LIFETIME DIET AND COGNITION IN OLDER PEOPLE

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Abstract

Dietary intake may impact upon the trajectory of older-age cognitive change and decline via nutritional mechanisms that contribute to brain health and functioning, and to the risk of chronic diseases associated with poorer late life cognitive outcomes.

Diet is a modifiable environmental exposure. As such, it provides an avenue for intervention to promote better cognitive functioning and delay or prevent cognitive impairment and dementia that are placing an increasing burden on older individuals, their families and the health system.

The majority of studies that have investigated the nutritional determinants of healthy cognitive ageing have done so within populations older than 65, but the long-term aetiology of cognitive change extends years and even decades prior to the onset of noticeable decline. Thus, the salience of diet to an individual's cognitive ageing trajectory is likely to extend back into the life-periods prior to older age. Even the longest prospective studies do not have dietary records extending over the lifetime; therefore, determining the relationship, if any, between earlier-life diet and later-life cognitive health requires an alternate approach to gathering lifetime dietary data.

The objective of this thesis was to develop a retrospective dietary reporting instrument to measure intake from multiple life-periods, then to investigate cross-sectional and longitudinal associations between lifetime diet and cognitive performance in cognitively healthy older-adults.

Studies 1 to 3 investigated the reliability and validity of the Lifetime Diet Questionnaire (LDQ); the dietary assessment instrument developed in the context

of the thesis to measure past diet. Study 1 was a preliminary study of dietary recall using the foods and frequencies of the LDQ. The strength of associations was tested between young adults' (n=203) recall of earlier adolescent diet, and one or more family members' recall of the same individual's diet over the same period. Study 2 assessed the test-retest reliability of LDQ's five life-periods in older adults (n=51). Both measures of reliability fell within acceptable limits. In Study 1, the average association between family members recall of an individual's past intake was 0.73, while in Study 2, the average test-retest reliability of the questionnaire across all life-periods in an older sample was 0.81. Study 3 (n=352) recruited participants from the EPOCH trial (a randomised controlled trial of Omega-3 fish oil on older-age cognitive change). The validity of long-term dietary recall was investigated by testing the associations between lifetime dietary patterns extracted from the LDQ, and the EPOCH participants' demographic and cardiovascular health variables. Lifetime dietary patterns were related to the demographic variables of age, sex, education, income, parental background, and childhood physical activity; patterns from childhood and adulthood also predicted cardiac medication use and cholesterol level in older age.

Studies 4 and 5 used the same cohort to examine the relationships between LDQ dietary patterns and cross-sectional cognitive performance (Study 4) and 18-month cognitive change over 4 time points (Study 5). After controlling for relevant covariates and current dietary intake, all dietary patterns from the childhood period predicted baseline level of cognitive performance, and a 'non-traditional Australian' pattern in middle age predicted 18-month cognitive change.

These preliminary findings have implications for the relevance of diet as a lifetime determinant of older-age cognitive health.

Declaration

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This thesis is dedicated to my parents

Katrina and Kevin,

and children

Therese, Rachel, and John

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Abbreviations

AA	Arachidonic acid
AD	Alzhemer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AIBL	Australian Imaging Biomarker and Lifetstyle Study
ALA	Alpha-linolenic acid
ALSPAC	Avalon Longitudinal Study of Parents and Children
ApoE	Apolipoprotein
AR1	First-order autoregressive covariance structure
BMI	Body Mass Index
CCFFQ	Cancer Council Food Frequency Questionnaire
CES-D	Centre for Epidemiological Studies Depression scale
CFA	Confirmatory Factor Analysis
CHAP	Chicago Health and Aging Project
C-PIB	Carbon-labelled Pittsburgh Compound-B
DHA	Docosahexaenoic acid
EFA	Exploratory Factor Analysis
ELSA	English Longitudinal Study of Ageing
EM	Expectation Maximization
EPA	Eicosapentaenoic acid
EPOCH	Older People, Omega-3, and Cognitive Health
FFQ	Food Frequency Questionnaire
*f*MRI	Functional Magnetic Resonance Imaging
FSR	Framingham Stroke Risk profile
Gc	Crystallised ability
Gf	Fluid ability
HDL	High Density Lipoprotein
ICC	Intra-class corelation co-efficient
IGC	Individual Growth Curve
kcal	Kilocalorie
LA	Linoleic acid
LBC-1921	The Lothian Birth Cohort of 1921

Abbreviations *(continued)*

LC-PUFA	Long-chain polyunsatufated fatty acid
LDL	Low Density Lipoprotein
LDQ	Lifetime Diet Questionnaire
LSADT	Longitudinal Study of Aging in Swedish Twins
MAR	Missing at Random
MCAR	Missing Completely at Random
MCI	Mild Cognitive Impairment
MeDi	The Mediterranean Diet
MMSE	Mini Mental State Examination
MRC - NHSHD	The Medical Research Council National Survey of Health and Development
OLS	Ordinary Least Squares
P &P	Paper and Pencil
PET	Positron Emission Tomography
RAVLT	Rey-Auditory Verbal Learning Test
ROS	Reactive oxygen species
SATSA	Swedish Adoption Twin Study of Aging
SEM	Structural Equation Model
SLS	Seattle Longitudinal Study
UN	Unstructured covariance structure
VIF	Variance Inflation Factor
VLSA	Victoria Longitudinal Study of Aging
WHICAP	Washington Heights-Inwood Columbia Aging Project
WMH	White Matter Hypertensities
WML	White Matter Lesions
YPAS	Yale Physical Activity Scale

Preface

The objective of this thesis was to develop an assessment instrument that measured lifetime dietary intake and investigate its associations with cognitive performance in cognitively healthy older adults. The thesis presents five studies; Study2, Study 3,and Study 4 are publications that are flanked by the unpublished results for Study 1 and Study 5.

