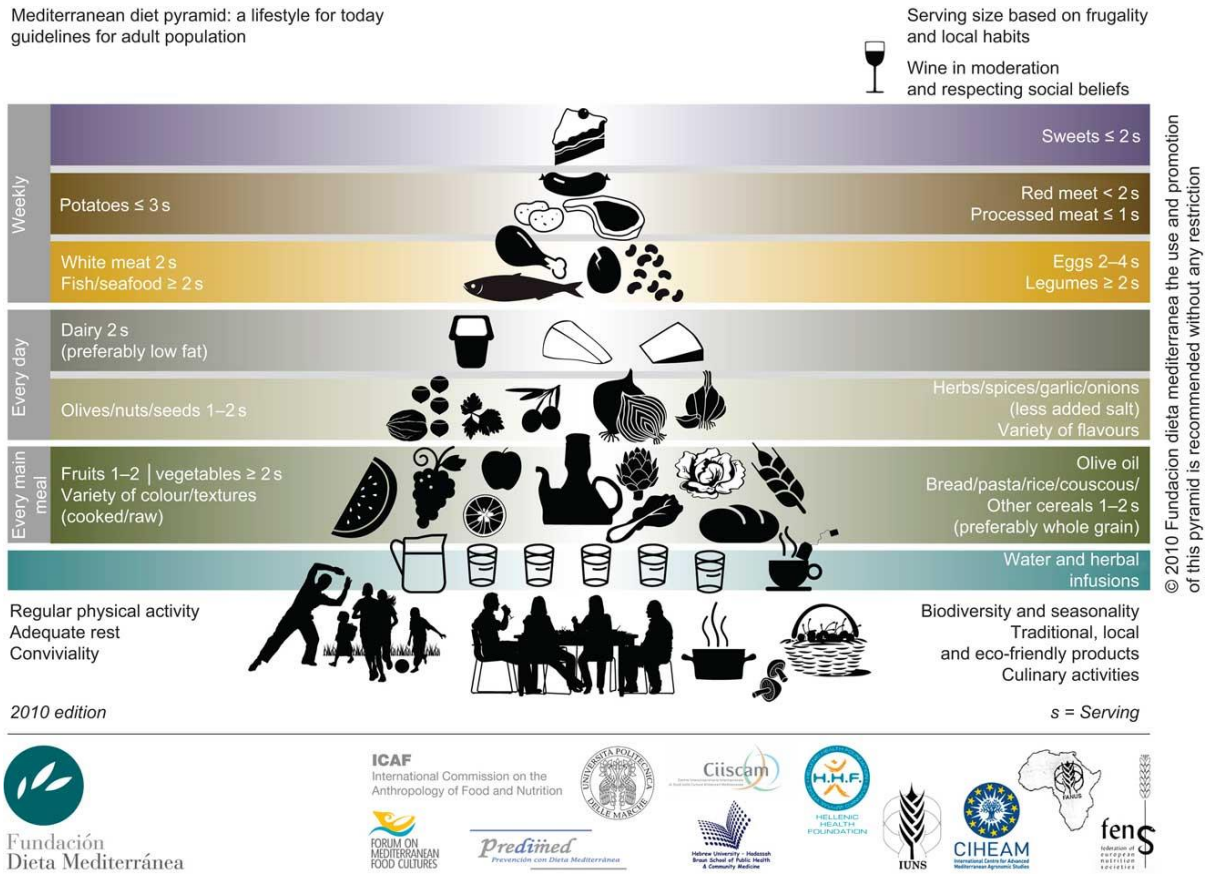

Figure 3 Mediterranean diet pyramid

Sourced from Bach-Faig *et al.* [76]

Mediterranean diet adherence in Australia

MedDiet adherence in Australia is generally low to moderate. Aridi *et al.* [79] analysed data from the National Nutrition and Physical Activity Survey (conducted between 2011-2013) and found that 20.5% of participants were in the lowest tertile of MedDiet adherence (0-3 out of 9), 65% of participants were in the middle tertile (4-6), and 13.9% were in the highest tertile (7-9). Another study, conducted by Davis *et al.* [80], investigated MedDiet adherence in an older Australian population over six months within an intervention group and a control group. The adherence scores at baseline were 7.1 ± 1.9 out of a total score of 15 in the intervention group, and 7.4 ± 2.4 in the control group, again demonstrating moderate adherence in this population. Similarly, Wade *et al.* [81] conducted an intervention study on older Australian adults, investigating the impacts of a MedDiet supplemented with dairy. They found that the participant average MedDiet adherence score was 5.4 out of 14 prior to

commencement of the trial. Once more, this shows a low to moderate adherence level within an Australian sample, corroborating the previous findings.

Results from the intervention studies by Davis *et al.* [80] and Wade *et al.* [81] demonstrate that, despite only moderate adherence levels in the Australian population in general, individuals can successfully achieve greater adherence to a MedDiet with intervention. In the former study, participants were able to adopt a MedDiet over a six-month period, significantly increasing adherence scores from baseline with an average score of 10.6 ± 1.7 after four months of intervention. Similarly, participants in the latter study were able to increase their score to 12.9 points out of 14, indicating a high level of adherence. This suggests that the MedDiet holds promise as a viable approach for enhancing the health of Australians, given the proven ability of individuals to adopt this dietary pattern.

2.4.2 MIND diet

The MIND diet was developed by Morris *et al.* [27] with the purpose of exerting protective effects on the brain. It was modelled on both the MedDiet and the Dietary Approaches to Stop Hypertension (DASH) diet. This dietary pattern, like the MedDiet, has an emphasis on plant-based foods with recommendations for lower intake of animal products and other foods high in saturated fat. However, unlike the MedDiet, the MIND diet specifically includes consumption of green leafy vegetables and berries, which have demonstrated protection against cognitive decline. Besides berries, Morris *et al.* [27] excluded fruit recommendations in the MIND diet as it was found, through a review of the literature, that prospective epidemiological studies of cognitive decline or dementia do not demonstrate any protective effect from general fruit consumption. Despite this, berries were included as they have been shown to provide protective benefits to cognition [27]. The MIND diet also does not recommend more than one fish meal per week which differs from MedDiet recommendations to consume up to six or more portions per week [1]. It was found that dementia risk was lowered with intake of just one fish meal per week, with no further benefits noted with additional fish consumption [27].

While the MedDiet generally recommends lower intake of discretionary choices, the MIND diet score includes specific categories for these foods, such as sweets and pastries, and fast

fried foods, of which lower consumption is recommended. In total, the MIND diet consists of 15 food categories: 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, fried/fast food). These food groups were included due to their relevance to incident dementia and cognitive decline [27].

2.5 Mediterranean and MIND diets for dementia prevention

The MedDiet and MIND diets are growing in popularity as a potential means to reduce dementia risk. Current research has demonstrated associations between higher MedDiet adherence and reduced dementia risk [82], as well as emerging evidence that the MedDiet can reduce low-grade systemic inflammation and oxidative stress, both of which have been proposed as risk factors for cognitive decline [21]. Similarly, research has shown that maintaining a moderate to high MIND diet adherence may decrease AD risk [28, 29], with evidence also suggesting that even moderate adherence may decrease this risk [28]. A summary of the current evidence supporting the potential protective role of the MedDiet and MIND diets on cognitive function and brain volume is presented in the following sections.

2.5.1 Mediterranean diet and cognitive function

Observational studies

Increased adherence to the MedDiet has been associated with better global cognitive function, as well as higher cognitive function across multiple domains, in both longitudinal and cross-sectional studies. In particular, higher MedDiet adherence has shown promising associations with memory, a domain often among the earliest affected by dementia. Karstens *et al.* [83] conducted a cross-sectional study on older adults in Chicago, Illinois (*n* = 82, mean age 68.8 years) and found higher MedDiet adherence was positively associated with learning and memory. Similarly, Ballarini *et al.* [84] and Anastasiou *et al.* [85] both analysed cross-sectional associations among older participants in Germany and Greece respectively (*n* = 512, mean age 69.5 ± 5.9 years; *n* = 1,865, mean age 73 ± 6 years) with varying levels of cognitive health, including participants with mild cognitive impairment

(MCI) and AD within the sample. Both studies found a positive association between higher MedDiet adherence and memory, including verbal and non-verbal memory. After excluding participants with MCI and AD, Anastasiou *et al.* [85] observed that results remained significant. Interestingly, Ballarini *et al.* [84] found no statistically significant association with working memory within their population. Longitudinal studies conducted by Rodrigues *et al.* [26] in Portugal (*n* = 76, mean age 66.4 ± 7.75 years) and Shannon *et al.* [86] in England (*n* = 8,009, mean age 55.0 years) have also identified increases in memory scores with higher MedDiet adherence in older populations.

In addition to seeing better memory scores with higher MedDiet adherence in their study population, Anastasiou *et al.* [85] also noted positive associations between the MedDiet and executive functioning in fully adjusted models. This is supported by Rodrigues *et al.* [26], who found that higher adherence to the MedDiet was associated with higher executive functioning scores. Contrary to these findings, and despite positive associations with memory, Karstens *et al.* [83] saw no association between executive function and higher MedDiet adherence.

Simple processing speed and verbal ability/language are additional domains that have shown positive associations with higher MedDiet adherence in a number of observational studies [85, 86, 87]. Karstens *et al.* [83], however, found no significant associations between MedDiet adherence and information processing. In addition to associations with specific cognitive domains, the MedDiet has been linked with higher global cognitive function [86, 88] and lower cognitive decline over time [88, 89]. Interestingly, the location in which studies were conducted seemed to be associated with differences in associations, with cross-sectional studies conducted in smaller sample sizes and in areas where MedDiet is predominantly consumed more likely to lead to positive associations.

Randomised controlled trials

While many observational studies have suggested that the MedDiet may be beneficial for cognitive function, a randomised controlled trial conducted by Knight *et al.* [90] in Adelaide, Australia showed no improvements in cognitive function after six months of MedDiet intervention. This study recruited 137 participants (mean age 72.1 ± 5.0 years) who were assigned either to a MedDiet, or a control diet in which they continued their usual dietary

intake. Memory, executive function, processing speed, visual-spatial ability, and global cognitive function were all assessed. However, the MedDiet group did not perform significantly better in any of these domains. Conversely, other randomised controlled trials have been conducted which have found encouraging results. Martínez-Lapiscina *et al.* [91] assessed 522 participants at high vascular risk in Navarra, Spain (mean age 74.6 ± 5.7 years), separating them into three intervention groups (MedDiet supplemented with extra-virgin olive oil, MedDiet supplemented with mixed nuts, and a low-fat control diet). Results indicated improvements in global cognition after 6.5 years in those adhering to both of the MedDiet interventions compared to the control diet. Valls-Pedret *et al.* [92] conducted a similar study in Barcelona, Spain, randomly assigning participants (*n* = 447, mean age 66.9 years) into three groups (MedDiet supplemented with extra-virgin olive oil, MedDiet supplemented with mixed nuts, and a control diet with advice to reduce dietary fat). After a median follow-up of 4.1 years, results were available for 334 participants. These demonstrated global and frontal cognitive improvements in the MedDiet group supplemented with olive oil, and significant memory improvement in the MedDiet group supplemented with mixed nuts, in comparison to the control group. Significant cognitive decline in global and frontal cognition, as well as memory, was seen in the control group at the end of the follow-up period compared to baseline. These results suggest that the MedDiet may require long-term adherence to exert beneficial effects on cognition, with supplementation of olive oil and/or mixed nuts being an important factor.

While many studies assessing MedDiet and cognitive function examine adherence to the MedDiet in its entirety, individual components of the MedDiet have also been associated with cognitive function. For example, green leafy vegetables have been associated with slower cognitive decline [93, 94] and better visuospatial and verbal abilities, while lower red meat intake has been associated with faster processing speed [87]. Similarly, Titova *et al.* [95] reported that lower self-reported meat intake was associated with higher scores obtained on the seven-minute screening test, a tool used in detection of AD, in a population of 1,016 older adults living in Sweden. However, this association was not statistically significant after adjusting for covariates.

Similar to the observational studies, findings from the RCTs suggest that location of study might be an important consideration, with studies conducted in Mediterranean countries often more likely to see positive effects.

2.5.2 MIND diet and cognitive function

Observational studies

Higher MIND diet adherence has been associated with better cognitive function in several studies, with current research suggesting that the MIND diet is superior to other plant-rich diets, such as the MedDiet, for improving cognitive function [31]. In a cross-sectional study by Wesselman *et al.* [96], consisting of 389 participants in Germany (mean age 69 ± 6 years), higher MIND diet adherence was associated with better memory in fully adjusted models. Similarly, in a longitudinal study consisting of 2,092 participants from the Framingham Heart Study in Massachusetts (mean age 61 ± 9 years), Melo van Lent *et al.* [30] also found a positive association between memory (visual and verbal) with MIND diet adherence, as well as higher global cognitive function, processing speed, and verbal comprehension/reasoning (mean follow-up time 66 ± 1.1 years). No significant associations were observed with cognitive decline. Additional longitudinal investigations have established links between the MIND diet and cognitive function. For instance, a study conducted by Cherian *et al.* [97] observed 106 participants from Chicago, Illinois (mean age 82.8 years) and discovered that individuals with higher adherence scores experienced a slower rate of global cognitive decline over a mean follow-up period of 5.9 years. Contrary to this, a prospective cohort study consisting of 16,058 women aged 70 and over from the Nurses' Health Study in North America did not find significant associations between MIND diet adherence and global cognitive decline over six years [98]. However, like previous studies, a higher MIND diet adherence score was associated with significantly higher verbal memory in all adjusted models [98].

Randomised controlled trials

Intervention trials investigating the impact of the MIND diet on cognitive function are currently scarce, with very few studies currently believed to be published. One study recruited 50 obese women (mean age 48 ± 5.4 years) in an RCT conducted in Iran, with 37 participants completing the study [99]. The intervention group contained 22 participants who

were instructed to follow a calorie-restricted modified MIND diet, while the control group included 15 participants who followed a calorie-restricted control diet over a period of three months. The results demonstrated a significant improvement in working memory within the intervention group compared to the control group, as well as better performance in tests assessing executive function and verbal recognition memory. The authors believed that this study was the first to investigate the effects of a short-term MIND diet intervention on cognitive function at the time of its publication. However, a more recent study has since been published, with recruitment of an older adult population and a larger sample size (*n* = 604) in the United States [100]. This study found no significant differences in cognition in those who followed a MIND diet over a three-year period compared to those on a control diet, both with mild caloric restriction. Global cognition was assessed, as well as four cognitive domains (episodic memory, semantic memory, executive function, perceptual speed), with similar improvements in global cognition scores observed in both groups.

2.5.3 Mediterranean diet and neuroimaging markers of dementia risk

Emerging evidence suggests that higher adherence to the MedDiet is associated with larger total brain volume [24] and less total brain atrophy over a three-year period [101] in older adult populations. Additionally, larger total grey matter volume [24, 102] and grey matter volume in the right parahippocampal gyrus and hippocampus [84] has also been observed. Karstens *et al.* [83] noticed a trend toward larger total hippocampal volume when comparing high MedDiet adherence to low adherence, although the results were not significant. Evidence has also been presented supporting the association between the MedDiet and larger total white matter volume [24], larger total dentate gyrus volume [83], greater cortical thickness in the orbitofrontal cortex, entorhinal cortex, and posterior cingulate cortex of the left hemisphere [103], and in the superior frontal region [24].

Despite this evidence, many studies have found no significant associations between MedDiet adherence and these brain volume measures. Pelletier *et al.* [104] assessed participants (mean age 73.0 years) from the Bordeaux Three-City study in France over an average of 8.9 years and found no significant association between MedDiet and grey matter or white matter volume in any brain region. Similarly, Titova *et al.* [95] conducted a cohort study on 194 Swedish participants aged 70 years at baseline with a five-year follow-up, but

found no associations between MedDiet adherence and total brain volume, total grey matter volume, or total white matter volume. Rodrigues *et al.* [26] noted a trend between higher adherence and larger total grey matter volume, however, the results were not significant in the fully adjusted model. While Luciano *et al.* [101] found a positive effect of MedDiet adherence on brain volume preservation in a Scottish cohort (*n* = 562, mean age 72.65 ± 0.72 years), they did not observe any significant protective effects on total brain volume, total grey matter volume, and total white matter volume in the fully-adjusted model. Differences in parcellation protocols used for analysis may explain some of the inconsistencies in these findings, as well as the use of varying dietary scoring methods and differing sample populations.

Like cognitive function, associations between individual components of the MedDiet and brain volume measures have been observed. Lower meat intake has been associated with increased total brain volume [24, 95] and total grey matter volume [24], with higher fish intake associated with an increase in total grey matter volume in the study by Gu *et al.* [24]. Luciano *et al.* [101], however, found no associations between meat and fish consumption and total brain volume or total grey matter volume.

2.5.4 MIND diet and neuroimaging markers of dementia risk

As the MIND diet is a relatively new dietary pattern, the existing body of research on it is not as extensive as that of the MedDiet, particularly regarding neuroimaging markers of dementia risk. Nevertheless, emerging evidence has shown positive associations between MIND diet adherence and preservation of the brain. In addition to observing protective effects of the MIND diet on various cognitive domains, Melo van Lent *et al.* [30] also found the MIND diet to be associated with larger total brain volume after adjusting for lifestyle and demographic covariates. However, no associations of statistical significance were seen with hippocampal volume or lateral ventricular volume. In another longitudinal study conducted in France over a median follow-up of 9.7 years (*n* = 175, mean age 75.8 ± 4.8 years), higher MIND diet adherence was associated with better white matter microstructure integrity, with no significant associations seen with grey matter volume [29]. Additionally, a study conducted by Agarwal *et al.* [105] found that higher MIND diet adherence was associated with 69% lower odds of hippocampal sclerosis in 581 deceased participants (*n* =

581, mean age at death 91.3 ± 6.1 years). The intervention trial conducted by Arjmand *et al.* [99] also analysed associations between the MIND diet and brain structure in their study population. The results demonstrated an increase in surface area of the inferior frontal gyrus in the MIND diet group compared to the control group. Conversely, the recent randomised controlled trial by Barnes *et al.* [100] revealed no differences in changes to white matter hyperintensity volume, hippocampal volume, or total grey and white matter volume between those following a MIND diet over three years compared to a control group. Given these mixed findings, additional research is warranted to better disentangle these associations. Moreover, exploring other regions of interest in the brain, especially those related to cognitive outcomes, is crucial for a comprehensive understanding of the potential benefits of the MIND diet.

2.6 Current limitations with Mediterranean diet adherence scoring

While there is encouraging evidence suggesting potential benefits of the MedDiet for cognitive function and brain volume, there is also evidence indicating no positive correlations between these factors and adherence to this dietary pattern. One possible explanation for the conflicting findings in the research may be the significant variation in how MedDiet adherence is assessed across different studies. Many *a priori* MedDiet scores exist in which higher intakes of healthier foods are awarded a higher number of points, and higher intakes of unhealthier foods are awarded a lower number of points (or no points) to achieve a total adherence score [1, 2, 32]. Each individual scoring method employs different scoring criteria, which can include the food groups assessed and overall range of the score. This creates discrepancies in perceived MedDiet adherence and reduces comparability between studies. These inconsistencies are highlighted in a study conducted by Milà-Villarroel *et al.* [106] wherein MedDiet adherence was assessed within the same population using 10 different *a priori* scoring methods. Mean adherence in this sample ranged from 22.7% to 87.7%, demonstrating the variability that can arise due to the application of many different scoring methods.

In addition to the lack of comparability owing to the variety of scoring systems used, inconsistency also exists between studies utilising the same scoring method due to the

process often employed to determine cut-off values for scoring. One of the most widely used MedDiet scores was developed by Trichopoulou *et al.* [32], in which participants are scored a 1 for consuming higher than the sex-specific within-population median intake for that particular food category, and 0 for consuming below this value. This method is appropriate within a Mediterranean population, such as Greece, in which the score was originally developed. However, in non-Mediterranean populations, such as Australia and the United States where this diet is not commonplace, this method creates inconsistent scoring of dietary components. Consequently, analysis of MedDiet adherence and health outcomes is often incomparable between studies [33], with varying findings presented. This is highlighted within the research conducted by Davis *et al.* [80]. This study demonstrated differing levels of adherence to the MedDiet within the same Australian sample when using sex-specific medians from the study population compared to using medians from the Greek cohort in the EPIC study conducted by Trichopoulou *et al.* [32]. Using the sample medians, baseline scores were 4.2 out of 10, whereas using the medians from the Greek cohort, baseline scores were lower at 2.8. This indicates that adherence scores may be inflated when utilising sex-specific medians from a Western sample population compared to using those from a Greek population, given the sex-specific medians would be lower in the former. Additionally, it is interesting to note that studies adopting the median intake values from the EPIC study's Greek cohort, which are typically higher than median intakes in Western populations, are more likely to observe associations between greater adherence and lesser cognitive decline and AD incidence [33]. This may be because individuals achieving higher adherence using Western population sex-specific medians may not be consuming a sufficiently high quantity of a MedDiet to elicit any protective benefits. In contrast, those achieving high adherence using the Greek sex-specific medians are likely to be consuming larger quantities of these foods, potentially providing more protection to the brain.

2.7 Summary

Dementia is an umbrella term for a number of diseases affecting the brain, with AD being the most prevalent among them. AD is characterised by brain atrophy and cognitive deterioration, with the latter often manifesting as an initial clinical symptom. Both the MedDiet and MIND diet emphasise a rich plant-based approach, exhibiting positive effects

on overall health. However, prior research provides mixed evidence on their potential to protect brain volume and cognition. The following chapter will investigate these dietary patterns within an older adult population to ascertain whether any potential associations with cognitive function can be identified.

3 Associations between Mediterranean diet and MIND diet adherence with cognitive function in older Australian adults

3.1 Chapter overview

This chapter aimed to determine whether there are any associations between higher adherence to the Mediterranean diet (MedDiet) or Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and cognitive function within a cross-sectional study of older Australian adults. Higher adherence to the MIND diet was positively associated with executive function after adjusting for sociodemographic and cardiovascular risk factors. However, this became non-significant after further adjusting for depression. No associations were seen between the MIND diet and global cognition or with any of the other cognitive domains. Further, no associations were found between the MedDiet and cognition. This may be attributed to the population recruited in this study who were generally healthy and highly educated. Inconsistencies in diet scoring due to limitations in dietary data may have also impacted results. Weighed food records are recommended in future studies to limit potential over- or under-reporting of dietary intake. Longitudinal studies would be beneficial to observe the effect of the MedDiet and MIND diet on cognitive decline in this population.

3.2 Abstract

Introduction

Reduced cognitive function is a hallmark of dementia, a cluster of diseases which currently have no cure or effective treatments. There is emerging evidence for the role of diet in the prevention of cognitive decline, particularly for the Mediterranean diet (MedDiet) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. However, the current findings are inconclusive and vary across studies which may be due to differences in methodologies.

Methods

Cross-sectional baseline data were used from 406 older adults from the ACTIVate study (65.5 ± 3.0 years old, 69.7% female), a prospective longitudinal cohort study aiming to examine associations between time-use and diet compositions, cognition, and brain function. Diet data was collected using the Australian Eating Survey (AES). Two scoring methods were used to calculate MedDiet adherence from the AES. MIND diet scores were additionally calculated using this data. Global cognitive function was assessed using Addenbrooke's Cognitive Examination III (ACE-III), and the Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess four cognitive domains (short-term and working memory, long-term storage and retrieval, executive function, processing speed). Linear regression models were used for data analysis in three adjusted models, with diet scores modelled as both continuous and categorical (tertiles) variables. Type II F tests were used to test for overall variable significance, with corresponding p-values adjusted for false discovery rate using the Benjamini-Hochberg method.

Results

Higher adherence to the MIND diet was associated with better executive function after adjusting for demographic variables (β ± SE = 0.044 ± 0.017, p = 0.009) and cardiovascular risk factors (β ± SE = 0.035 ± 0.017, p = 0.036). However, the latter did not survive false discovery rate adjustment. Additionally, after further adjusting for depression, the association was no longer statistically significant. No associations were found between the

MIND diet and the other cognitive domains or with global cognitive function. Furthermore, no associations were elucidated between the MedDiet and cognitive outcomes.

Conclusion

MedDiet was not associated with cognitive function in a sample of healthy older adults. While the MIND diet was associated with executive function in this study, results should be interpreted with caution as the effect size was low, and significance was lost after adjusting for depression. Analysis of longitudinal data in the current population would be beneficial to assess the relationship between the MedDiet and MIND diet and cognitive decline. Future research should focus on populations with varying levels of health and education, whilst avoiding the use of MedDiet scoring systems utilising sex-specific medians.

3.3 Introduction

Dementia is currently the second leading cause of death in Australia and the leading cause of death for Australian women [107]. More recently, dementia became the leading cause of disease burden in Australians aged 65 years and over [4]. At present, there are limited choices for pharmacological interventions capable of slowing or preventing the progression of dementia, with those currently available still in the early trial phases and not indicated for all [108, 109]. Consequently, the focus for prevention has shifted towards alternative approaches. It is believed that around 40% of dementia is potentially preventable through modifiable risk factors [110], with increasing evidence pointing to the role that diet may play.

Healthful diets, such as those high in vegetables and certain antioxidants, have been linked to lower cognitive decline [13, 111], a promising finding given that cognitive deficits are more pronounced in those with dementia compared to what is typically observed in normal ageing [7]. Specifically, a growing body of research indicates that both the Mediterranean diet (MedDiet) as well as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet can exert protective effects against cognitive deficits. The MedDiet and MIND diet both focus on a rich intake of plant-based foods and whole grains, with minimal consumption of foods high in saturated fat such as red meat and discretionary foods. For detailed definitions of the MedDiet and MIND diet please see chapter 2, section 2.4 (pages

18-21). As well as showing benefits for global cognition [30, 86, 88] and reduced cognitive decline [88, 89, 97], these dietary patterns have also demonstrated an association with higher function in several cognitive domains including memory [26, 30, 83, 84, 85, 86, 96, 99], executive function [26, 85, 99], and processing speed and verbal ability/language [30, 85, 86, 87]. At present, the number of studies investigating the MIND diet are not as prevalent as the MedDiet. However, they have thus far demonstrated promising results, with current evidence suggesting that the MIND diet may be more effective than the MedDiet and other plant-based diets for dementia prevention [31]. Despite compelling favourable evidence for these dietary patterns, studies have also been published demonstrating no protection against cognitive decline, and no beneficial impact on general cognitive function and in specific domains [30, 90, 98, 112]. This makes it challenging to draw definitive conclusions regarding the efficacy of these dietary patterns for dementia prevention. For further information on the associations between the MedDiet and MIND diet and cognition based on previous evidence, please see chapter 2, sections 2.5.1 and 2.5.2 (pages 21-25).

A key limitation of previous research is that many studies have utilised inconsistent scoring methods to determine MedDiet adherence, which leads to difficulty comparing results across studies and may assist in explaining why research findings differ. In addition to a variety of scoring methods utilised, which can output varying levels of adherence to the MedDiet even within the same population [106], issues can arise even between studies utilising the same scoring method due to the process often employed to determine cut-off values for scoring. Trichopoulou *et al.* [32] developed an *a priori* scoring method to calculate MedDiet adherence, in which participants are scored a 1 for consuming higher than the sex-specific within-population median intake for each food category within the MedDiet, and 0 for consuming below this value. Using the sex-specific median values of intake is appropriate within a Mediterranean population such as Greece, where the score was originally developed. Nonetheless, in non-Mediterranean populations such as Australia, where this diet is less prevalent, this approach introduces inconsistencies in scoring due to the greater variability in diets within these populations. Given that this is one of the most widely used MedDiet scores in the current literature, analysis of MedDiet adherence and health outcomes are often incomparable between studies, with varying findings presented. Utilisation of scoring methods with pre-determined cut-off values would enhance the

comparability across studies and aid in the ability to provide recommendations on whether adopting a MedDiet can positively influence cognition, as well as how closely this diet should be adhered to.

The present study aims to investigate the association between adherence to the MedDiet and MIND diet and cognitive function in older Australian adults using diet data obtained from the Australian Eating Survey (AES). Diet scoring methods using pre-set cut-off values will be used rather than the use of sex-specific medians to determine score cut-offs. It is hypothesised that higher adherence to these diets will be associated with higher global cognition and memory scores.

3.4 Methods

3.4.1 Study population

The study population was comprised of individuals from the ACTIVate study, a prospective longitudinal cohort study of older adults residing in Adelaide, South Australia and Newcastle, New South Wales. Details about the aims and design of the ACTIVate study have been described previously [34]. Participants recruited were aged between 60 and 70 years at the time of enrolment. The Montreal Cognitive Assessment-Blind (MoCA-B) was administered to screen for dementia, with a cut-off score of 13 out of 22 used to identify significant cognitive impairment and thus exclusion from the study. Participants with diagnoses of intellectual or physical impairment, neurological or psychiatric conditions were also excluded, as well as those with history of stroke. Four-hundred and twenty-six participants were successfully enrolled at baseline, with 226 recruited in Adelaide and 200 in Newcastle. The study was approved by the University of South Australia's Human Research Ethics Committee (202639), and all participants gave written informed consent.

3.4.2 Procedure

Participants living in Adelaide attended the University of South Australia Clinical Trial Facility, and those residing in Newcastle attended the University of Newcastle Functional Imaging Laboratory for baseline data collection. Visits consisted of acquisition of written informed consent, followed by blood pressure and anthropometric measurements.

Completion of general health and dietary assessments were then conducted, followed by administration of cognitive tests [34].

3.4.3 Dietary assessment

Dietary intake was assessed via administration of the AES, a semi-quantitative food frequency questionnaire (FFQ) that has been validated against four-day weighed food records (WFR) for use in adult populations [113]. The AES includes 120 food and beverage items and allows for the determination of habitual intake over a six-month period by asking participants to indicate how often they consumed each item or items from within a given group (e.g., English muffin, bagel or crumpet). Participants were provided with multiple choice options from which to answer (e.g., never, less than 1 per month, once per week, 2-4 per week). Natural portion sizes were used to determine serving sizes where applicable, such as one apple. Serving sizes for other items were determined using data derived from the National Nutrition Survey published in 1998 and from unpublished data from the Australian Bureau of Statistics [113]. Additionally, the inclusion of a separate questionnaire to assess oil intake was used as this information is not captured by the AES. This survey was based on the polyunsaturated fatty acids questionnaire developed by Swierk et al. (2011).

3.4.4 Mediterranean diet scores

In order to calculate MedDiet scores from the AES diet data, two distinct scoring methodologies were employed. The rationale behind selecting two scoring systems is due to the variety of scoring systems available, with no single score having been identified as superior to the others. Both scoring systems chosen are literature-based, however, the authors have focused on different aspects of the literature to guide score creation. The first score, hereafter referred to as P-Med Score, was developed by Panagiotakos *et al.* [1] and comprises 11 dietary components (non-refined cereals, potatoes, fruits, vegetables, legumes, fish, red meat and products, poultry, full fat dairy, olive oil, alcohol), with each component scored from 0-5 depending on adherence to the traditional Greek MedDiet (Appendix 1). Olive oil intake was measured in mL/day, with a score of 0 assigned for no consumption, 1 for <10mL/day, 3 for 10-20mL/day, and 5 for >20mL/day. Possible MedDiet score ranged from 0 to 55, where higher scores corresponded to greater adherence. This

scoring method was chosen as it derives its cut-off values for each food group from the suggested intake according to the MedDiet pyramid. This scoring method also includes an additional group for potatoes which is not typically separated from vegetables in the MedDiet pyramid, but was included separately due to the reported benefits on cardiovascular disease risk markers due to the presence of vitamins C, B1, and B2, niacin, carbohydrates, fibre, potassium and magnesium [1].