Change and decline in cognitive abilities inevitably accompany ageing. Identifying modifiable environmental exposures that predict better cognitive functioning in older people potentially contributes to reducing the risk of decline and dementia that undermine quality of life for the rapidly increasing older proportion of the population. Dietary intake is one such exposure that potentially influences older-age cognitive status via nutritional mechanisms that support brain health and functioning, and by influencing the risk of chronic diseases that in turn predict poorer cognitive outcomes in older age.

A serious impediment to understanding the role of dietary intake in older-age cognitive health is the long-term aetiology of cognitive change; this applies regardless of whether the outcome is 'normal' age-related decline, or pathological decline and dementia. The antecedents of an individual's cognitive ageing trajectory are the result of numerous genetic and environmental interactions that reach back across the lifetime and even prenatally (Benton, 2010b). Therefore, it is likely that any dietary impact on later life cognition is the product of a lifetime's intake.

Due to logistic constraints, the majority of research that examines associations between diet and older-age cognitive performance has utilised a

measure of diet in later life, and at one time-point only. In the minority of studies that have assessed diet at multiple time points, the period between assessments was relatively short in comparison to the decades that comprise lifetime dietary exposure.

The current investigation between recalled lifetime diet and cognitive functioning was carried out in a sample of older adults participating in the EPOCH trial (Danthiir, Burns, Nettelbeck, Wilson, & Wittert, 2011), an 18-month randomised controlled trial of omega-3 fish oil on older-age cognitive functioning. These participants were screened for dementia and medical conditions known to impact on cognitive functioning; so decline, if any, occurring over the period of the trial would be within the context of normal ageing. It is important to emphasise that although the research for this thesis was performed in a non-clinical population, the potential findings are relevant to informing prevention strategies for pathological cognitive ageing. Indeed, the assessment of cognitive performance and cognitive change in populations without evidence of impairment is an important approach in the prevention of dementia (Sperling et al., 2011). It has been demonstrated in numerous prospective studies that those who later develop Alzheimer's disease consistently perform more poorly on cognitive tests during the prior dementia-free period from many years earlier (Elias et al., 2000; Twamley, Ropacki, & Bondi, 2006). Thus, the identification of modifiable environmental factors (in this case past dietary intake)that predict differential cognitive outcomes offer potential pathways for prevention, or at least delay of the debilitating clinical symptoms of dementia and decline (Singh-Manoux & Kivimäki, 2010).

It will be apparent that the thesis scope is broad and crosses the boundaries of a number of research disciplines including psychology, nutrition, neuroscience, and both life-course and nutritional epidemiology. What constitutes assumed knowledge in one discipline is not necessarily well recognised in another. For the sake of clarity, an overview of the thesis structure follows and some contextual background to its content is provided.

The thesis is presented in three sections. Section A is the literature review comprising three chapters. Chapter 1 commences with an overview of cognitive ability measurement and the methodological issues inherent in determining if and when cognitive decline occurs in normally functioning adults. The chapter then draws on a broad spectrum of research to demonstrate that individual differences in the cognitive ageing trajectory are determined by genetic, environmental, and health factors that operate across the lifetime to affect later life cognitive functioning[1]. These factors theoretically may act as moderators or mediators in any potential relationship between lifetime intake and cognition, so some explanation of their relevance to cognitive ageing is appropriate. Additionally, a number of variables representing these factors were used as covariates in subsequent analyses.

The chapter concludes with a discussion of the 'brain reserve' heuristic as a mechanistic explanation for cognitive ageing, and consequently promotes a life course approach to identify the determinants of healthy cognition in older age. Thus, the context is created for assessing the contribution of a lifetime's exposure

[1] Nutritional intake is one of these factors, but it is not addressed at this point; its particular long-term relevance to cognition will be discussed in chapter two of the literature review.

to any potential environmental predictor of individual differences in older-age cognitive outcomes.

Chapter 2 focuses specifically on the nutritional aspect of the thesis. Adequate early-life nutritional intake is essential for normal brain growth and cognitive development. If nutritional deprivation impacts on the development of cognitive ability during childhood, which also predicts later-life cognitive status, then a strong rationale is evident for the need to assess diet from early-life periods when evaluating the impact of dietary intake on later-life cognition. Therefore, the first part of the chapter outlines theoretical evidence for the essential role of nutrients to early-life cognitive development. Nutrient mechanisms are also relevant to brain ageing and underpin the hypothesised role for nutritional intake as a buffer against age-related decline (Gómez-Pinilla, 2008; Uauy & Dangour, 2006). The nutritional influences on brain ageing will be discussed focusing on those nutrients that are hypothesised to have particular relevance.

The potential impact of diet on cognitive ageing has led to an explosion of studies with divergent designs, predictors, and outcomes, but with a common underlying aim of demonstrating whether what we eat can lessen the growing burden of cognitive impairment in an ageing population. The majority of such studies assess the nutritional or dietary intake of participants who have already reached older age; but the focus of this thesis is the potential impact of dietary intake from life periods prior to old age. Consequently, an overview of findings is presented from the very few studies that have examined the effect of diet from an earlier time period on older age cognition.

As stated, the objective of the thesis was to examine the potential influence of diet from across the whole life time on older-age cognition. To achieve this aim,

it was necessary to assess dietary intake from many decades earlier. Chapter 3 discusses approaches to past dietary recall and the methodological issues and limitations that need to be acknowledged and addressed.

The validity, and consequently the utility of long-term dietary recall are controversial. Section B of the thesis consists of studies one to three, presented as individual chapters that test the reliability and validity of lifetime dietary recall as assessed by the newly developed LDQ.