The second MedDiet score, hereafter referred to as S-Med Score, was based on the score developed by Sofi *et al.* [2]. This method includes nine different food categories (fruit, vegetables, legumes, cereals, fish, meat and meat products, dairy products, alcohol, olive oil), with each component incurring a score from 0-2 (Appendix 2). Food groups reflective of a typical MedDiet (fruit, vegetables, cereals, legumes, fish) gained 2 points for the highest consumption category, 1 point for the middle category and 0 points for the lowest category. Food groups atypical of the MedDiet (meat and meat products, dairy products) were scored 2 points for the lowest category, 1 point for the middle category and 0 points for the highest consumption category. Alcohol was scored 1 point for the lowest consumption category, 2 points for the middle category and 0 points for the highest category. Olive oil was given a score of 0 for occasional use (<10mL/day), a score of 1 for frequent use (10-20mL/day), and a score of 2 for regular use (>20mL/day). Possible total score for this method ranged from 0 to 18, with higher scores corresponding to greater adherence. For this study, serve sizes calculated by the AES were used to determine one portion of fruits, vegetables, cereals, legumes, fish, meat and meat products, and dairy products, rather than using the weighted portion sizes originally outlined by Sofi et al. as food weight in grams was not available. This scoring method was chosen as it utilises a different method to that of the P-Med Score for determining scoring cut-off values. Rather than modelling this scoring system on the traditional MedDiet pyramid, this study utilised data from prospective cohort studies investigating MedDiet and health outcomes to determine cut-off values for intake of each food group for score calculation.

3.4.5 MIND diet score

The MIND diet score was developed by Morris *et al.* [27] and includes 15 food categories: 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans,

whole grains, seafood, poultry, olive oil, wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, fried/fast food) (Appendix 3). A score of 1 was given for olive oil consumption if used as the primary oil, otherwise a score of 0 was applied. The other components were scored 0, 0.5, or 1 depending on consumption frequency, with a possible total score ranging from 0 to 15, where a higher score indicates greater adherence. The consumption frequencies for the fried/fast food category were altered from 4+ times/week to 5+ times/week for a score of 0, and from 1-3 times/week to 1-4 times/week for a score of 0.5 to align with the data obtained from the AES. Pineapple was included within the 'berries' category as these food items were grouped together in the AES.

3.4.6 Cognitive assessment

Addenbrooke's Cognitive Examination III (ACE-III) was administered by trained interviewers at each testing site to assess global cognitive function. The ACE-III assesses cognitive function across five domains: attention, memory, fluency, language, and visuospatial ability. Scores from each domain were pooled to obtain a total score ranging from 0 to 100, with a higher score representing higher cognitive function. The ACE-III has been validated for use as a screening tool for cognitive deficits seen in frontotemporal dementia and Alzheimer's disease (AD) and displays high internal reliability (Cronbachs $\alpha = 0.88$), high sensitivity (1.00), and high specificity (0.96) for dementia detection with a cut-off score of 88 [(114)].

Tests were also administered from the Cambridge Neuropsychological Test Automated Battery (CANTAB), with composite scores computed for four cognitive domains (short-term and working memory, long-term storage and retrieval, executive function, and processing speed). Briefly, raw scores were converted to standardised z-scores using the baseline population mean and standard deviation and averaged to form each composite using the Cattell-Horn-Carroll-Miyake cognitive domain taxonomy as a guiding framework. This taxonomy was chosen by the wider group working on the ACTIVate study due to its separation of cognitive sub-domains of interest such as short-term and working memory. The outcome measures utilised to construct each cognitive composite are presented in Table 1. Further information on this process was detailed in the paper by Mellow *et al.* [(115)].

Table 1 CANTAB tests and outcome measures included within each cognitive domain

Cognitive domain	CANTAB test	CANTAB outcome measure
Short-term and working memory	Verbal Recognition Memory (VRM)	Immediate recognition (total correct)
		Immediate free recall (total correct distinct words)
	Paired Associates Learning (PAL)	Total errors (adjusted)
		First attempt memory score
Long-term storage and retrieval	Verbal Recognition Memory (VRM)	Delayed recognition (total correct)
Executive function	Multitasking Test (MTT)	Total incorrect responses
		Median response latency multitasking cost
		Median response latency incongruency cost
	One Touch Stockings of Cambridge	Problems solved on first choice
		Median latency to first choice
Processing speed	Reaction Time (RTI)	Median simple reaction time
		Median 5-choice reaction time
		Median simple movement time
		Median 5-choice movement time

CANTAB, Cambridge Neuropsychological Test Automated Battery.

3.4.7 Covariates

Covariates included in the current study were age (years), sex, education (number of years of formal education), body mass index (BMI), total energy intake (kJ/day), physical activity (minutes/day), smoking (never, former, or current), diabetes, hypertension, hyperlipidaemia, and depression status. Information on age, sex, education, and smoking status was collected at participants' baseline interview. Total energy intake was calculated based on responses to the AES. Average minutes per day of physical activity was based on accelerometry data obtained over a seven-day period, as described elsewhere [115]. Measurements of weight (kg) and height (metres) were used to calculate BMI. Hypertension history was determined by measured blood pressure (average of 3 measurements $\geq$140 mmHg systolic or $\geq$90 diastolic), self-reported medical diagnosis, or current use of hypertensive medications. Diabetes history and hypercholesterolaemia were determined by self-reported medical diagnosis or current use of medications. Depression was assessed using the Center for Epidemiologic Studies Depression (CES-D) scale which is a self-rated score ranging from 0 to 60, in which a higher score is associated with higher symptomatology. A cut-off score of 16 was used to indicate presence of depression [116].

3.4.8 Statistical analysis

Statistical analysis was performed using R Statistical Software v4.1.2 [117]. Adherence to each dietary score was divided into tertiles for descriptive purposes and for use in the main analyses. To examine any differences in participant baseline characteristics between differing levels of diet adherence, mean and standard deviations are presented for continuous variables and percentages given for categorical variables within each tertile. Differences between tertiles for each score were evaluated using analysis of variance (ANOVA) for continuous variables and Chi-Square test for categorical variables.

In the main analyses, diet scores were analysed as both continuous variables (linear) and categorical variables (tertiles). Multiple linear regression models were used to examine the association between each dietary score with each of the four cognitive domains as well as global cognitive function, with adjustments for covariates across three models as described below. Type II F tests were then used to test for overall significance, and corresponding p-values from each model were adjusted for false discovery rate using the Benjamini-

Hochberg method [118]. Results are presented in-text as β-coefficients and standard errors (SE), with p-values reported in-text representing corrected values from ANOVA outputs.

Three models were used to adjust for a range of covariates in a stepwise manner. Model 1 adjusted for potential confounders with the most recognised evidence for association with AD including age, sex, education, BMI, and physical activity [10, 28]. Additionally, total energy intake was included in this model due to its relevance to diet and the impact this may have on dietary adherence scores. Model 2 adjusted for model 1 plus cardiovascular risk factors which have been shown to mediate dietary effects on dementia, including smoking status, diabetes, hypertension, and hyperlipidaemia [28]. Model 3 adjusted for model 2 plus depression status which may act as an effect mediator but has a complex cause and effect relationship with dementia, with reverse causation possible [10, 28].

Sensitivity analyses

Analyses were repeated as described previously with participants stratified by sex (male and female). Additional analyses were also conducted with participants stratified by age (60 to 65, 66 to 70).

3.5 Results

Of the 426 participants recruited in this study, 406 had valid data for both dietary and cognitive assessments. 7 participants had invalid dietary data, 2 were missing dietary data, and 11 were missing cognitive data. Invalid dietary assessment data was determined based on the following energy intake criteria: <2,092kJ or >14,644kJ for women and <3,347kJ or >17,573kJ for men [119].

Baseline participant characteristics

The study population was on average 65.5 ± 3.0 years of age and primarily female (70.7%), with a mean education of 16.5 ± 3.2 years. Table 2 shows participant characteristics according to tertiles of adherence to each of the dietary scores, where a higher tertile number represents higher dietary adherence. Within the MIND diet score, there were more females present in the group with high adherence (tertile 3) compared to low adherence (tertile 1), with a higher proportion also evident in the group with medium adherence

(tertile 2) compared to low adherence. Mean BMI was lower in those with medium and high adherence to the P-Med Score and MIND diet compared to the lowest adherence. The MIND diet also showed a lower BMI in those with high adherence compared to medium adherence, while the S-Med Score only showed lower BMI for high adherence compared to low adherence. Participants achieving medium and high adherence to the P-Med Score had higher levels of physical activity than those with lowest adherence, while those with high MIND diet adherence had higher levels of physical activity than those with low adherence. Further, prevalence of hypertension was lower in those with medium and high adherence to the MIND diet compared to the lowest adherence.

Associations between diet adherence and cognitive function

P-Med Scores ranged from 23 to 47 (out of 55, mean = 34.4 ± 4.2), while scores ranged from 4 to 17 (out of 18, mean = 11.1 ± 2.3) for the S-Med Score (Figure 1). MIND diet scores ranged from 4 to 13.5 (out of 15, mean = 9.3 ± 1.6) (Figure 1).

Table 2 Participant baseline characteristics according to tertiles of Mediterranean and MIND diet scores

Characteristic	**P-Med Score**				**S-Med Score**				**MIND diet score**			
	Tertile 1 (16-33)	Tertile 2 (34-36)	Tertile 3 (37-47)	*p*-value	Tertile 1 (4-10)	Tertile 2 (11-12)	Tertile 3 (13-17)	*p*-value	Tertile 1 (4-8.5)	Tertile 2 (9-10)	Tertile 3 (10.5-13.5)	*p*-value
n	160	118	128		155	139	112		140	155	111	
Age, mean ± SD, years	65.4 ± 2.9	65.4 ± 3.01	65.7 ± 3.01	0.624	65.4 ± 3.0	65.6 ± 3.0	65.5 ± 2.9	0.706	65.2 ± 3.06	65.3 ± 2.8	66.1 ± 3.0	0.054
Sex, % female	64.4	72.0	77.3	0.052	64.5	74.8	74.1	0.099	58.6	76.8	77.5	**<0.001*** **
Education, mean ± SD, years	16.5 ± 3.2	16.1 ± 3.09	17.0 ± 3.3	0.133	16.6 ± 3.3	16.3 ± 3.0	16.8 ± 3.3	0.582	16.3 ± 3.4	16.6 ± 3.2	16.7 ± 2.9	0.593
BMI, mean ± SD	28.4 ± 5.5	26.2 ± 4.4	25.8 ± 4.9	**<0.001*** **	27.9 ± 5.3	26.8 ± 5.1	25.8 ± 4.6	**0.003** **	28.2 ± 5.7	26.9 ± 4.8	25.4 ± 4.4	**<0.001*** **
Total energy (kJ/day), mean ± SD	8562.3 ± 2721.1	8803.2 ± 2520.5	9209.2 ± 2290.6	0.098	8615.8 ± 2754.7	8789.0 ± 2472.1	9200.2 ± 2290.4	0.173	8991.1 ± 2754.1	8920.8 ± 2385.1	8523.0 ± 2470.1	0.306
Physical activity (mins/day), mean ± SD	248.3 ± 79.2	276.1 ± 82.9	275.0 ± 77.8	**0.004** **	255.5 ± 80.9	273.5 ± 86.3	267.0 ± 72.6	0.162	249.5 ± 75.8	267.7 ± 81.4	279.7 ± 83.3	**0.012***

Smoking, % never	56.9	65.3	58.6	0.507	58.7	59.7	61.6	0.484	60.0	60.0	59.5	0.987
Diabetes, %	7.5	6.8	1.6	0.064	7.1	5.8	2.7	0.283	3.6	7.1	5.4	0.410
Hypertension, %	53.8	44.9	46.9	0.290	51.0	51.1	43.8	0.424	59.4	43.2	44.1	**0.011***
Hyperlipidaemia, %	40.0	33.9	33.6	0.439	36.1	36.0	36.6	0.994	40.0	31.0	38.7	0.221
Depression, %	7.5	5.9	6.3	0.853	7.7	7.2	4.5	0.542	10.0	5.8	3.6	0.113

Abbreviations: P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; *n*, sample size; SD, standard deviation; BMI, body mass index; kJ, kilojoules; mins, minutes.
Participant characteristics were compared between tertiles for each score using ANOVA for continuous variables and Chi-Square test for categorical variables.
*p < 0.05, **p < 0.01, ***p < 0.001.

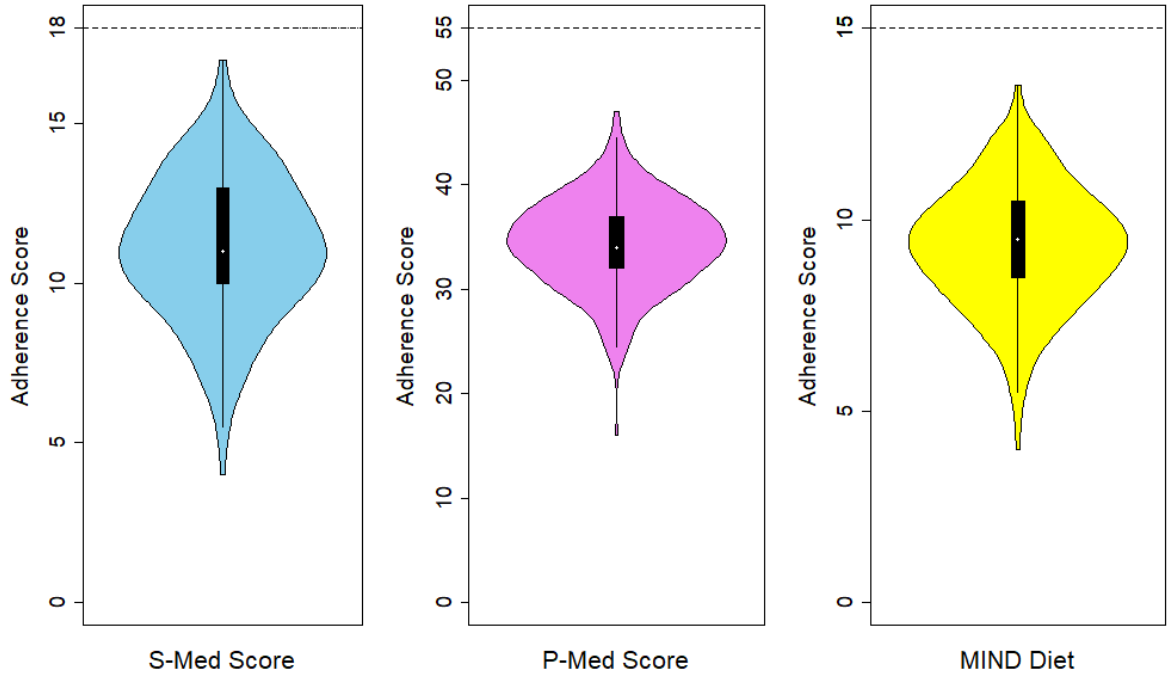

Figure 1 Violin plots of dietary adherence scores for the S-Med Score, P-Med Score and MIND diet. Adherence scores for each dietary pattern are presented on the y-axes, showing minimum and maximum achievable scores (maximum score is denoted with a dashed line). The central black box represents the interquartile range, spanning from the first quartile to the third quartile. The central white dot represents the median of the data.

Relationships between cognition and diet were analysed using both linear (continuous) and non-linear (categorical) variable types for dietary adherence scores. As the findings were similar for both sets of models, the effect estimates for the continuous linear associations are presented in Table 3 and discussed in the main text. The categorical (tertile) estimates are available in Supplementary Table 1.

Higher MIND diet adherence was associated with higher executive function (β ± SE = 0.044 ± 0.017, p = 0.009) after adjusting for covariates in model 1 (age, sex, education, BMI, energy intake, physical activity). A significant association remained after adjusting for cardiovascular risk factors (model 1 + smoking status, diabetes, hypertension, hyperlipidaemia) (β ± SE = 0.035 ± 0.017, p = 0.036). However, further adjustment for depression in model 3 attenuated this association (β ± SE = 0.033 ± 0.017, p = 0.051). After false discovery rate adjustments were applied, significance was lost for model 2 (p = 0.145), but still remained for model 1 (p = 0.025). No significant associations were found between

the MIND diet and any of the other cognitive domains or global cognition in all adjusted models ($p \geq 0.05$).

There were no observed relationships between either of the MedDiet scores and cognition in any of the adjusted models ($p \geq 0.05$).

Sensitivity Analyses

Significant associations were identified among females between MIND diet adherence and global cognition ($p = 0.043$), as well as with executive function ($p = 0.022$) in model 1 (Supplementary Table 2). However, significance for both associations did not survive false discovery rate adjustment. Conversely, no associations were observed between any dietary patterns and cognitive function in males (Supplementary Table 3).

Within the younger age group (60-65 years), a significant association was found between MIND diet adherence and executive function ($p = 0.009$) in model 1 (Supplementary Table 4). This significance persisted even after correcting for false discovery rate ($p = 0.032$). However, significance was lost upon further adjustment for covariates in models 2 and 3. No associations were evident in the older age group (66-70 years) (Supplementary Table 5).

Table 3 Statistical output of ANOVA type II F tests for cognitive outcomes among participants in the ACTIVate study, with dietary scores modelled as continuous variables

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	0.026	0.873	0.873	0.856	0.356	0.711	1.306	0.254	0.630	0.018	0.894	0.894	0.729	0.394	0.889
	Model 2	0.001	0.980	0.993	0.524	0.470	0.805	1.336	0.248	0.507	0.133	0.716	0.772	0.247	0.619	0.825
	Model 3	0.001	0.980	0.993	0.569	0.451	0.733	1.331	0.250	0.540	0.141	0.708	0.767	0.246	0.621	0.807
S-Med Score	Model 1	0.335	0.563	0.643	0.801	0.371	0.661	1.644	0.201	0.535	0.625	0.430	0.527	0.568	0.451	0.876
	Model 2	0.434	0.510	0.578	0.492	0.483	0.829	1.262	0.262	0.539	0.364	0.547	0.734	0.201	0.654	0.850
	Model 3	0.431	0.512	0.626	0.439	0.508	0.825	1.200	0.274	0.594	0.235	0.629	0.814	0.264	0.608	0.790
MIND diet	Model 1	0.066	0.798	0.798	0.118	0.731	0.929	0.024	0.876	0.876	6.802	**0.009**	**0.025***	0.520	0.471	0.877
	Model 2	0.001	0.971	0.990	0.011	0.918	0.965	0.032	0.858	0.903	4.421	**0.036**	0.145	1.680	0.196	0.587
	Model 3	0.001	0.974	0.990	0.005	0.947	0.970	0.020	0.888	0.962	3.851	0.051	0.187	1.463	0.227	0.646

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [1]; S-Med Score, Mediterranean diet score developed by Sofi et al. [2]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for age, sex, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression.

Bold denotes statistical significance ($p \leq 0.05$). * denotes *p*-values that remained significant after false discovery rate adjustment.

3.6 Discussion

This study investigated the associations between adherence to a MedDiet and cognitive function, as well as adherence to the MIND diet and cognitive function, within an older adult population in Australia. Results demonstrated that participants with higher adherence to the MIND dietary pattern performed better in executive functioning tasks compared to those with lower adherence after adjusting for covariates in model 1 (age, sex, education, BMI, energy intake, physical activity) and model 2 (model 1 + smoking, diabetes, hypertension, hyperlipidaemia). After further adjusting for depression, this association became non-significant, suggesting that depression may have confounded the initial associations that were seen. It is also important to note that significance did not survive false discovery rate adjustment for model 2, which further reduces the reliability of these findings.

Previous research has demonstrated positive associations between the MIND diet and other cognitive domains including memory, processing speed, verbal comprehension/reasoning, and general cognitive function. Yet, less research exists on the effect of this dietary pattern on executive functioning. The initial significant findings in the present study are consistent with a recent randomised controlled trial conducted in obese women in Iran by Arjmand *et al.* [99], in which participants adhering to a calorie-restricted MIND diet demonstrated significantly greater performance in tests assessing executive function compared to a calorie-restricted control diet. It is worth mentioning that this study did not adjust for any potential confounding factors such as education and depression. The sample population was also quite different to that of the present study, consisting of a younger cohort of obese women (mean age = 48 ± 5.38 years), and therefore the benefits seen cannot necessarily be generalised to other population groups such as older adults in Australia. In contrast, Wesselman *et al.* [96] conducted a cross-sectional analysis examining data from 389 older German participants (mean age = 62 ± 6 years), which did not uncover any notable correlations between adherence to the MIND diet and executive function. Furthermore, a randomised controlled trial was conducted on older adults (mean age 70.4 ± 4.2) in which 301 participants were assigned to a MIND diet and 303 to a control diet, both with caloric restriction [100]. No significant differences were found in changes to executive function

between the two groups over a 3-year period. This further supports the results observed after adjusting for depression within the present study, particularly given that the sample populations were more closely aligned.

Participants with higher MIND diet adherence did not exhibit significantly better performance in any of the other cognitive domains or on scores of global cognition compared to those with lower adherence. Similar results were seen in the cross-sectional study by Wesselman *et al.* [96] which, in addition to finding no associations with executive function, also uncovered no significant associations between MIND diet adherence and language, working memory, or visuospatial functioning. However, it was found that higher adherence was associated with better memory in fully adjusted models. Other studies have also found associations between higher MIND diet adherence and better visual and verbal memory [30, 98, 99], as well as better global cognitive function and processing speed [30]. Additionally, a slower rate of global cognitive decline over a mean follow-up time of 5.9 years was seen by Cherian *et al.* [97], although results from the Nurses' Health Study conflict with these findings, reporting no significant associations between MIND diet adherence and global cognitive decline over six years [98].

Prior studies have indicated that executive dysfunction ranks among the most common cognitive impairments in major depressive disorder, as noted by Cotrena *et al.* [120]. This observation might clarify the reason for the loss of significance in the present study's results following adjustments for depression. This is particularly noteworthy given that depression prevalence was lower among those exhibiting higher adherence to the MIND diet. Although the observed association between depression and MIND diet adherence did not reach statistical significance ($p = 0.113$), with a relatively small number of total depression cases ($n = 27$), a cross-sectional study involving 3,176 Iranian adults did identify a significant association between greater adherence to the MIND diet and lower odds of depression [121]. Contrary to this, a study involving 15,980 adults in Spain found no evidence of reduced depression risk with higher MIND diet adherence over a 2-year period [122]. Given these conflicting findings, it would be advantageous for future research to investigate the relationship between MIND diet and depression risk. Furthermore, exploring whether depression moderates the association between the MIND diet and executive function could offer valuable insights.

Higher adherence to the MedDiet revealed no significant associations with any cognitive domains or with global cognition for either MedDiet score. These findings are consistent with a previous randomised controlled trial involving 137 participants (mean age 72.1 ± 5.0 years) who were assigned to either a MedDiet, or a control diet in which they continued their usual dietary intake [90]. Memory, executive function, processing speed, visual-spatial ability, and global cognitive function were all assessed. However, the MedDiet group did not perform significantly better in any of these domains after six months of intervention. Other studies have supported these findings, demonstrating no associations between MedDiet and a reduction in global cognitive decline [112], as well as across a number of cognitive domains including executive function, information processing [83], and working memory [84]. Nevertheless, several studies have uncovered opposing findings, reporting positive correlations between MedDiet adherence and memory [26, 83, 84, 85, 86], executive functioning [26, 85], simple processing speed and verbal ability/language [85, 86, 87], global cognitive function [86, 88], as well as lesser cognitive decline over time [88, 89].

When examining the studies discussed in the preceding paragraph, there were no clear or consistent patterns observed between the MedDiet scoring metrics used and the findings of each study. It was noted, however, that of the three studies showing a lack of association between MedDiet and cognition (whether globally or in specific domains), one used a modified version of the P-Med Score [83], while the other two used the original score developed by Trichopoulou *et al.* [32], using sex-specific within-population median values of intake to calculate scores [84, 112]. It is interesting to acknowledge that both studies using the latter score were conducted in non-Mediterranean populations, while other studies that have utilised this score within Mediterranean populations demonstrated only positive associations between MedDiet and cognition [32, 89]. This suggests that it may not be appropriate to employ the use of sex-specific medians to calculate MedDiet adherence within non-Mediterranean populations as adherence levels are likely to be inflated due to general low adherence of the population, potentially impacting the associations observed with cognition. This supports the conclusions from Morris [33], who determined that studies adopting the traditional number of Greek servings used in the original scoring metric tended to demonstrate associations between higher MedDiet adherence and less cognitive decline and AD incidence compared to studies utilising sex-specific medians. Despite these findings,

studies employing scores that utilise cut-off values drawn from traditional Greek servings have also demonstrated a lack of association between MedDiet adherence and cognition, with the present study and that by Karstens *et al.* [83] adopting the P-Med Score without seeing any positive results. Regardless, consistency in MedDiet scoring is vital to increase comparability between studies and interpretability of information to the public. While many studies have observed positive impacts of the MedDiet on cognition, there are no consistent guidelines on what high adherence to this dietary pattern looks like, thus making it difficult to provide specific advice.

There are several explanations that could be posed for the non-significant findings in the present study. Firstly, the population investigated in this study were a cognitively healthy, well-educated cohort, with relatively low disease burden. The average number of formal education years within this study sample was 16.5 years, suggesting many participants undertook tertiary education. It has been documented that higher education is associated with higher cognitive reserve and therefore higher cognitive function in older adults [123]. This can be seen within the ACE-III scores in the present study, which had a mean of 95.6 out of a total 100, with scores ranging from 72 to 100. The high mean and limited range of this sample makes it difficult to find meaningful differences within the data.

Secondly, the age of the sample population may have also influenced findings, with some studies suggesting that benefits of diet to cognition may only become evident beyond a certain age threshold. For instance, Wade *et al.* [124] observed improvements in cognitive function with higher adherence to a MedDiet over a five-year period in participants aged 70 years and above. However, no such associations were observed for those under 70 years of age. Given the mean age of the population in the present study was 65.5 years, with no participants aged above 70 at baseline, it may be plausible that any potential benefits of MedDiet or MIND diet adherence were not yet evident within cognitive function scores obtained at the time of this study.

Limitations of the AES may have also impacted the findings of this study. The S-Med Score uses weight of food in grams to determine portion sizes for score cut-offs. This information was unable to be obtained from the AES, and instead the generic portion size determined by the AES was used for each food/food group to calculate scores. This may have caused

discrepancies in scoring outcomes compared to other studies utilising this method. Portion sizes for the P-Med Score are not defined, and therefore the portion sizes determined by the AES were used in this scoring method as well. Again, this may have caused some discrepancies in scoring compared with previous studies. Additionally, a number of food items were unable to be individually extracted from the AES such as the separation of some wholegrains from refined cereals. Berry consumption was also unable to be accurately determined, a food item which is categorised individually in the MIND diet score. It has been identified that berries may be protective of cognitive decline due to their high flavonoid content [125], which is the rationale underpinning the separation of berries from the larger fruit group in this scoring method. However, the AES combines berries and pineapple into one question, meaning that exact berry consumption was unable to be determined and may have resulted in the calculation of higher scores.

Finally, the cross-sectional design of this study presents another potential rationale for the absence of significant findings. This design only allows for dietary adherence to be captured at a singular time point. It is plausible that adherence to a particular diet may need to occur over a prolonged duration for cognitive benefits to manifest. Given that we were unable to determine any changes in adherence levels over time, the duration of participants' consistent adherence to these diets remains unknown.

This study has a number of strengths. Firstly, data was collected at two different Australian sites, allowing for a larger and more diverse population to be recruited. The sample size was comparable to other cross-sectional studies investigating MedDiet adherence and cognition [84, 87], and was much larger than some [26, 83]. Secondly, the ACE-III chosen to measure global cognition has been validated for use as a screening tool for cognitive deficits seen in frontotemporal dementia and AD, while the cognitive test battery chosen to measure specific cognitive domains (CANTAB) was robust and has been validated for use with older adults and people with dementia to measure neuropsychological functions. As these tests are automated, they allow for sensitivity in detecting minor changes that cannot be detected in manual tests, such as in reaction time which has been associated with cognitive decline [126].

Limitations of this study include low spread of cognitive performance scores across the sample. This may have limited the ability to detect associations in relation to diet and cognition. There were also limitations with the use of the AES as discussed earlier, and in general FFQs are not considered as accurate as WFRs. This is due to the way in which FFQs often group foods together due to the impracticality of including an individual question for each type of food. For example, breakfast cereals are grouped together into one question in the AES. This grouping of cereals means that important information cannot be extracted from this data such as whether the cereals consumed were of the wholegrain variety, or if they were highly processed sugary cereals. Another disadvantage of FFQs is that they generally only allow for an indication of how often foods are consumed (e.g., 2-6 serves per week, 1-3 serves per month). Definitions of serving sizes are not typically presented, leading to participants answering based on their own beliefs of what a serve looks like. WFRs, on the other hand, provide an accurate weighed measurement of each food consumed, with no guesswork required on exactly how much was eaten. While the AES has been validated against WFRs, it may be that a WFR still provides a more accurate analysis of dietary intake, particularly when used to determine MedDiet and MIND diet adherence in which small differences in intake levels of food groups can alter the adherence score. However, given the substantial effort required from participants to complete WFRs, this study opted for FFQs as a more pragmatic approach for gathering dietary data, especially given the large sample size. Finally, it is crucial to recognise that as this study utilised cross-sectional data, it does not allow for any causal inferences to be made regarding diet adherence and cognitive function.

In summary, the results of this study suggest that higher adherence to the MIND diet may be associated with executive function, while the MedDiet is not associated with better cognitive function in this cohort. Further research is needed with utilisation of a more accurate method of capturing dietary intake such as WFRs. Longitudinal analysis of this cohort would also be beneficial to capture rate of cognitive decline, which may be impacted by MedDiet or MIND diet adherence over time. It is recommended that future studies utilise scoring methods without the use of within-population sex-specific medians to calculate scores to improve comparability across studies.

3.7 Supplementary tables

Supplementary Table 1 Statistical output of ANOVA type II F tests for cognitive outcomes among participants in the ACTIVate study, with dietary scores modelled as tertiles

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	0.018	0.893	0.893	0.023	0.879	0.973	0.001	0.989	0.989	0.073	0.787	0.831	0.346	0.557	0.897
	Model 2	0.074	0.786	0.858	0.158	0.691	0.885	0.006	0.939	0.939	0.000	0.995	0.995	0.018	0.894	0.926
	Model 3	0.075	0.785	0.928	0.109	0.742	0.804	0.004	0.951	0.951	0.002	0.964	0.964	0.008	0.927	0.927
S-Med Score	Model 1	0.046	0.831	1.000	0.051	0.822	0.939	0.018	0.893	0.893	0.585	0.445	0.526	0.499	0.480	0.875
	Model 2	0.101	0.751	0.819	0.174	0.677	0.880	0.008	0.931	0.931	0.189	0.664	0.797	0.051	0.822	0.931
	Model 3	0.101	0.751	0.888	0.154	0.695	0.772	0.008	0.927	0.927	0.177	0.675	0.816	0.054	0.817	0.878
MIND diet	Model 1	0.005	0.943	0.943	0.205	0.651	0.920	0.003	0.955	0.955	4.618	**0.032**	0.086	0.421	0.517	0.865
	Model 2	0.073	0.787	0.858	0.081	0.777	0.777	0.022	0.882	0.903	3.315	0.069	0.208	0.924	0.337	0.834
	Model 3	0.075	0.785	0.927	0.073	0.788	0.853	0.015	0.903	0.903	3.00	0.084	0.182	0.823	0.365	0.790

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for age, sex, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression.

Bold denotes statistical significance ($p \leq 0.05$).