Study 1 used a sample of convenience from the University of Adelaide to test the inter-rater reliability of the questionnaire for the long term recall of foods using the frequency options of the LDQ. Study 2 recruited participants from the Adelaide Ageing and Cognitive Change Study and assessed test-retest reliability of lifetime dietary recall for each of the five life-periods of the questionnaire (Hosking, Danthiir, Nettelbeck, & Wilson, 2011). The questionnaire's utility as a dietary assessment instrument was investigated in Study 3 (Hosking & Danthiir, 2013). In this study a subsample from the EPOCH trial (Danthiir, V. et al., 2011) completed the LDQ. Exploratory factor analysis extracted theoretically plausible dietary patterns for each life period. Associations were then examined between these dietary patterns and the demographic and cardiovascular health variables from the EPOCH cohort. The aim was to test whether dietary intake, as assessed by the LDQ, predicted these variables in a manner commensurate with the established relationships in the literature between diet and both demographics, and health outcomes.

Section C of the thesis consists of studies 4 and 5, together with a concluding discussion. These two studies aimed to fulfil the overarching objective of the thesis by examining whether recalled lifetime dietary intake predicted older-

age cognitive performance after controlling for relevant covariates. Study 4 (Hosking, Nettelbeck, Wilson, & Danthiir, 2013) assessed cross-sectional associations between the lifetime dietary patterns from the LDQ and the comprehensively assessed cognitive outcomes of the EPOCH trial. Study 5 tested whether lifetime dietary patterns predicted cognitive change over 18-months using the cognitive outcomes from the four time points of the trial.

SECTION A: LITERATURE REVIEW

Chapter 1 Cognitive Ageing

1.1 Introduction

Lifetime dietary intake potentially predicts individual differences in cognitive ability measures amongst cognitively healthy older people. To investigate this proposition, cognition needs to be measured. The chapter begins, therefore, with a summary of the differing approaches used to measure cognitive abilities, which is followed by a discussion of the inherent methodological issues in defining age-related cognitive change. The next section addresses the question of what factors account for the heterogeneity of older-age cognitive functioning, and examines the heuristic of 'reserve' as a theoretical framework for cognitive ageing research. Finally, the application of a life course approach is recommended to investigate the determinants of differential decline, so providing the rationale for investigating the lifetime impact of dietary intake on older-age cognition.

1.2 Measurement of Cognitive Abilities

Unlike measures of physical function such as heart rate, blood pressure, and lung volume, cognitive measures can only be inferred indirectly by assessing performance on tasks that represent these abilities (Salthouse, 2010b). The outcome measures used to assess cognitive functioning in older age are drawn from research perspectives that have on the whole evolved independently from each other, with little communication or collaboration between the different

traditions (Salthouse, 2010a). In order to navigate the landscape of cognitive ageing research, an overview is presented of the different approaches to measuring cognitive ability in the context of its particular application in studies of older[2] populations.

1.2.1 The psychometric perspective

The term psychometric was used by Francis Galton in 1879 when he published a paper in the journal 'Brain' entitled 'Psychometric Experiments'. He described psychometry as *"the art of imposing measurement and number upon operations of the mind, as in the practice of determining the reaction-time of different persons"* (Galton, 1879, p. 149). The zeitgeist of late 19th century Europe, England, and North America propelled the quantification of mental functioning, and throughout the first part of the 20th century multiple tests of intellectual ability were developed. This was driven in part by the opportunity to apply a mental testing regime to the selection and screening of the army during World War 1, and the post-war commercialisation of mental testing (Wasserman & Tulsky, 2005). The foundations of modern intelligence testing were laid during this period with the development of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1939); the subtests of which were derived from these early testing measures (Boake, 2002).

The long and frequently controversial history of psychometrics spans over 100 years but at its centre were two definitive early findings; that individuals' scores on multiple tests of cognitive ability were correlated (Spearman, 1904), and that

[2] The age an individual becomes an 'older' adult is arbitrary, but the Australian census categorises all those who are > 65 years as 'older Australians'. Salthouse (2010a) makes the wry observation that in cognitive ageing research, an 'older adult' refers to anyone who is10 years older than the researcher!

general cognitive ability was best represented by a number of separate cognitive domains (Thurstone, 1936).

The technique of factor analysis, developed by Louis L Thurstone in the mid-1930s, allowed for the extraction of separate ability factors from the analysis of test battery correlation matrices, and paved the way for the development of hierarchical models of cognitive abilities. Factors were defined by the tests that loaded most highly on them. Thurstone obtained scores from 56 tests administered in a 15 hour test battery to university students. He interpreted seven primary mental ability factors from the factor analysis of this test battery: spatial visualisation, perceptual speed, numerical facility, verbal comprehension, associative memory, verbal fluency, and reasoning (Wasserman & Tulsky, 2005). These primary mental ability factors have been used extensively in psychometric research, and have been particularly relevant in the cognitive ageing literature. The Primary Mental Abilities were later used by Schaie as the foundation for the test battery in the Seattle Longitudinal Study (SLS) (Schaie, 2005); arguably one of the most comprehensive and influential 20th century longitudinal studies of cognitive ageing.

Further development of factor analytic techniques by Raymond B. Cattell led to the demonstration of two separate general higher order ability factors rather than one general factor as had been proposed by Charles Spearman nearly 40 years earlier (Spearman, 1904). Cattell named these two higher order factors crystallised ability (Gc) and fluid ability (Gf) (Cattell, 1963); he described these abilities as follows:

Crystalliszed ability loads more highly on those cognitive performances in which skilled judgement habits have become crystallized (whence its name) as the result

> *of earlier learning application of some prior, more fundamental general ability to these fields, Thurstone's Verbal and Numerical primaries, or achievement in geography or history, would be examples of such products. Fluid general ability on the other hand, shows more in tests requiring adaptation to new situations, where crystallized skills are of no particular advantage* (Cattell, 1963, pp. 2-3).

Cattell and his student John Horn later expanded the number of higher order factors from two to five by adding visualisation, retrieval capacity, and cognitive speed (Horn & Cattell, 1966). In the early 1990s, Horn added a further factor representing an individual's speed of reacting and making decisions (reaction time and decision speed) and finally, after collaborating with Richard Woodcock, factors for quantitative ability and broad reading/writing ability were also added to the model (Alfonso, Flanagan, & Radwan, 2005).

The most recent definitive *"empirically based psychometric taxonomy of human cognitive abilities"* (McGrew, 2005, p. 146) was developed by John Carroll and built on the foundations laid by Cattell and Horn. Carroll collated and re-analysed 461 separate data sets that spanned 50 years of ability testing. His resulting three stratum model had a general ability factor at the highest level, eight or more second-order broad ability factors (that included a Gf and Gc factor), and greater than 65 first order narrow ability factors. It was published in his monumental opus 'Human Cognitive Abilities: A survey of factor-analytic studies' (Carroll, 1993).

The earlier differentiation by Cattell between fluid and crystallised abilities proved pivotal to later cognitive ageing research. Cattell had already hypothesised that Gf and Gc would have differing developmental trajectories (Cattell, 1963) and in 1967, Horn and Cattell put this theory to the test by factor analysing 23 tests of

mental ability administered to 297 participants (the majority being prisoners) aged 14-61 years, divided into five age groupings. Their results demonstrated significantly higher mean levels of fluid ability functioning in younger adults than older adults; although the number of participants in the each age group was not large (approximately 40-60 people in each group (Horn & Cattell, 1967). Poorer performance on cognitive tests by older adults had been observed by others (including David Wechsler) in the 1920s and 1930s (Salthouse, 2010a), but the finding that ageing systematically and differentially appeared to affect higher order cognitive abilities provided much of the impetus and theoretical framework for later studies of between-age-group comparisons on cognitive performance (Salthouse & Ferrer-Caja, 2003), and the longitudinal evaluation of growth and decline across separate abilities within the Gf-Gc framework (McArdle, Hamagami, Meredith, & Bradway, 2000).

It is timely to emphasise at this point that although the hierarchical model of cognitive abilities is at the centre of the psychometric tradition of ability measurement, in the words of Ian Deary, the broad factors are not informative of *"anything in our heads...there is no art to reading the mind's construction in confirmatory or exploratory factor analytic diagrams"* (Deary, 2000, pp. 17-18).

1.2.2 The information processing perspective

In comparison to the psychometric perspective that measures the products of cognition, the information processing perspective focuses on measuring the processes that underpin performance. It was based on the perceived necessity to give the factors of the psychometric ability approach psychological and physiological substrates (Das, Kirby, & Jarman, 1975). According to Robert Sternberg, information processing *"is generally defined as the sequence of mental*

operations and their products involved in performing a cognitive task" (Sternberg, 1981, p. 1182).

Sternberg provided the driving theoretical force behind the implementation of a reductionist approach to intellectual abilities (Deary, 2000). In his book 'Intelligence, Information Processing, and Analogical Reasoning' Sternberg introduced componential analysis, a technique designed to

> *...identify the component mental operations underlying a series of related information-processing tasks and to discover the organization of these component operations in terms of their relationships both to each other and to higher-order constellations of mental abilities* (Sternberg, 1977, p. 65).

Sternberg demonstrated the application of componential analysis by breaking down a reasoning task (e.g. sugar is to sweet as lemon is to?) into a flow-chart style processing model with the components of reasoning labelled as encoding, inferring, mapping, justification, and preparing-responding. Performance at each of these stages and the interrelationships between stages were then studied (Floyd, 2005). The splitting of mental tests into mental units without utilizing constructs from lower levels of psychological or biological research made the cognitive components approach essentially self-sufficient (Deary, 2000), but it was hindered by the apparently arbitrary nature of the components, the sheer number of the possible components for any given task, and the extensive testing required to test the validity of the hypothesised components (Floyd, 2005; Miller, 1999).

During the middle to late 1970s and 1980s the cognitive correlates approach to abilities emerged. It drew on the knowledge gained of basic processes of mental functioning in regard to lexical, numerical, or visual-spatial stimuli, and incorporated the revival of interest in the relationship between these basic

processes and higher order cognitive abilities (Miller, 1999). The goal of the cognitive-correlates approach was to integrate psychometrics and mainstream cognitive psychological research by providing a theoretical framework for psychometric abilities:

> *Instead of trying to draw theoretical conclusions from correlating scores on one empirically derived test (e.g. reasoning) with scores on another empirically derive test (e.g. vocabulary), as differential researchers have done, the cognitive correlates researcher draws theoretical conclusions from correlating scores on an empirically derived test with parameters generated by a cognitive model of some aspect of mental functioning (e.g. memory scanning)*[3] (Sternberg, 1981, p. 1182).

The abilities that were the focus of the cognitive correlates approach were not only drawn from the psychometric tradition. Luria in the mid 1960s had mapped the effects of brain lesions in particular brain areas onto psychological functioning (1966). Neuropsychological research had contributed significantly to understandings of the association between brain functioning and a range of cognitive functions via the cognitive deficits that were apparent in those with brain localised brain damage (Lezak, Howieson, & Loring, 2004). Neuropsychology recognised a number of cognitive functions that informed the information processing approach; for example, attention, working memory, long-term memory, and perception. Higher level functions included speech and language, decision making, and executive control (Glisky, 2007). In line with the cognitive-correlates approach, Kyllonen and Crystall examined the association between a

[3] Memory scanning is a task developed by Saul Sternberg (Sternberg, 1969), as opposed to Robert Sternberg, the proponent of the cognitive correlates approach. The Memory Scanning task asks participants to state as quickly as possible whether a target digit or letter appears in a previously memorised set of digits or letters.

neuropsychological construct (working memory) and a psychometric construct (reasoning ability) using confirmatory factor analysis; it was found that these two constructs were highly correlated (0.8 to 0.9), suggesting considerable overlap between them (Kyllonen & Christal, 1990).