Supplementary Table 2 Statistical output of ANOVA type II F tests for cognitive outcomes among female participants in the ACTIVate study

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	2.073	0.151	0.264	0.610	0.436	0.762	1.806	0.180	0.401	0.274	0.601	0.644	1.205	0.273	0.555
	Model 2	2.301	0.131	0.356	0.287	0.593	0.998	1.427	0.233	0.514	0.036	0.849	0.849	0.699	0.404	0.889
	Model 3	2.282	0.132	0.391	0.330	0.566	0.933	1.440	0.231	0.555	0.046	0.830	0.830	0.662	0.416	0.767
S-Med Score	Model 1	2.522	0.113	0.220	1.134	0.288	0.504	2.227	0.137	0.319	1.088	0.298	0.422	1.462	0.228	0.506
	Model 2	2.566	0.110	0.304	0.725	0.395	0.870	1.643	0.201	0.442	0.566	0.453	0.545	0.927	0.337	0.740
	Model 3	2.580	0.109	0.328	0.665	0.416	0.831	1.604	0.207	0.496	0.455	0.501	0.601	0.990	0.321	0.770
MIND diet	Model 1	4.117	**0.043**	0.114	0.000	0.999	0.999	0.013	0.910	0.966	5.279	**0.022**	0.078	0.221	0.639	0.894
	Model 2	3.107	0.079	0.218	0.084	0.772	0.995	0.000	0.997	0.997	2.364	0.125	0.345	0.012	0.914	0.991
	Model 3	3.148	0.077	0.232	0.107	0.744	0.938	0.001	0.978	0.978	2.068	0.152	0.364	0.003	0.958	0.958

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [1]; S-Med Score, Mediterranean diet score developed by Sofi et al. [2]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for age, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression. Dietary scores were modelled as continuous variables.

Bold denotes statistical significance ($p \leq 0.05$).

Supplementary Table 3 Statistical output of ANOVA type II F tests for cognitive outcomes among male participants in the ACTIVate study

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	2.572	0.112	0.193	0.012	0.912	0.912	0.006	0.940	0.940	1.316	0.254	0.540	0.000	0.999	0.999
	Model 2	2.411	0.124	0.340	0.122	0.728	0.880	0.069	0.793	0.974	1.731	0.191	0.416	0.065	0.799	0.969
	Model 3	2.533	0.115	0.344	0.121	0.729	0.966	0.062	0.803	0.997	1.764	0.187	0.449	0.046	0.830	0.914
S-Med Score	Model 1	0.897	0.346	0.411	0.431	0.514	0.765	0.003	0.955	0.955	0.059	0.809	0.809	0.198	0.657	0.937
	Model 2	0.826	0.366	0.664	0.270	0.605	0.871	0.002	0.963	0.989	0.053	0.819	0.819	0.647	0.423	0.665
	Model 3	0.984	0.324	0.687	0.268	0.606	0.949	0.005	0.946	0.977	0.070	0.791	0.808	0.528	0.469	0.804
MIND diet	Model 1	1.968	0.163	0.230	0.240	0.625	0.860	0.009	0.926	0.926	0.738	0.392	0.549	2.744	0.101	0.555
	Model 2	2.118	0.149	0.409	0.353	0.554	0.909	0.085	0.771	0.943	0.868	0.354	0.465	3.267	0.074	0.561
	Model 3	2.422	0.123	0.368	0.346	0.558	0.988	0.071	0.791	0.980	0.797	0.374	0.517	2.977	0.087	0.680

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for age, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression. Dietary scores were modelled as continuous variables.

Supplementary Table 4 Statistical output of ANOVA type II F tests for cognitive outcomes among participants aged 60-65 in the ACTIVate study

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	0.684	0.409	0.573	2.643	0.106	0.403	1.342	0.248	0.579	0.243	0.623	0.649	0.036	0.850	0.990
	Model 2	0.627	0.429	0.879	1.713	0.192	0.581	1.262	0.263	0.917	0.012	0.912	0.993	0.307	0.580	0.932
	Model 3	0.624	0.431	0.892	1.729	0.190	0.592	1.260	0.263	0.933	0.009	0.926	0.991	0.305	0.581	0.930
S-Med Score	Model 1	1.451	0.230	0.330	0.434	0.511	0.894	1.606	0.207	0.482	0.334	0.564	0.666	0.205	0.652	0.985
	Model 2	1.283	0.259	0.653	0.423	0.516	0.811	1.492	0.223	0.819	0.223	0.637	0.864	0.063	0.802	0.998
	Model 3	1.253	0.264	0.729	0.383	0.537	0.806	1.524	0.218	0.874	0.185	0.667	0.834	0.069	0.793	0.980
MIND diet	Model 1	0.737	0.392	0.548	2.204	0.139	0.387	0.053	0.818	0.818	6.937	**0.009**	**0.032***	0.554	0.457	0.991
	Model 2	0.462	0.497	0.833	0.801	0.392	0.682	0.004	0.952	0.966	3.803	0.053	0.270	2.541	0.113	0.619
	Model 3	0.422	0.517	0.849	0.684	0.409	0.701	0.009	0.924	0.968	3.542	0.061	0.368	2.436	0.120	0.718

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [1]; S-Med Score, Mediterranean diet score developed by Sofi et al. [2]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for sex, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression. Dietary scores were modelled as continuous variables.

Bold denotes statistical significance ($p \leq 0.05$). * denotes *p*-values that remained significant after false discovery rate adjustment.

Supplementary Table 5 Statistical output of ANOVA type II F tests for cognitive outcomes among participants aged 66-70 in the ACTIVate study

Diet score		Global cognition			Short-term memory			Long-term memory			Executive function			Processing speed		
		F	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*	*F*	*p*	*adj.p*
P-Med Score	Model 1	1.689	0.196	0.228	0.536	0.465	0.814	0.233	0.630	0.964	0.961	0.328	0.533	1.806	0.181	0.409
	Model 2	1.004	0.318	0.389	0.807	0.371	0.597	0.037	0.847	0.878	1.161	0.283	0.622	1.086	0.230	0.470
	Model 3	1.015	0.315	0.420	0.795	0.374	0.656	0.043	0.836	0.884	1.109	0.294	0.645	1.036	0.310	0.466
S-Med Score	Model 1	0.369	0.544	0.544	0.062	0.804	0.952	0.152	0.698	0.905	0.108	0.743	0.867	0.120	0.730	0.730
	Model 2	0.184	0.668	0.735	0.001	0.971	0.971	0.002	0.967	0.967	0.013	0.909	0.909	0.020	0.887	0.887
	Model 3	0.156	0.693	0.776	0.002	0.969	0.969	0.014	0.908	0.908	0.001	0.973	0.973	0.000	0.997	0.997
MIND diet	Model 1	0.342	0.559	0.559	1.500	0.223	0.390	0.002	0.964	0.964	0.250	0.618	0.788	0.314	0.576	0.806
	Model 2	0.441	0.507	0.558	1.222	0.271	0.497	0.008	0.929	0.929	0.155	0.695	0.849	0.197	0.658	0.823
	Model 3	0.398	0.529	0.635	1.208	0.274	0.548	0.001	0.989	0.989	0.096	0.757	0.855	0.096	0.757	0.909

Abbreviations: *F*, F statistic; *p*, *p*-value; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for sex, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression. Dietary scores were modelled as continuous variables.

4 Associations between Mediterranean diet and MIND diet adherence with brain volume and cognitive performance in older Australian adults

4.1 Chapter overview

In the previous chapter, higher adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was initially found to be associated with better executive function within an older Australian population. However, this association was attenuated after adjusting for depression. No other significant associations were noted between this diet and global cognition or with any other cognitive domains. Furthermore, no associations were seen between the Mediterranean diet and global cognitive function or with any of the domains. Building on these findings, the current chapter aimed to determine whether adherence to these diets is associated with brain volume within the same older adult population, with a secondary aim to investigate whether any interactions are present between each dietary pattern and brain volume, with cognition as the outcome.

4.2 Abstract

Introduction

Brain regions impacted by Alzheimer's disease neuropathologies frequently exhibit decreased volume prior to the onset of cognitive impairment. Recent findings indicate that following a Mediterranean diet (MedDiet) may offer protective benefits to brain volume, while emerging evidence also underscores the potential advantages of adopting the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. This study aims to explore associations between MedDiet and MIND diet adherence and brain volume in an older Australian population of adults.

Methods

Cross-sectional data from 390 participants were included from the ACTIVate study (65.5 ± 3.0 years old, 69.0% female). Diet data were collected using the Australian Eating Survey (AES). Adherence to the MedDiet and MIND diet were calculated using the AES, with two different MedDiet scores used. One was developed by Panagiotakos *et al.* [1] (P-Med Score), with the other developed by Sofi *et al.* [2] (S-Med Score). Measures of brain volume (total brain volume, total grey matter volume, total white matter volume, hippocampal volume) were obtained via magnetic resonance imaging. Linear regression models were used for data analysis in three adjusted models, with diet scores modelled as continuous variables. Subsequently, Type II F tests were employed to test for overall variable significance, and the associated p-values underwent adjustment for false discovery rate using the Benjamini-Hochberg method.

Results

Higher adherence to the S-Med Score was associated with higher total brain volume (β ± SE = 1.751 ± 0.666, p = 0.009), white matter volume (β ± SE = 1.466 ± 0.521, p = 0.005), and hippocampal volume (β ± SE = 0.027 ± 0.011, p = 0.021) after adjusting for demographic and cardiovascular variables and depression. However, no significant associations were found between the S-Med Score and total grey matter volume. Significance was lost after adjusting for false discovery rate for total brain volume in models 2 and 3, and for

hippocampal volume in all models. No significant associations were found between the P-Med Score or the MIND diet with any of the brain volume measures. Significant interactions were found between hippocampal volume and the P-Med Score for long-term memory scores ($\beta = -0.059$, $p = 0.017$), and between hippocampal volume and MIND diet for long-term memory scores ($\beta = -0.172$. $p = <0.01$). For those with lower hippocampal volumes (below the sample mean volume), higher adherence to the P-Med Score was associated with higher long-term memory scores. In those with higher hippocampal volumes (above the sample mean), higher adherence to the P-Med Score was associated with lower long-term memory scores. The same observations were seen for the MIND diet with hippocampal volume and long-term memory.

Conclusion

Collectively, these findings provide preliminary cross-sectional evidence that MedDiet adherence is associated with greater white matter volume, based on the S-Med Score. Additionally, higher P-Med Score adherence appears to be more beneficial for those with a smaller hippocampal volume for long-term memory. Validation of these results should be pursued through a longitudinal study approach.

4.3 Introduction

Dementia, the leading cause of disease burden in Australians aged 65 and over [4], poses a significant challenge, with over 400,000 Australians currently estimated to be living with the condition. Projections indicate that this number is expected to double by 2058 [127], emphasising the need for development of suitable interventions aimed at reducing dementia risk. Accelerated atrophy of brain regions affected by dementia-related neuropathologies has been observed prior to the manifestation of cognitive decline and clinical diagnosis of mild cognitive impairment and Alzheimer's disease (AD) [8]. This long preclinical period provides an opportunity for early identification and implementation of prevention strategies. With limited availability of thoroughly tested and effective medications for treating or slowing dementia progression, research has redirected its focus to prevention through modifiable risk factors such as nutrition [9].

A recent systematic review demonstrated an association between poorer diet quality and reduced brain volume [14], highlighting the potential for a healthier diet to contribute to brain preservation. Of particular interest is the Mediterranean diet (MedDiet), which has been previously associated with reduced dementia risk [82], as well as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, which has demonstrated similar effects [28, 29]. Detailed descriptions of the MedDiet and MIND diet can be found in chapter 2, section 2.4 (pages 17-20). Higher MedDiet adherence has been associated with less total brain atrophy over a 3-year period [101]. Furthermore, this diet has also been correlated with greater total brain volume, total white matter volume, and total grey matter volume [24], as well as larger grey matter volume in the right parahippocampal gyrus and hippocampus [84] in cross-sectional analysis. Evidence has also suggested that higher MedDiet adherence is related to greater volume in the dentate gyrus [83], and greater cortical thickness in the orbitofrontal cortex, entorhinal cortex, and posterior cingulate cortex of the left hemisphere [103], and in the superior frontal region [24]. Research on the MIND diet is not as extensive as the MedDiet due to its relatively recent inception. However, there has been evidence of a number of positive associations between MIND diet adherence and preservation of brain volume. This includes correlations with greater total brain volume [30], increased surface area of the inferior frontal gyrus [99], and lower odds of hippocampal sclerosis [105]. There are also findings which contradict this, showing no associations between

these dietary patterns and various brain volume measures [26, 29, 30, 83, 95, 101, 104]. This leads to difficulties in discerning the true impact that both the MedDiet and MIND diet may have on preservation of brain volume in the interest of dementia prevention. For further information describing the associations between the MedDiet and MIND diet and neuroimaging markers of dementia risk, please see chapter 2, sections 2.5.3 and 2.5.4 (pages 25-27).

The aim of the present study is to further investigate the association between adherence to the MedDiet and MIND diet and brain volume in older Australian adults using diet data obtained from the Australian Eating Survey (AES). It is hypothesised that higher adherence to the MedDiet will be associated with larger total brain volume, total white matter volume, total grey matter volume, and hippocampal volume. Further, it is hypothesised that higher adherence to the MIND diet will be associated with larger total brain volume and hippocampal volume. In addition, an exploratory aim of this study is to examine potential interactions between diet, brain volume, and cognition within this population. It is of interest to explore whether differences in brain volume may alter the association between dietary adherence and cognitive outcomes.

4.4 Methods

4.4.1 Study population and screening

The study population was comprised of individuals from the ACTIVate study, a prospective longitudinal cohort study of older adults residing in Adelaide, South Australia and Newcastle, New South Wales. Details about the aims and design of the ACTIVate study have been described previously [34]. Participants recruited were aged between 60 and 70 years at the time of enrolment and consist of the same cohort recruited for the previous study described in Chapter 3. The Montreal Cognitive Assessment-Blind (MoCA-B) was administered to screen for dementia, with a cut-off score of 13 (out of 22) used to identify significant cognitive impairment and thus exclusion from the study. Participants with history of stroke were also excluded. Four-hundred and twenty-six participants met inclusion criteria and were enrolled at baseline, with 226 recruited in Adelaide and 200 in Newcastle. The study was approved by the University of South Australia's Human Research Ethics Committee (202639), and all participants gave written informed consent.

4.4.2 Procedure

Participants living in Adelaide attended the University of South Australia Clinical Trial Facility, and those residing in Newcastle attended the University of Newcastle Functional Imaging Laboratory for baseline data collection. Visits consisted of acquisition of written informed consent, followed by blood pressure and anthropometric measurements. Completion of general health and dietary assessments were then conducted, followed by administration of cognitive tests. Participants were provided with Axivity monitors to obtain accelerometry data over a 7-day period. Magnetic resonance imaging (MRI) scans were conducted at a subsequent visit approximately one week later at the South Australian Health and Medical Research Institute in Adelaide, and at the Hunter Medical Research Institute in Newcastle [34].

4.4.3 Dietary assessment and scoring

Dietary intake was assessed via administration of the AES, a semi-quantitative food frequency questionnaire (FFQ) that has been validated against four-day weighed food records (WFR) for use in adult populations [113]. Further description on the AES is detailed in chapter 3, section 3.4.3 (page 36). Additionally, the inclusion of a separate questionnaire to assess oil intake was used as this information is not captured by the AES. This survey was based on the polyunsaturated fatty acids questionnaire developed by Swierk *et al.* [128].

Two MedDiet scores were used in this study (referred to as P-Med Score and S-Med Score). Information on these scoring methods is described in chapter 3, section 3.4.4 (pages 36-37). The rationale behind selecting two scoring systems is due to the variety of scoring systems available, with no single score having been identified as superior to the others. Both scoring systems chosen are literature-based, however, the authors have focused on different aspects of the literature to guide score creation.

The MIND diet score is a relatively new dietary pattern, developed in 2015 by Morris *et al.* [27]. A description of this dietary pattern can be found in chapter 3, section 3.4.5 (page 37-38).

4.4.4 MRI acquisition

MRI scans were performed using 3T scanners in Adelaide (Siemens Skyra) and Newcastle (Siemens Prisma), using a 64-channel head and neck coil. The MRI protocol consisted of four MRI sequences (T1-weighted structural scan, T2 FLAIR, diffusion weighted imaging, resting-state functional MRI). For this study, only the T1-weighted structural scans were used for volumetric calculation. Scanning parameters are shown in Table 1.