The information processing perspective has been instrumental in cognitive ageing research in its attempts to provide mechanistic explanations for the age-related changes in higher order abilities. For example, studies have examined the associations between ageing, executive control, and attention (Verhaeghen & Cerella, 2002); between age, working memory, episodic memory, spatial ability, and speed of processing (Verhaeghen & Salthouse, 1997); and an influential paper by Salthouse examined the role of processing speed in explaining the age-related variance in fluid intelligence (Salthouse, 1996).

Inspection time (IT) is lower-level task measuring speed of processing and has been extensively examined in terms of its relations with increasing age and higher order abilities (Nettelbeck, 2011). Inspection Time is defined as *"the delay between onset of a target and the onset of a following masking figure at which judgements meet a predetermined high level of accuracy"* (Nettelbeck, 2001, p. 460). Over 25 years of research has demonstrated a moderately strong relationship between IT and general cognitive ability, with meta-analysis of 92 studies (> 4,000 participants) reporting a corrected mean correlation of -.51 (Grudnik & Kranzler, 2001). Within the context of cognitive ageing, IT has been associated with 18-month longitudinal decline on working memory performance, and slowing IT correlated with fluid reasoning performance also at 18-months (Gregory, Nettelbeck, Howard, & Wilson, 2008). In terms of basic information processing measures IT has been of particular interest in cognitive ageing research due to the

hypothesis that it may serve as an early biomarker of age-related decline (Deary, Johnson, & Starr, 2010; Gregory et al., 2008; Gregory, Nettelbeck, & Wilson, 2009).

A more detailed examination of the relations between age, higher order abilities, and information processing measures is beyond the scope of this discussion but both Deary (2000) and Nettelbeck (2011) provide comprehensive accounts.

1.2.3 Screening for dementia: The Mini Mental State Examination

In any study that aims to recruit cognitively healthy older adults, identifying, and excluding those who are suffering from impairment or dementia is essential.

The most widely used screening instrument for this purpose is the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). This test was originally developed within a psychiatric context to overcome the burden of lengthy diagnostic batteries on the elderly and impaired. It covers a variety of cognitive domains, but excludes questions concerning mood, abnormal mental experiences, and thinking. The MMSE is a short test, usually completed in approximately 10 minutes, consisting of 30 questions that assess orientation to time and place, short and delayed memory recall, registration, constructional ability, language, and the ability to understand and follow instructions (Molloy & Standish, 1997). Cognitive performance as measured on the MMSE varies within the population by age and education ranging from a mean of 29 for those 18-24 years of age to 25 for individuals 80 years and older. Years of education predicts population scores with a median score of 29 for those with at least nine years of schooling, 26 for those with five to eight years of schooling, and 22 for those with zero to four years of schooling (Crum, Anthony, Bassett, & Folstein, 1993). The cut-

off score for dementia screening in older populations is generally as accepted as being 24 although a recent study suggests this score should be increased to 27 in older well educated populations to achieve a correct classification of cognitive impairment (O'Bryant et al., 2008).

Although the MMSE was originally designed as a screening instrument, it's simple and brief administration procedure, including a validated telephone version (Newkirk et al., 2004), have lead to its in inclusion in large epidemiological studies of ageing where comprehensive cognitive assessment is logistically challenging. The MMSE has been shown to correlate at up to .78 with the verbal sub-scale of the WAIS and .66 with the performance scale; modest to high correlations have also been found with neuropsychological measures such as working memory span, digit span, and Trails B. Failure to obtain significant correlations occur, however, when the average MMSE score is 27 or above due to the lack of variability in the MMSE score distribution (Tombaugh & McIntyre, 1992).

In cognitively healthy participants, therefore, use of the MMSE as the sole measure of cognitive functioning is unlikely to be particularly sensitive to either cross-sectional differential performance, or age related decline. A 5 year longitudinal study of the MMSE in normal ageing in fact found that, in a group of French community residents aged 65 years and older, scores rose from time 1 to time 2 (most likely due to testing effects) and only very marginally decreased over the five years (.02 points for those 65-70, up to .57 points for those 85 years) (Jacqmin-Gadda, Fabrigoule, Commenges, & Dartigues, 1997).

1.3 Decline According to Design: Cross-sectional and Longitudinal Approaches to Cognitive Ageing in Healthy Populations

Overall, the dominant interpretation of cross-sectional relations between chronological age and cognitive abilities has been that they represented average developmental change (Salthouse, 2010a) . According to this interpretation, age-related declines in abilities (with the exception of vocabulary) are relatively large and begin in early adulthood for measures of speed, reasoning and memory.

Salthouse had articulated this position almost 20 years earlier by the following:

> *Although nearly every other conceivable issue seems to have been debated, the fundamental fact that intelligence as assessed by traditional intelligence tests with cross-sectional procedures exhibits more or less continuous decline across successive age groups beginning at about age 25-30 has not been disputed. Many psychologists like Spearman (1927) have been impressed with the "tragic import" of these finding and have speculated that humans are already too old for their best work at age 30, rather than 50 or 70* (Salthouse, 1988, p. 81).

Salthouse's claim that the continual decline in intelligence measures from age 25-30 had not been disputed was not entirely accurate. Approximately 10 years earlier a lively and somewhat heated exchange had occurred between researchers regarding when cognitive change begins (Baltes & Schaie, 1976; Horn & Donaldson, 1976, 1977; Schaie & Baltes, 1977). Data from the SLS (Schaie, 1994) showed that with the exception of numeric skill and perceptual speed, most cognitive abilities at the latent construct level (including inductive reasoning) actually improved from young adulthood to age 60; although in accord with cross-

sectional designs, it was clear that by the mid 70s significant average decrement was apparent for all

abilities except verbal ability, which was maintained into advanced old age (Schaie, 1994; Schaie, 2005).