Table 1 MRI scan parameters and resolution for T1-weighted structural scans

Site/Scanner	Matrix size (mm^3)	Voxel size (mm^3)	TE (msec)	TR (msec)	FA (degree)	T1 (msec)
Adelaide, 3T Siemens SKYRA	256x256x208	1x1x1	2.90	2300	9	900
Newcastle, 3T Siemens PRISMA	256x256x208	1x1x1	2.91	2300	9	900

Abbreviations: TE, echo time; TR, repetition time; FA, flip angle.

Prior to MRI scanning, each participant underwent an MRI safety check. Total scanning time for each participant was 5 minutes and 12 seconds for T1 scans. Upon completion of scans, files were sent to CSIRO in Brisbane for processing.

4.4.5 Brain volume assessment

A similar analysis approach to that of Mellow *et al.* [129] was followed to assess brain volume. Initially, grey matter, white matter, and cerebrospinal fluid tissue volumes were acquired utilising an internally developed application of the expectation maximisation algorithm [130] applied to 3D T1 magnetisation prepared rapid gradient echo images. Brain parcellation was then completed using the NeuroMorphometrics parcellation atlas and Learning Embeddings for Atlas Propagation method [131] to acquire cortical and subcortical grey matter volumes.

To adjust for differences in head size among participants, regression analysis was conducted using intracranial volume (measured using MRI) as the independent variable and brain volume as the dependent variable. Within the same model, adjustments were made for variations in data collection site, as well as for distortion correction which was not uniformly applied to all scans during data collection. Corrected values were then carried forward to analyses.

Within this study, a number of volumetric measures were explored including total brain volume, total grey matter volume, total white matter volume, and hippocampal volume.

4.4.6 Cognitive assessment

Addenbrooke's Cognitive Examination III (ACE-III) was administered by trained interviewers at each testing site to assess global cognitive function. Tests were also administered from the Cambridge Neuropsychological Test Automated Battery (CANTAB), with composite scores computed for four cognitive domains (short-term and working memory, long-term storage and retrieval, executive function, and processing speed). Further information on these assessment tools is provided in chapter 3, section 3.4.6 (page 38-39).

4.4.7 Covariates

Covariates included in the current study were age (years), sex, education (number of years of formal education), body mass index (BMI), total energy intake (kJ/day), physical activity (minutes/day), smoking (never, former, or current), diabetes, hypertension, hyperlipidaemia, and depression status. Information on age, sex, education, and smoking status was collected at participants' baseline interview. Total energy intake was calculated based on responses to the AES. Average minutes per day of physical activity was based on accelerometry data obtained over a seven-day period. Measurements of weight (kg) and height (metres) were used to calculate BMI. Hypertension history was determined by measured blood pressure (average of 3 measurements $\geq$140 mmHg systolic or $\geq$90 diastolic), self-reported medical diagnosis, or current use of hypertensive medications. Diabetes history and hypercholesterolaemia were determined by self-reported medical diagnosis or current use of medications. Depression was assessed using the Center for Epidemiologic Studies Depression (CES-D) scale which is a self-rated score ranging from 0 to 60, in which a

higher score is associated with higher symptomatology. A cut-off score of 16 was used to indicate presence of depression [116].

4.4.8 Statistical analysis

Statistical analysis was performed using R Statistical Software v4.1.2 [117]. Adherence to each dietary score was divided into tertiles for descriptive purposes only. Mean and standard deviations are presented for continuous variables. Percentages are given for categorical variables within each tertile to examine any differences in participant baseline characteristics between differing levels of diet adherence. Differences between tertiles for each score were evaluated using analysis of variance (ANOVA) for continuous variables and Chi-Square test for categorical variables.

In the main analyses, diet scores were treated as continuous (linear) variables. Multiple linear regression models were used to explore the association between each dietary score and brain volume measures, with adjustment for covariates across three models as described below. Type II F tests were then used to test for overall variable significance, and corresponding p-values from each model were adjusted for false discovery rate using the Benjamini-Hochberg method [118]. In-text results are presented as β-coefficients and standard errors (SE), with p-values representing corrected values from ANOVA outputs.

To explore whether brain volume moderates the relationship between diet adherence and cognitive function, interactions between diet adherence and brain volume for each cognitive outcome were investigated using linear regression models. Adjustments were made for all covariates included in model 3 as described below. To explore significant interactions further, population mean values were determined for the relevant brain volume measure and dietary adherence score, such that participants were grouped into low/low, low/high, high/low, or high/high groups based on brain volume and dietary adherence, respectively. The relevant mean cognitive score was then graphed for each group (as z-scores).

Three models were used to adjust for a range of covariates, with additional covariates added to the models as they progressed from model 1 to model 3. Model 1 adjusted for potential confounders with the most recognised evidence for association with AD including

age, sex, education, BMI, and physical activity [10, 28]. Additionally, total energy intake was included in this model due to its relevance to diet and the impact this may have on dietary adherence scores. Model 2 adjusted for Model 1 plus cardiovascular risk factors, which have been shown to mediate dietary effects on dementia (smoking status, diabetes, hypertension, and hyperlipidaemia) [28]. Model 3 adjusted for Model 2 plus depression status which may act as an effect mediator but has a complex cause and effect relationship with dementia, with reverse causation possible [10, 28].

4.5 Results

Out of the initial 426 participants recruited for this study, 390 individuals had valid data for both dietary and brain volume assessments. Invalid dietary assessment data was determined based on energy intake criteria (<2,092kJ or >14,644kJ for women and <3,347kJ or >17,573kJ for men) [119].

Baseline participant characteristics

The study population was on average 65.5 ± 3.0 years of age and primarily female (69.0%), with a mean education of 16.5 ± 3.2 years. Participant characteristics according to tertiles of adherence to each of the dietary scores is presented in Table 2, where a higher tertile number represents higher dietary adherence.

Associations between diet adherence and brain volume

P-Med Scores ranged from 16 to 47 (out of 55, mean 34.4 ± 4.3), while the S-Med Score spanned from 4 to 17 (out of 18, mean 11.1 ± 2.3). MIND diet scores varied between 4 and 13.5 (out of 15, mean 9.3 ± 1.6). Mean total brain volume was 1090.5 mL (range 997.0 to 1168.8 mL), mean grey matter volume was 596.1 mL (range 519.9 to 647.8 mL), mean white matter volume was 494.4 mL (range 426.9 to 590.8 mL), and mean hippocampal volume was 6.25 mL (range 2.68 to 7.65 mL).

Table 3 presents the associations between MedDiet adherence scores and brain volume measures, as well as associations between the MIND diet and brain volume measures. After

adjusting for demographic and cardiovascular variables, as well as depression, higher adherence to the S-Med Score was found to be significantly associated with higher total brain volume (β ± SE = 1.751 ± 0.666, p = 0.009), total white matter volume (β ± SE = 1.466 ± 0.521, p = 0.005), and hippocampal volume (β ± SE = 0.027 ± 0.011, p = 0.021). After adjustment for false discovery rate, the S-Med Score was no longer significantly associated with total brain volume in models 2 and 3, or with hippocampal volume in all models. No significant associations were observed between the S-Med Score and total grey matter volume. Additionally, there were no significant associations between the P-Med Score or the MIND diet and any of the brain volume measures.

Interactions between diet adherence, brain volume, and cognition

Significant interactions were observed between the P-Med Score and hippocampal volume for long-term memory (β = - 0.059, *p* = 0.017) (Figure 1), and between the MIND Diet and hippocampal volume for long-term memory (β = - 0.172, *p* = <0.010) (Figure 2). As displayed in Figures 1 and 2, interactions followed similar trends across both models. Participants with lower hippocampal volume (i.e., below the sample mean volume) had higher long-term memory scores if they also had high adherence to either the P-Med Score or MIND diet. Conversely, participants with higher hippocampal volume demonstrated lower long-term memory scores if they also had higher dietary adherence to the P-Med Score or MIND diet.

Table 2 Participant baseline characteristics according to tertiles of Mediterranean and MIND diet scores

Characteristic	**P-Med Score**				**S-Med Score**				**MIND diet score**			
	Tertile 1 (16-33)	Tertile 2 (34-36)	Tertile 3 (37-47)	*p*-value	Tertile 1 (4-10)	Tertile 2 (11-12)	Tertile 3 (13-17)	*p*-value	Tertile 1 (4-8.5)	Tertile 2 (9-10)	Tertile 3 (10.5-13.5)	*p*-value
N	155	113	122		151	127	112		136	149	105	
Age, mean ± SD, years	65.4 ± 2.9	65.5 ± 3.0	65.7 ± 3.0	0.738	65.5 ± 2.9	65.6 ± 2.9	65.6 ± 2.9	0.933	65.3 ± 3.1	65.4 ± 2.8	66.0 ± 3.0	0.153
Sex, % female	62.6	70.8	75.4	0.064	63.6	72.4	72.3	0.187	56.6	75.8	75.2	**<0.001*** **
Education, mean ± SD, years	16.5 ± 3.3	16.1 ± 3.1	16.8 ± 3.3	0.241	16.5 ± 3.4	16.3 ± 3.0	16.7 ± 3.3	0.651	16.3 ± 3.5	16.6 ± 3.3	16.6 ± 2.9	0.631
BMI, mean ± SD	28.3 ± 5.4	26.2 ± 4.3	26.0 ± 4.8	**<0.001*** **	28.0 ± 5.3	26.7 ± 5.0	25.8 ± 4.5	**0.002** **	28.1 ± 5.7	27.0 ± 4.6	25.4 ± 4.4	**<0.001*** **
Total energy (kJ/day), mean ± SD	8676.4 ± 2743.0	8729.3 ± 2555.7	9177.5 ± 2287.0	0.227	8652.6 ± 2738.5	8800.0 ± 2540.9	9167.6 ± 2298.9	0.263	9076.8 ± 2758.1	8861.5 ± 2398.9	8534.3 ± 2493.1	0.263
Physical activity (mins/day), mean ± SD	252.0 ± 81.6	277.3 ± 82.8	276.5 ± 78.4	**0.014***	259.3 ± 82.8	274.7 ± 88.0	268.6 ± 71.9	0.290	252.4 ± 76.6	270.1 ± 83.5	281.1 ± 83.2	**0.023***

Smoking, % never	56.8	64.6	57.9	0.555	57.6	59.8	61.3	0.504	58.8	60.8	58.1	0.977
Diabetes, %	7.1	7.1	1.6	0.087	7.3	4.7	3.6	0.386	3.7	7.4	4.8	0.363
Hypertension, %	54.2	45.1	47.1	0.284	51.0	52.0	44.1	0.424	60.4	43.2	43.8	**0.006****
Hyperlipidaemia, %	36.8	35.4	32.8	0.786	34.4	34.6	36.6	0.927	38.2	30.2	38.1	0.277
Depression, %	8.4	5.3	6.6	0.607	8.6	7.1	4.5	0.423	10.3	6.0	3.8	0.125

Abbreviations: P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; *n*, sample size; SD, standard deviation; BMI, body mass index; kJ, kilojoules; mins, minutes.
Participant characteristics were compared between tertiles for each score using ANOVA for continuous variables and Chi-Square test for categorical variables.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3 Statistical output of ANOVA type II F tests for brain volume outcomes among participants in the ACTIVate study

Diet score		Total brain volume			Total grey matter volume			Total white matter volume			Hippocampal volume		
		F	*p*-value	*adj.p*	*F*	*p*-value	*adj.p*	*F*	*p*-value	*adj.p*	*F*	*p*-value	*adj.p*
P-Med Score	Model 1	2.037	0.154	0.279	0.004	0.985	0.985	3.350	0.068	0.136	2.500	0.115	0.230
	Model 2	1.694	0.194	0.356	0.069	0.793	0.952	3.550	0.060	0.139	2.492	0.115	0.461
	Model 3	1.690	0.194	0.421	0.069	0.793	0.937	3.541	0.061	0.156	2.488	0.116	0.501
S-Med Score	Model 1	7.093	**0.008**	**0.030***	0.650	0.421	0.674	7.335	**0.007**	**0.014***	5.628	**0.018**	0.073
	Model 2	6.671	**0.010**	0.061	0.378	0.539	0.647	7.771	**0.006**	**0.017***	5.558	**0.019**	0.114
	Model 3	6.912	**0.009**	0.058	0.427	0.514	0.625	7.909	**0.005**	**0.017***	5.400	**0.021**	0.135
MIND diet	Model 1	0.046	0.830	0.830	0.017	0.896	0.947	0.027	0.870	0.870	0.304	0.581	0.662
	Model 2	0.115	0.735	0.735	0.007	0.931	0.992	0.255	0.614	0.737	0.170	0.680	0.806
	Model 3	0.154	0.695	0.695	0.002	0.969	0.984	0.284	0.595	0.782	0.136	0.712	0.808

Abbreviations: *F*, *F* statistic; *adj.p*, *p*-value adjusted for false discovery rate; P-Med Score, Mediterranean diet score developed by Panagiotakos *et al.* [(1)]; S-Med Score, Mediterranean diet score developed by Sofi et al. [(2)]; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

Model 1 was adjusted for age, sex, education, BMI, energy intake, and physical activity. Model 2 was additionally adjusted for smoking status, diabetes, hypertension, and hyperlipidaemia. Model 3 further adjusted for depression. Dietary scores were modelled as continuous variables.

Bold denotes statistical significance ($p \leq 0.05$). * denotes *p*-values that remained significant after false discovery rate adjustment.

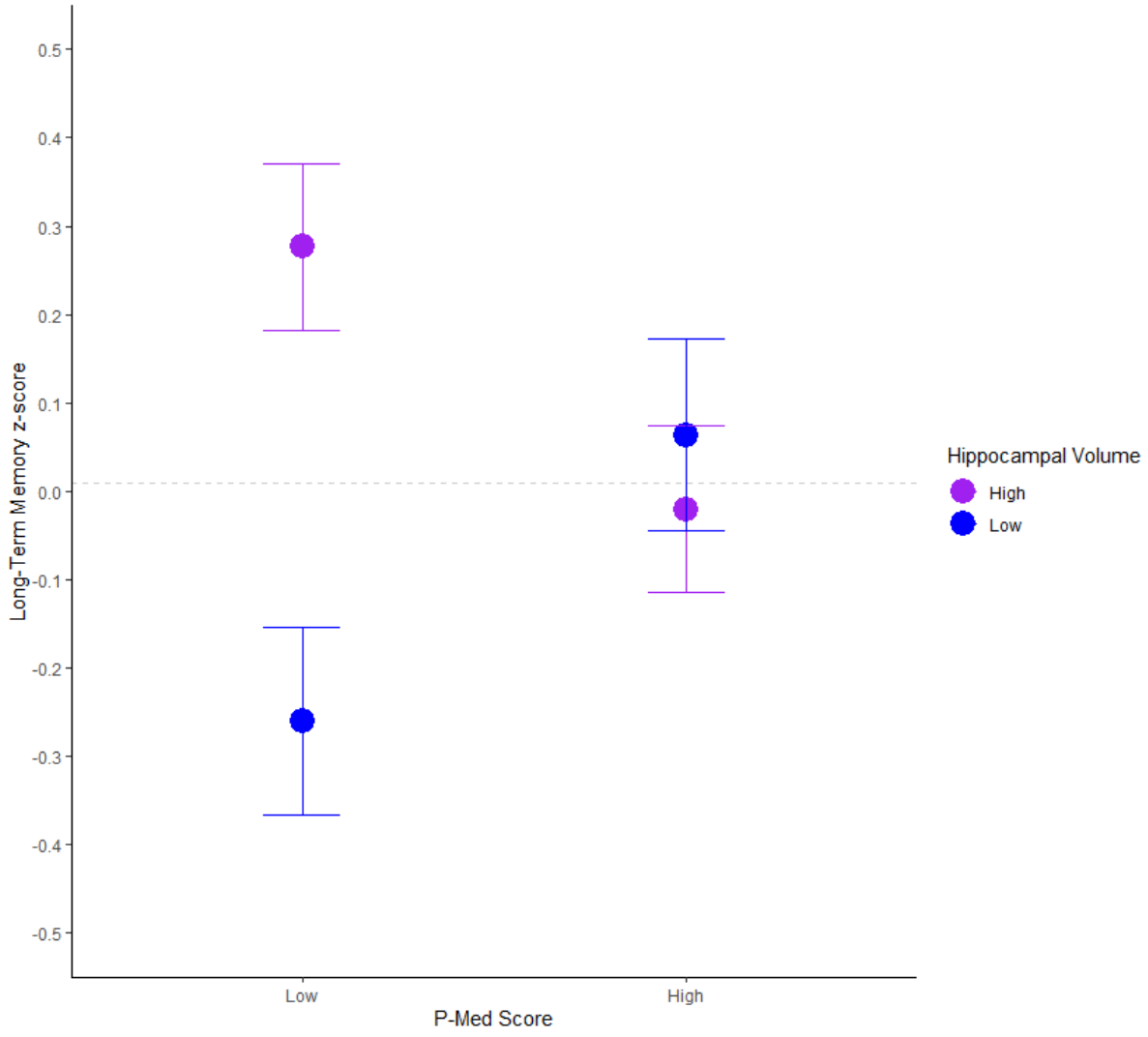

Figure 1 Association between P-Med Score and long-term memory by hippocampal volume. Mean long-term memory z-score (0.009) for the sample is indicated with a dashed line. Population mean values were determined for hippocampal volume (6.3 mL) and P-Med Score (34.4), with individuals below the mean categorised into 'low' categories, and individuals above the mean categorised into 'high' categories.