1.3.1 Methodological considerations: Cross-sectional studies

A serious challenge to the instantiation of age-related cognitive decline by cross-sectional findings is the conflation of chronological age with birth cohort (Hofer & Sliwinski, 2006). This limitation was highlighted by Baltes and Schaie in the debate referred to earlier regarding the discrepancy between cross-sectional versus longitudinal methodologies

> *....we continue to argue that a major share of developmental differences in intelligence during adulthood and old age (for the variables, samples, and historical period studied) is due to generational-cohort effects and not to ontogenetically invariant aging processes* (Baltes & Schaie, 1976, p. 723).

Put simply, age related differences between people do not necessarily imply ageing. Year of birth determines an individual's generation or cohort which is defined by particular environmental exposures and socialisation experiences. If these experiences differ between cohorts, and are relevant to cognitive performance (e.g. educational priorities and opportunities), then it is possible that cohort effects, rather than ageing itself, are responsible for age-related differences in cognitive functioning (Alwin, 2009).

A particularly salient example of this is the finding that unstandardised IQ scores (as tested by the WAIS and similar test batteries) have increased across successive generations over the last century in most countries. These gains are

particularly evident in measures of reasoning or Gf which increased 1.5 standard deviations for those tested in 1980 compared to those tested in 1950 (Flynn, 1987, 1998). This phenomenon was described by James Flynn in the late 1980s and has become known as the 'Flynn Effect' (Herrnstein & Murray, 1994). The implication for comparisons of cognitive functioning between older and younger people is that cohort-based differences in reasoning scores contribute to the findings of cross-sectional decline on fluid measures of performance in older people (Zelinski & Kennison, 2007). In the Long Beach Longitudinal Study of Aging (Zelinski & Kennison), this hypothesis was tested by using a time-lagged sequential design. Longitudinal performance was examined for two cohorts of participants whose baseline ages were 55 to 82; the cohorts were born 16 years apart, so the first evaluation was in 1978 for cohort one, and 1994 for cohort two. Latent growth models demonstrated that at age 74 there were cohort effects on measures of reasoning, recall, space and vocabulary; although the strength of these effects varied by task, with larger effects of cohort found for the more fluid measures than crystallised ones (Zelinski, Kennison, Watts, & Lewis, 2009). These findings do not negate the role of ageing in age-related performance differences but, rather, they demonstrate the need to account for cohort effects when interpreting such differences in age-heterogeneous samples.

Cross-sectional designs are useful for preliminary investigation and hypothesis generation (Hofer & Sliwinski, 2006), but the inferences that can be drawn regarding age differences in cognitive performance are limited. Measurement at a single point is a function of initial individual differences, cumulative developmental change, as well as within-person variability and measurement error (Hofer & Piccinin, 2010). Particularly relevant to the

investigation of age differences in cognitive measures is that, inevitably, some of those in older age groups are likely to have pre-clinical cognitive impairment, or be in the early stages of undiagnosed dementia, thereby increasing the apparent decrements in performance in relation to younger adults (Alwin, McCammon, Wray, & Rodgers, 2008).

The biases inherent in cross-sectional measurement therefore necessitate using longitudinal designs to investigate within person change rather than infer ageing effects from analysis of between person age differences (Hofer & Piccinin, 2010). This is not to say that longitudinal designs do not have limitations (Salthouse, 2010a), but these limitations can often be overcome, or at least accounted for methodologically or statistically in longitudinal studies (Hofer & Sliwinski, 2006). The statistical methods available for longitudinal data are able to separate within-person variability and co-variability from between-person differences. These different levels of analyses enable the contribution of both between and within sources of variability to be assessed (Hofer & Piccinin, 2010).

1.3.2 Methodological considerations: Longitudinal studies

A major criticism of longitudinal designs is the biasing of test scores by repeated measurement occasions over time; a phenomenon known as 're-test effects' (Salthouse, 2010b). Re-test gains of 0.1 to 0.6 SD units of test performance have been found for periods of up to one year. In adults aged between 18 and 58 years, seven or more years need to pass before positive retest effects are no longer detectable (Salthouse, Schroeder, & Ferrer, 2004). These findings, however, are not necessarily generalisable due to individuals' differential responses to multiple testing occasions (Hofer & Sliwinski, 2006).

Re-test effects can be dealt with in longitudinal designs by using sequential sample comparisons in which a new independent sample is drawn from the same cohort at each test occasion (Schaie, 2005). Alternatively, the effects of age and testing occasion can be modelled separately to estimate the linear changes in retest gains as distinct from age changes (Ferrer, Salthouse, Stewart, & Schwartz, 2004). Hofer and Sliwindski (2006) suggested, however, that retest effects may be best considered as an outcome of interest, and become a focus for investigation of change in learning processes over time in relation to the varying constructs under consideration.

Attrition is another threat to the internal validity in longitudinal studies in that all those tested at baseline may not be available for subsequent measurement (Schaie, 2005). Although there are 'state of the art' (Schafer & Graham, 2002) methods for dealing with missing data, longitudinal studies pose particular challenges; in particular, many missing data methods require the assumption that data are at least Missing At Random (MAR) if not Missing Completely At Random (MCAR). In longitudinal cognitive ageing studies, missingness (attrition) is frequently related to ill-health, frailty, or mortality; all of which are potential modifiers of the cognitive outcomes being measured, which means that the missing data do not meet the MAR assumptions. Also, the under-representation in subsequent sessions of those from the original cohort who had became ill or died could attenuate associations between advancing age and cognitive functioning (Salthouse, 2010b). But Schaie (2005) has cautioned against interpreting inflated levels of cognitive functioning (due to the remaining sample being an 'elite' group) as being synonymous with levels of cognitive change. Data from the SLS demonstrated that it was initially higher functioning individuals who declined

more quickly. Also, that those who dropped out were more likely to have been worse performers and the greatest attrition occurred early in the study. This meant that those who remained in the study were in fact more likely to be greater decliners than those who dropped out early, thereby resulting in an over estimation rather than attenuation of rates of cognitive change (Schaie, 1988).