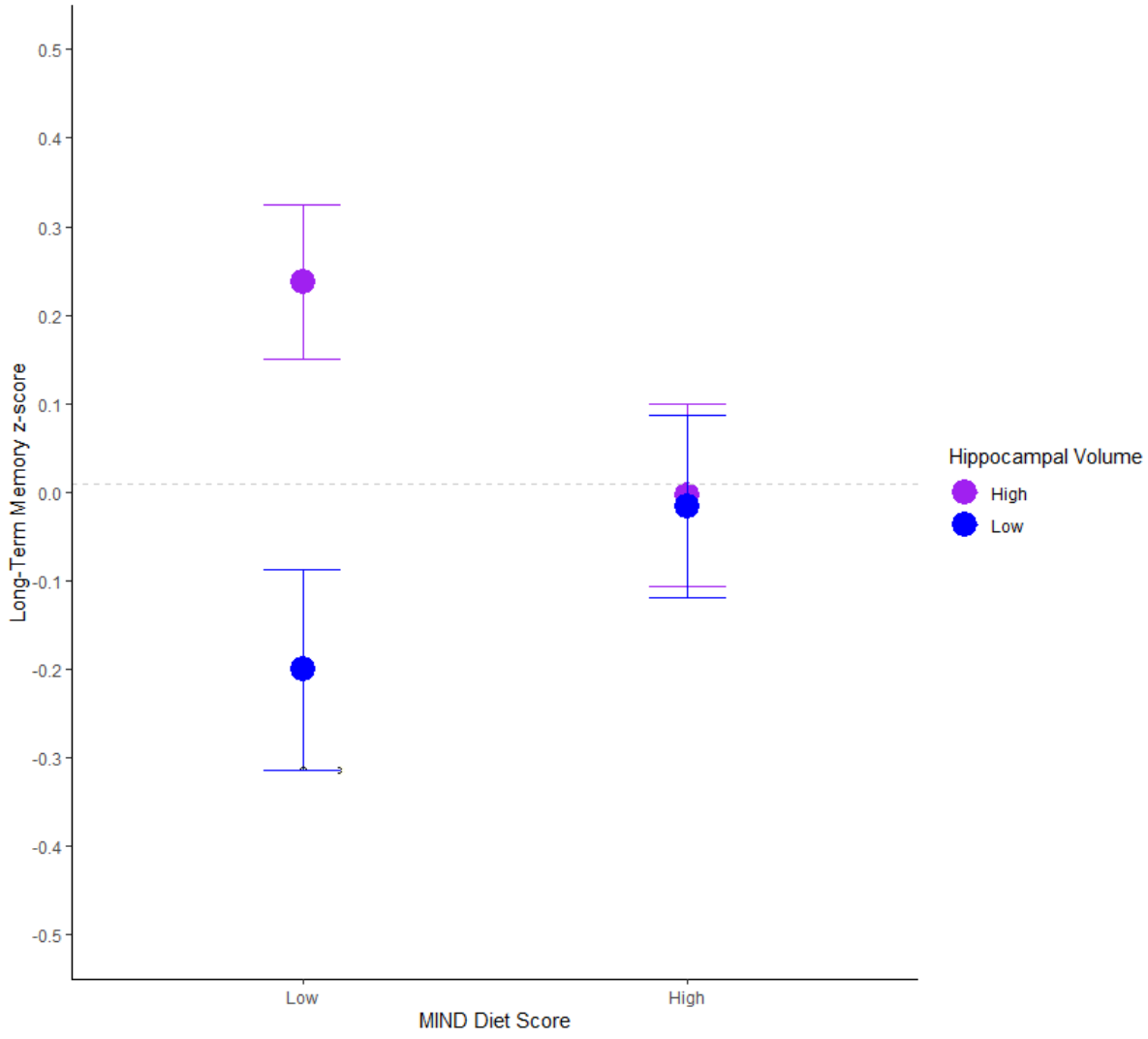

Figure 2 Association between MIND diet score and long-term memory by hippocampal volume. Mean long-term memory z-score (0.009) for the sample is indicated with a dashed line. Population mean values were determined for hippocampal volume (6.3 mL) and MIND diet score (9.3), with individuals below the mean categorised into 'low' categories, and individuals above the mean categorised into 'high' categories.

4.6 Discussion

This study aimed to investigate the associations between adherence to the MedDiet and brain volume in an older adult population in Australia, as well as associations between adherence to the MIND diet and brain volume within the same population. Participants with higher adherence to the S-Med Score demonstrated larger total brain volume, total white matter volume, and hippocampal volume compared to those with lower adherence. However, it is important to note that significance did not survive adjustments for false discovery rate for total brain volume in models 2 and 3, and for hippocampal volume in all models.

The initial findings in this study are consistent with a previous cross-sectional study conducted by Gu *et al.* [24] involving 674 cognitively normal elderly adults (mean age 80.1 years). It was found that individuals with a higher adherence to the MedDiet exhibited larger total brain volume and total white matter volume compared to those with lower adherence. A positive association was also observed between increased MedDiet adherence and greater grey matter volume in the hippocampus, although the analysis did not encompass the entire hippocampus (white matter was not included). Gu *et al.* [24] also found a significant association between the MedDiet and larger total grey matter volume which was not elucidated in the present study. Conversely, a prospective cohort study of 194 older adults (aged 70 years at baseline) conducted over a five-year follow-up period did not find any significant associations between the MedDiet and total brain volume, total grey matter volume or total white matter volume [95].

Interestingly, while positive associations were seen between brain volume and the S-Med Score, no such associations were found with the P-Med Score. While the food categories included in both scores are similar, there are some differences. The P-Med Score distinguishes potatoes as a separate food category from vegetables, and separates poultry from other meats, contrary to the S-Med Score. Additionally, the P-Med Score designates full-fat dairy as a distinct food category, while the S-Med Score includes all dairy in their scoring. There are also differences in the cut-off values used to calculate the adherence score for each food group. The S-Med Score rates each food category on a scale of 0-2 based on daily intake, while the P-Med Score assigns a score of 0-5 for each food category

depending on weekly intake. Generally, a higher intake of healthful food categories is required to achieve the highest scoring category for the P-Med Score compared with the S-Med Score, as well as higher intake of less healthful food categories to achieve the lowest score. One exception to this pertains to the scoring of alcohol. An increase in alcohol consumption correlates with a reduction in score under the P-Med scoring method. However, the S-Med Score assigns the highest value to the middle category of alcohol consumption, with the highest category receiving the lowest score. Given this difference in scoring, it may be worth controlling for alcohol consumption in future studies. Additionally, it is worth highlighting that the P-Med Score is derived from the original MedDiet pyramid, whereas the S-Med Score is based on a comprehensive review of literature investigating the MedDiet and its impact on health outcomes. The S-Med Score incorporates data from prospective cohort studies conducted in both Mediterranean and non-Mediterranean countries. This divergence in the scoring methodology might explain why significant associations between brain volume and the S-Med Score were observed, while no such associations were found with the P-Med Score.

Another intriguing distinction between the food groups included in the two scores is that the S-Med Score combines refined and wholegrain cereals within the same category, contrary to the P-Med Score, which only includes a group for non-refined cereals. Notably, wholegrain consumption has been linked with lower risk of all-cause dementia and AD dementia [(132)]. Hence, one might expect that higher adherence to the P-Med Score, which emphasises non-refined cereals, would be associated with larger brain volume. However, it is worthwhile mentioning that the AES utilised in this study only distinguishes between wholegrains and refined grains in the context of bread consumption, but not for other grain and cereal products. This means that participants could have scored higher on the P-Med Score despite consuming most of their grain intake as refined grains, which may explain why the results are not as expected. Furthermore, it is possible that the protective effect of wholegrain consumption on dementia risk occurs via other mechanisms, such as improving glycolipid metabolism, modulating intestinal flora, protecting neurons from neurotoxins, or even reflecting a higher socioeconomic status and better overall health among individuals consuming more wholegrains [(132)].

No significant associations were observed between higher adherence to the MIND diet and larger brain volume in any regions when compared to lower adherence. These findings align with evidence from a longitudinal study conducted by Melo van Lent *et al.* [30] involving 1,904 participants who underwent MRI analysis, in which no associations were found between the MIND diet and hippocampal volume. Furthermore, these results are consistent with those from another longitudinal study carried out by Thomas *et al.* [29] in France, with a median follow-up period of 9.7 years. This study similarly observed no significant association between higher MIND diet adherence and total grey matter volume. However, Thomas *et al.* did find a positive association between MIND diet adherence and total brain volume, contrary to the findings of the present study. It is important to note that Thomas *et al.* used an adapted version of the MIND diet score to better align with a French population which could be a contributing factor to their positive findings. Additionally, the findings of the present study deviate from those reported by Agarwal *et al.* [105], who reported that higher MIND diet adherence was associated with a 69% lower odds of hippocampal sclerosis in a sample of 581 deceased participants. The mean age of participants at death was 91.3 ± 6.1 years, which is markedly higher than the average age of participants in the present study. This suggests that the MIND diet may not elicit any detectable effects on brain preservation until after 70 years of age. Given the limited extent of research on the relationship between the MIND diet and brain volume at present, further exploration is warranted to better understand this association.

An additional exploratory aim was incorporated within this chapter which investigated whether brain volume moderated the relationship between dietary adherence scores and cognitive function. Results showed large differences in long-term memory performance between high and low hippocampal volume groups with low MedDiet adherence, whilst there were minimal differences between groups with high adherence. It is worth highlighting that long-term memory z-scores for those with higher MedDiet adherence were very close to the overall mean value for the sample population (0.009) regardless of hippocampal volume (low = − 0.017, high = − 0.003). Overall, the findings suggested that individuals with a smaller hippocampal volume may experience greater long-term memory benefit from increased adherence to the P-Med Score, in contrast to those with a larger hippocampal volume. Ballarini *et al.* [84] carried out a comparable investigation involving 512

participants with a mean age of 69.5 ± 5.9 years. In their study, they found that brain volume in the hippocampal and parahippocampal regions acted as a mediator in the relationship between adherence to the MedDiet and memory, supporting the results found in the present study. Again, however, it is interesting to note significant findings recorded for one of the MedDiet scores, while the other score did not exhibit the same observations. This may be due to differences in the scoring methodologies as described earlier. Similar results were seen for the MIND diet with long-term memory performance and hippocampal volume.

Considering that intracranial volume was adjusted for within this population, we may cautiously infer that individuals exhibiting lower hippocampal volume in this group potentially experience more accelerated atrophy in this specific region. Hippocampal atrophy has previously been associated with memory dysfunction, particularly in the context of long-term memory [133]. However, intriguingly, it seems that individuals with higher adherence to either a MedDiet or a MIND diet do not display diminished memory in the presence of hippocampal atrophy, a pattern observed in those with lower adherence within this population. Given these findings, one might conclude that there may be a protective effect associated with greater adherence to these dietary patterns, mitigating the impact of hippocampal atrophy on memory function. Notably, the study conducted by Ballarini *et al.* [84] revealed that higher MedDiet adherence is correlated with less amyloid and hyperphosphorylated tau protein pathology, both hallmarks of dementia. This observation suggests a potential mechanism through which the protective effect might manifest. In conclusion, these insights propose a potential avenue for further investigation into the relationship between dietary patterns, hippocampal volume, and memory outcomes.

This study possesses several strengths. Firstly, information was gathered from two distinct locations in Australia, enabling the recruitment of a more varied population and resulting in a relatively substantial sample size. Secondly, focusing on older adults in this study allowed for a greater likelihood of detecting significant findings as this population may demonstrate higher dementia neuropathologies in comparison to recruiting a younger sample. Furthermore, the MRI analysis pipeline employed in this study demonstrated strong agreement with FreeSurfer, another widely used pipeline. A further strength of this study is

that it is believed to be the first of its kind to examine the relationship between MIND diet adherence and brain volume within an Australian sample. Additionally, it is also believed to be the first study to explore whether brain volume moderates the relationship between dietary adherence scores and cognitive function within an Australian population. Finally, with numerous MedDiet scores used in the literature, the application of two different scores within this study provided an opportunity to determine whether adherence to one score may elicit positive effects on the brain compared to another score.

Several limitations should be acknowledged in this study. Firstly, there were differences between the way food intake data was collected by the AES and the diet scoring systems used in this study. The S-Med Score relies on weight measurements in grams to determine portion sizes for score cut-offs, however the AES did not provide this information. Instead, generic portion sizes determined by the AES were used to calculate scores for each food or food group. Similarly, the portion sizes for the P-Med Score were not defined, and therefore the portion sizes determined by the AES were also applied in this scoring method. These discrepancies in scoring methods may have introduced variations in adherence levels compared to previous studies. Moreover, certain food items could not be individually extracted from the AES, such as the separation of some wholegrains from refined cereals. Accurate determination of berry consumption, which is a specific item in the MIND diet score, was also challenging as the AES combines berries and pineapple into one question. This makes it impossible to determine true berry consumption and may have resulted in higher diet scores. Additionally, it should be noted that FFQs are not considered the gold standard for dietary data collection. However, due to the high participant burden associated with weighed food records, FFQs were chosen as the more practical method for dietary data collection in this study, considering the large sample size. The use of only one regional volume is another limitation of this study, as well as inclusion of only volumetric measures without consideration of other structural and functional connectivity measures which were not included due to time constraints. It would be beneficial to explore these in future research. Lastly, it is crucial to note that as this study utilised cross-sectional data, it does not allow for any causal inferences to be made regarding the relationship between MedDiet or MIND diet adherence and brain volume. Overall, it is important to interpret the findings of the present study with caution. Although greater brain volume was significantly

associated with higher adherence to the S-Med Score, the effect size was relatively minor. This population was also reasonably healthy, without extensive variation seen in dietary intake and brain volume, limiting the ability to detect potential differences between participants. Consequently, further research is necessary to gain a better understanding of this association.

To summarise, the findings of this study suggest that higher adherence to the S-Med Score is associated with larger total white matter volume, with some evidence existing for correlations between this dietary score and total brain volume and hippocampal volume. However, no significant associations were observed between brain volume and the P-Med Score or the MIND diet. Interaction analysis findings suggest that higher adherence to the MedDiet or MIND diet may be beneficial for long term memory in those with lower hippocampal volume. Further research is warranted, potentially with the utilisation of a more precise method of capturing dietary intake such as WFRs. Additionally, conducting longitudinal analysis within this cohort would be valuable in capturing changes in brain volume over time within individuals which may elucidate results not seen in the present study.