1.3.2.1 Longitudinal studies: measurement invariance

One other pertinent methodological consideration in longitudinal studies is the equivalence of test measures and the constructs they represent over time (Ferrer et al., 2004). Although the same tests may be used on the same people at each time-point, it does not necessarily follow that the same underlying constructs will be measured. Intra-individual changes that are related to factors apart from the target variable of interest may cause people to respond differently to ability measures from one testing session to the next. (Nesselroade & Estabrook, 2009). For the measurement of change to be psychologically meaningful, the manifest variables by which the change is quantified must represent the same underlying qualities (Meredith & Horn, 2001).

The first level of measurement invariance is configural invariance. In this condition, the same observed variables of the latent construct are specified at each occasion, although their numerical relationships with that construct may differ over time. Metric factorial invariance pre-supposes configural invariance but refers to the specific relationships between the latent variables and the manifest variables. There are three levels of increasingly restrictive metric invariance that can be tested. In weak factorial invariance, the numerical factor loading of each indicator takes the same value across time-points. Strong factorial invariance adds the requirement that the measurement intercept of each indicator also to be

invariant over time, and finally, strict factorial invariance requires, in addition to the factor loading and intercept, that the unique variances for each manifest variable are also equal over time (Ferrer & Ghisletta, 2011).

It is also possible to test the hypothesis of invariance at the construct or latent level rather than at the level of the observed variables. If factor loadings and intercepts fail to exhibit longitudinal invariance at this second-order level, then it cannot be assumed that the same constructs are necessarily being measured over time. In this situation, apparent longitudinal changes in the construct may represent qualitative shifts in the construct itself rather than quantitative growth or decline (Hertzog & Nesselroade, 2003).

1.4 Individual Differences In Cognitive Ageing Trajectories.

It is apparent from the previous discussion that cross-sectional and longitudinal studies will lead to disparate estimations of the average cognitive ageing trajectory in terms of both the *if* and *when* of decline. Nonetheless, even conservative estimates report that most people will have declined significantly on at least one ability by age 60, and that all abilities (with the exception of acculturated knowledge) on average show significant decrements by the mid-70s (Schaie, 2005). Population level analyses, however, obscures the heterogeneity that exists in ageing trajectories at the individual level (Hofer & Alwin, 2008; Willis & Schaie, 2005). In longitudinal data from the SLS, mid-life performance was measured at 3 time points over 14 years (from age 46 to 60) and on average appeared stable on all six of the abilities measured; verbal meaning, spatial orientation, inductive reasoning, number, word fluency, and delayed recall. When, however, change in ability level over time was examined for three abilities at the *individual* level, in all three of the abilities, Number Ability, Word Fluency, and

Delayed Recall, participants could be classified as 'Decliners' 'Improvers', or 'Stable', according to being one standard error of measurement or greater over the 14-year period (Willis & Schaie, 2005).

Another study that has investigated age-related cognitive change at the individual level is The Religious Order Study (Bennett, Schneider, Arvanitakis, & Wilson, 2012). Participants were 694 Catholic clergy members who were 65 years or older and free of AD at baseline. Annual assessments were carried out for 6 years using a battery of 21 tests of cognitive functioning that represented the domains of semantic memory, working memory, perceptual speed, and visuospatial ability. On average, performance declined on each domain over the study period. When individual patterns of change were examined using random effect models, substantial heterogeneity was evident in each cognitive domain; a few people exhibited precipitous decline while others remained stable, declined, or improved slightly. Although decline was more common in older people, variability was evident at all ages, and change in cognitive function in old age appeared highly specific to the individual (Wilson, Beckett et al., 2002).

A study with shorter follow-up (approximately three years) examined cognitive decline in 369 adults > 60years who had been categorised into three groups representing normal function, those with Mild Cognitive Impairment (MCI), or those with dementia. Psychometrically matched measures of episodic memory, semantic memory, and executive function were administered annually (Mungas et al., 2010). In the cognitively normal group there was a small but significant average change over time in episodic memory and executive functioning. At the individual level, the majority did not decline but a small subgroup of 12% declined at a particularly rapid rate and progressed to MCI or dementia. This rate of decline was

equal to or exceeded that in the MCI and dementia subgroups (Mungas et al., 2010).

The heterogeneity apparent in rates of cognitive decline amongst non-impaired older adults poses the question as to what factors account for people's differing cognitive ageing trajectories? This is an important question. Discriminating between unmodifiable and modifiable determinants of age-related decline provides a theoretical framework in which to formulate strategies to prevent or delay such decline. Moreover, it is essential when assessing the hypothesised impact of any factor on late life cognition that the role of other potential contributing factors is understood (Salthouse, 2010a). The following section will address some of the factors that predict individual differences in cognitive ageing outcomes.

1.4.1. Prior ability

The largest single predictor of cognitive ability in older age is the level of cognitive functioning from early life (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman, Starr, Fox, & Whalley, 2004; Riley, Snowdon, Desrosiers, & Markesbery, 2005; Snowdon et al., 1996). Whether those with a higher level of ability experience less decline in older age is a theoretically and methodologically complex question, with no straightforward answer[4]. Intuitively, it could be expected that being cognitively more capable would ensure more available resources to compensate for the effects of ageing or dementia, thereby potentially slowing the rate of decline (Stern, 2006). However, early longitudinal studies of prior ability and cognitive aging yielded inconsistent results (for a review see

[4] as is apparent in the title of a current article investigating this topic 'Is age kinder to the initially more able? Yes and no (Gow et al., 2012)

Deary, MacLennan, & Starr (1998). Moreover, in the majority of these studies prior ability was equated with either IQ or education level measured at the initial testing point, which was often in later adulthood or early old age. Ideally, the influence of pre-morbid cognitive ability on later cognitive decline is best assessed by using the earliest possible direct measure of cognitive ability to avoid the 'contamination' by lifestyle, socio-economic, or health factors that may adversely affect abilities, even by early adulthood (Bourne, Fox, Deary, & Whalley, 2007).