5 General discussion

5.1 Overview

As life expectancy increases, so too does the incidence of age-related diseases such as dementia and Alzheimer's Disease (AD). In Australia, dementia is a significant health and social issue as it poses considerable challenges to individuals, families, and the healthcare system. Not only does this disease have an enormous impact on those affected and their families, but it is also a major financial burden on health care systems, with a projected cost of around 26.6 billion dollars over the next 20 years [134]. Addressing the impact of dementia requires a comprehensive approach that includes research into prevention, early intervention, and better treatment options. Physical activity, obesity, and smoking status have all been identified as potentially modifiable risk factors for dementia, with diet now being explored to determine the impact it may have on dementia risk. Promising results have been observed for the Mediterranean Diet (MedDiet) in reducing cognitive decline and slowing brain atrophy, with early research into the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet also demonstrating positive outcomes. Despite this, many studies also exist that have not found associations between these diets and measures of dementia risk. Many inconsistencies are present in MedDiet adherence scoring, making it difficult to draw comparisons between studies. Furthermore, as a relatively new dietary pattern, research into the MIND diet, particularly regarding its effects on brain volume, is limited.

For this thesis, data were collected and analysed from baseline participants of the ACTIVate study, which consisted of over 400 older adults from Adelaide and Newcastle. Adherence to the MedDiet and MIND diet was assessed along with cognitive function and brain volume to determine the potential impact of these diets on correlates of dementia risk.

5.2 Main findings

5.2.1 Mediterranean diet

Two MedDiet scoring methodologies were utilised within this thesis. The first was developed by Panagiotakos *et al.* [1] (P-Med score) and the second score was created by Sofi *et al.* [2] (S-Med Score).

No associations were observed between the MedDiet and cognitive function for either MedDiet score. This is consistent with a previous randomised controlled trial that reported no significant improvements in multiple cognitive domains following MedDiet intervention [90], with other studies supporting these findings [83, 84, 112]. However, other research has demonstrated a positive relationship between MedDiet adherence and higher cognitive function in various domains [26, 83, 84, 85, 86, 87, 88, 89]. With many MedDiet scoring systems in circulation, and differences in scoring methodology present even when utilising the same score, it is possible that this could explain why findings are so inconsistent across studies.

While the current study did not elucidate any benefit to cognition with higher MedDiet adherence, it did find a positive association between MedDiet adherence and brain volume. Specifically, higher adherence to the S-Med Score was associated with higher total brain volume, white matter volume, and hippocampal volume, although the only association that survived false discovery rate adjustment in fully adjusted models was with white matter volume. On the contrary, no associations were observed with higher adherence to the P-Med Score and brain volume measures. This may be attributed to variations between the two scoring methods, including differences in food categories and cut-off values used. The P-Med Score is based on the traditional MedDiet pyramid, whilst the S-Med Score was modelled on a review of the literature surrounding MedDiet and health outcomes, suggesting this may be a more appropriate model to follow when aiming to confer protective benefits to the brain.

When examining the interplay of MedDiet adherence, brain volume, and cognition within a single model, it was found that higher adherence to the P-Med Score may be more beneficial on the long-term memory of individuals with lower hippocampal volume compared to higher hippocampal volume. There is a possibility that enhanced adherence to

the MedDiet may offer protective effects on memory, potentially reducing the consequences of hippocampal atrophy on memory function. One proposed explanation is that the correlation between higher adherence to a MedDiet and decreased amyloid and hyperphosphorylated tau protein (p-tau) pathology [84] could serve as a potential mechanism by which the protective effect is realised. Given the recent evidence suggesting the use of blood-based biomarkers to measure concentrations of phosphorylated tau proteins within the brain [135], there may exist a potential avenue for future research to explore associations between the MedDiet and p-tau pathology.

Overall, further research is still needed on the MedDiet to determine its true potential for dementia prevention. While this dietary pattern may not be associated with higher cognitive function, certain iterations, such as the S-Med Score, may provide neuroprotective benefits relating to brain volume.

5.2.2 MIND diet

Higher adherence to the MIND diet was initially associated with greater executive function. This relationship persisted after adjusting for demographic variables and cardiovascular risk factors. However, statistical significance diminished after further adjusting for depression. It is also important to note that, while significant associations were seen in the initial models, the effect size observed was relatively small, and significance was lost after false discovery rate adjustment in models 2 and 3. In comparison to the initial findings of this study, a randomised controlled trial conducted in 2022 on obese women in Iran found positive associations between executive function and a calorie-restricted MIND diet compared to a calorie-restricted control diet [99]. It is pertinent to highlight, however, that this study utilised a different population to that which was used in this thesis, and depression was not adjusted for in their statistical model. Conversely, a cross-sectional study more closely aligned with the present study demonstrated no association between MIND diet adherence and executive function in a sample of 389 older adults (mean age = 69 ± 6 years) [96]. Similarly, a more recent randomised controlled trial conducted by Barnes *et al.* [100] on 604 older adults (mean age = 70.4 ± 4.2 years) found no differences in executive function changes over a 3-year period between participants assigned to a MIND diet, and those assigned to a control diet. Given the sample population in these studies aligns more closely

with the population in the present study, it may be concluded that there is insufficient evidence to suggest any benefits of adherence to the MIND diet on executive function in older adults.

Furthermore, participants who followed the MIND diet more closely within the present study did not exhibit notably superior performance in any other cognitive domains or global cognition when compared to those with lower adherence to the diet. This observation is consistent with the results of the study conducted by Barnes *et al.* [100], where no disparities in episodic memory, semantic memory, or perceptual speed were identified between participants following the MIND diet and those adhering to a control diet. While these findings have been supported previously [96, 98], they diverge from other earlier research results [30, 97, 98, 99].

Regarding neuroprotective effects of the MIND diet on volumetric measures, no associations were seen between higher adherence to this dietary pattern and any of the brain volume measures. These findings corroborate prior research [29, 30], including the work of Barnes *et al.* [100], although conflicting evidence is also present which has shown associations with less hippocampal sclerosis and preserved white matter microstructure with MIND diet adherence [29, 105]. Research on the MIND diet and brain volume is currently quite minimal, and further research is suggested to obtain a better understanding of these associations.

When analysing how MIND diet adherence, brain volume, and cognition interacted within a single model, it was suggested that greater adherence to the MIND diet had a more positive association with the long-term memory of individuals with smaller hippocampal volume as opposed to those with larger hippocampal volume. Similar to the MedDiet, it may be proposed that higher adherence to the MIND diet offers protection to memory function by mitigating the known impact of hippocampal atrophy on this cognitive domain. Notably, the MIND diet has been linked to lower global AD pathology and less β-amyloid load [136], suggesting a potential mechanism by which protection may occur.

Given these results, the MIND diet cannot currently be recommended as a protective dietary pattern against development of dementia. While recent findings by Barnes *et al.* [100] are disappointing for the prospects of the MIND diet for this purpose, it is crucial to

acknowledge the limited research available on the MIND diet's impact on cognition and brain volume. Consequently, there is a need for additional investigation to gain a more comprehensive understanding of these correlations and any potential benefits of this dietary pattern.

5.3 Strengths and limitations and directions for future research

The studies included within this thesis have several strengths. Briefly, strengths include the use of two different sites for data collection, recruitment of an older adult population, utilisation of two different MedDiet scoring systems, and administration of a reliable magnetic resonance imaging (MRI) parcellation protocol and cognitive assessment tools. Additionally, one of the greatest strengths of this study is that it is the first to examine the relationship between MIND diet adherence and brain volume within an Australian sample. Furthermore, this study is the first to investigate the interrelationships among diet, brain volume, and cognition within an Australian population.

However, this study is not without its limitations. Given the cross-sectional design of this study, cognitive decline and reduction in brain volume over time were unable to be measured. Longitudinal studies are recommended to capture these changes over time which may elucidate results not observed within the cross-sectional data used within this study. A lack of spread in the data was also present, particularly for cognitive scores and brain volume measures, potentially limiting the associations able to be detected. Given the good cognitive health and education of the population utilised in this thesis, recruitment of a more diverse population may prove beneficial in determining further correlations between diet and cognition and brain volume.

Limitations relating to diet capture and scoring were also present. The use of food frequency questionnaires (FFQs), while a reliable and validated method of capturing dietary data, limits the extent of information that can be obtained regarding dietary intake of participants. FFQs often group foods together for practicality, such as combining different breakfast cereals into a single question. Consequently, important details such as the distinction between wholegrain and sugary processed cereals cannot be captured from the data. Another drawback of FFQs is that they only provide an estimate of food consumption

frequency (e.g., 2-6 servings per week, 1-3 servings per month), while also relying on participants' estimations of portion sizes without provision of clear serving size definitions, which can introduce subjectivity. In future, it is recommended that weighed food records (WFR) are used to obtain dietary data rather than FFQs to capture dietary intake more accurately. WFRs provide a more accurate measurement of food intake, without the need for participants to estimate amounts consumed, and are considered the gold standard for dietary data collection. Although the Australian Eating Survey used in this research has been validated against WFRs, it is possible that WFRs would provide a more precise analysis, especially for determining adherence to the MedDiet and MIND diet in which small differences in food group intake can affect the adherence scores. As the MedDiet and MIND diet scoring methods are quite sensitive, the use of diet data captured by FFQs may impact the final adherence score achieved by participants compared to a more accurate method such as a WFR. The MedDiet and MIND diet scoring metrics also come with limitations, with the P-Med Score and MIND diet scores having no specifications for what constitutes one serving of each food category, potentially resulting in inaccurate scoring and incomparability across studies. Future research should focus on utilisation of a consistent approach to determining MedDiet adherence. The use of multiple scoring methods and presence of inconsistencies between the same scoring metrics reduces comparability across studies, making it difficult to draw conclusions from the current available body of evidence.

The moderate adherence of this population to the MedDiet and MIND diet may have limited the associations able to be detected in relation to both cognition and brain volume. It is possible that higher adherence to these diets is needed to see stronger positive associations with these outcome measures. Certainly, this was touched on in chapter 2 (see page 22), whereby observational cohort studies conducted in countries more typically associated with regular Mediterranean food consumption (Spain and Greece) appeared to have more consistent and robust findings. Additional analysis of other high quality dietary patterns that may be adhered to more closely by Australians, such as the Australian Dietary Guidelines, may be beneficial to include in future studies.

Finally, it would be of interest to explore the effects of both the MedDiet and MIND diet on white matter microstructure integrity and white matter hyperintensity volume (WMHV). The white matter microstructure of the brain refers to the neural architecture that forms

bundles of myelinated nerve fibres [137]. It is responsible for facilitating the development of higher-level cognitive functioning [137], with a loss of integrity suggested as one of the key mechanisms leading to age-related cognitive decline [138, 139]. Increased reduction in white matter microstructural integrity in the brains of those with AD has been observed across many brain regions, including the frontal, occipital, and temporal lobes, compared to that which is seen in normal ageing [140, 141]. This suggests that changes in white matter microstructure begin in the preclinical stages of AD and may provide a potential target for early dementia prevention. In addition, WMHV has been associated with an increased risk of dementia in a number of studies focusing on the general middle-aged and elderly population [142]. The underlying mechanism of this association is not yet understood, however, evidence suggests that WMHV may indicate microvascular damage to the brain [142]. Again, this would be a beneficial avenue to explore regarding the impact that diet may have on protecting against these lesions.

5.4 Conclusion

Taken together, the findings of this thesis suggest that higher adherence to a MedDiet, specifically under the guidelines outlined by Sofi *et al.*, may provide protective benefits to total white matter volume. Longitudinal studies are recommended to establish causal inferences from these associations. Additionally, further research is needed to determine the true impact of the MedDiet on cognitive function, considering the surplus of mixed results existing within the current body of evidence. While the MIND diet was associated with higher executive function, findings are not robust, with a small effect size noted as well as loss of significance after adjusting for depression. This warrants further investigation, particularly given that research into the MIND diet is currently not as extensive as that of the MedDiet. Additional research is also advisable to investigate potential relationships between adherence to the MIND diet and measures of brain volume. Overall, these results contribute further knowledge to the current body of evidence and will be useful in directing future research studies.

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Appendices

Appendix 1 Mediterranean diet scoring metric adapted from Panagiotakos *et al.* [1]

		Frequency of consumption (servings/wk or otherwise stated)					
Non-refined cereals		Never	1-6	7-12	13-18	19-31	>31
	Score	0	1	2	3	4	5
Potatoes		Never	1-4	5-8	9-12	13-18	>18
	Score	0	1	2	3	4	5
Fruits		Never	1-4	5-8	9-15	16-21	>21
	Score	0	1	2	3	4	5
Vegetables		Never	1-6	7-12	13-20	21-32	>32
	Score	0	1	2	3	4	5
Legumes		Never	<1	1-2	3-4	5-6	>6
	Score	0	1	2	3	4	5
Fish		Never	<1	1-2	3-4	5-6	>6
	Score	0	1	2	3	4	5
Red meat and products		<1	2-3	4-5	6-7	8-10	>10
	Score	5	4	3	2	1	0
Poultry		<3	4-5	5-6	7-8	9-10	>10
	Score	5	4	3	2	1	0
Full fat dairy products		<10	11-15	16-20	21-28	29-30	>30
	Score	5	4	3	2	1	0
Use of olive oil in cooking (times/wk)		<10		10-20		>20	
	Score	1		3		5	
Alcoholic beverages (mL/day)		<300	300	400	500	600	>700 or 0
	Score	5	4	3	2	1	0

Abbreviations: wk, week; mL, millilitres.

Appendix 2 Mediterranean diet scoring metric adapted from Sofi *et al.* [2]

		Frequency of consumption		
Fruit		<1 serve/d	1-2 serves/d	>2 serves/d
	Score	0	1	2
Vegetables		<1 serve/d	1-2.5 serves/d	>2.5 serves/d
	Score	0	1	2
Legumes		<1 serve/wk	1-2 serves/wk	>2 serves/wk
	Score	0	1	2
Cereals		<1 serve/d	1-1.5 serves/d	>1.5 serves/d
	Score	0	1	2
Fish		<1 serve/wk	1-2.5 serves/wk	>2.5 serves/wk
	Score	0	1	2
Meat and meat products		<1 serve/d	1-1.5 serves/d	>1.5 serves/d
	Score	2	1	0
Dairy products		<1 serve/d	1-1.5 serves/d	>1.5 serves/d
	Score	2	1	0
Alcohol		<1 AU/d	1-2 AU/d	>2 AU/d
	Score	1	2	0
Olive oil		<10mL/d	10-20mL/d	>20mL/d
	Score	0	1	2

Abbreviations: d, day; wk, week; AU, alcohol unit; mL, millilitres.

Appendix 3 Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet scoring metric

	Frequency of consumption		
Green leafy vegetables	≤2 serves/wk	>2 to <6 serves/wk	≥6 serves/wk
Other vegetables	<5 serves/wk	5 to <7 serves/wk	≥1 serve/d
Berries	<1 serve/wk	1 serve/wk	≥2 serves/wk
Nuts	<1 serve/m	1/m to <5 serves/wk	≥5 serves/wk
Olive oil	Not primary oil used		Primary oil used
Butter, margarine	>2 tbs/d	1-2 tbs/d	<1 tbs/d
Cheese	≥7 serves/wk	1-6 serves/wk	<1 serve/wk
Wholegrains	<1 serve/d	1-2 serves/d	≥3 serves/d
Fish (not fried)	Rarely	1-3 serves/m	≥1 serve/wk
Beans	<1 serve/wk	1-3 serves/wk	>3 serves/wk
Poultry (not fried)	<1 serve/1k	1 serve/wk	≥2 serves/wk
Red meat and products	≥7 serves/wk	4-6 serves/wk	<4 serves/wk
Fast fried foods	≥5 times/wk	1-4 times/wk	<1 time/wk
Pastries and sweets	≥7 serves/wk	5-6 serves/wk	<5 serves/wk
Wine	>1 glass/d or never	1/m to 6 glasses/wk	1 glass/d
Score	*0*	*0.5*	*1*

Abbreviations: wk, week; d, day; m, month; tbs, tablespoon.