Two British longitudinal cohorts provide unique data to evaluate the contribution of early-life cognitive ability to later-life decline: the Lothian Birth Cohort 1921 (LBC1921) (Deary, Gow, Pattie, & Starr, 2011) and the Medical Research Council National Survey of Health and Development (MRC NSHD) (Wadsworth, Kuh, Richards, & Hardy, 2006). In both these cohorts, measures of early life cognitive ability were available; for the LBC1921, tests at age 11 of verbal fluency, logical memory and Raven's Matrices, and for the MRC NSHD participants, tests at age 11 and age 15 of verbal memory and search speed.

Gow, et al. (2012) comprehensively analysed the LBC1921 and the MRC NSHD data using latent growth curve analysis within a structural equation modelling (SEM) framework. Early life cognitive ability from the LBC1921 was used to predict cognitive change on both a general cognitive ability factor and individual tests of reasoning, memory, and executive function over three time points from ages 79 to 87. Similar analyses were conducted in the middle-aged MRC NSHD cohort, with change assessed over two time points at age 43 and 53, but with only two tests as markers for each latent factor. Results indicated higher early life ability as protective against 10 year mid-life decline (from 43-53 years) on a latent cognitive factor from tests of verbal memory and search speed, and in

search speed when considered separately. There was no association, however, with decline in very old-age, (from 79-87 years) on either the general cognitive ability factor or any of the individual tests. The authors cautioned against making a definitive interpretation of the outcomes as indicating life-period-specific differential influences of early life ability on later rate of decline. They also highlighted multiple methodological limitations including greater power to detect effects in the mid-life cohort (n=3,362) compared to the LBC1921 (n=200), and selective attrition in the older cohort. Those who were recruited at 79 were the survivors of the original cohort and may have differed from the younger cohort on a number of socio-economic factors that were determined by early-life ability in addition to predicting frailty or mortality (Gow et al., 2012).

1.4.2 Genetic determinants

Much of the information about the genetic causes of ability differences in old age has come from various samples based on the Swedish Twin Registry (Harris & Deary, 2011). Identical twins share all their genes, so any ability differences between pairs are due to environmental influences. Fraternal twins share half their genes, so the similarity in abilities of identical and fraternal twin pairs can be compared in order to estimate how important genetic effects might be (Pedersen, 2000). Longitudinal studies using latent growth curve analyses have separated genetic and environmental sources of influence on individual differences in both initial ability and rate of change within the Swedish Adoption /Twin Study of Aging (SATSA) (Reynolds et al., 2005) and the Longitudinal Study of Aging in Danish Twins (LSADT) (McGue & Christensen, 2001). In the SATSA cohort, the cognitive domains of verbal ability, spatial ability, memory, and processing speed were assessed at four time points over 13 years by 10 measures; g was derived

from the first principal component of the cognitive measures. All participants were older than 65 at baseline. The LSADT cohort consisted of twins over 70 years and was examined with measures of category fluency, digit span, and a 12-item list recall on four testing occasions. Subsequently, and in additional cohorts, these measures were repeated over six testing occasions with participants meant ages of 77 at baseline and 89 on final follow-up (McGue & Christensen, 2007).

Findings from both the SATSA and LSADT cohorts were consistent in identifying stability over time in the heritability component of both general cognitive ability and the individual cognitive domains for the 'younger' old age (mean age 65); Reynolds et al. (2005) found intercept heritability estimates ranging from .52 for digit span to .85 for symbol digit coding, with a heritability estimate of .91 for *g*. For those in the 8th and 9th decade of life, however, the influence of genetic factors steadily decreased and environmental influences accounted for more of the variability in performance. Likewise, it was non-shared environmental factors rather than genetic determinants that accounted for the variance in the rate of linear cognitive change for both cohorts with heritability estimates reported as either minimal, or non-existent (Lee, Henry, Trollor, & Sachdev, 2010).

1.4.2.1 Apolipoprotein E (ApoE)

Possessing the Apoe *ε*-4.genotype increases the risk for developing late onset AD, and those homozygous for the *ε*-4 allele are between 10 and 12 times more likely to be afflicted (Wisdom, Callahan, & Hawkins, 2011). ApoE is a plasma protein combined with a lipid that is responsible for carrying cholesterol and other fats thorough the bloodstream and it is also associated with processes involved with neuronal repair. The gene coding for ApoE is located on chromosome 19 and

there are three allelic variations; ε-2, ε-3, and ε-4. Individuals possess two alleles of ApoE, inheriting one from each parent, so there are potentially six genotypes of ApoE. The ε-3 is the most commonly occurring with gene frequencies of approximately 80% in Caucasian populations, followed by ε-4 and ε-2, with frequencies of 14% and 8% respectively (Small, Rosnick, Fratiglioni, & Backman, 2004; Wisdom et al., 2011).

The role of ApoE status on non-impaired older-age cognitive ability and cognitive change has been the focus of intense research with the most recent meta-analysis of cross-sectional associations between ApoE epsilon combinations and cognitive performance representing a total of 40,942 participants and 70 studies. The majority of study populations consisted of older adults > 65 years, although a number of included studies examined performance in middle-aged and younger adults. This meta-analysis of cross-sectional studies indicated that the carriers of ApoE ε-4 performed significantly worse on measures of episodic memory, executive functioning, and overall global cognitive ability; in addition, a small effect was found for the unfavourable impact of ApoE ε-4 on perceptual speed. Finally, increasing age was associated with greater differences between ApoE ε-4 carriers and non-carriers on measures of global cognition and episodic memory (Wisdom et al., 2011).

ApoE variant status does not exert an equal impact on men and women's risk for dementia. Women who possess the ApoE ε-3/ε-4 genotype are at approximately fourfold increased risk, whereas men with this genotype show little to no increased risk (Payami). Moreover, ApoE ε-4 women are likely to have the greater plaque and neurofibrillary tangle pathology at autopsy (Corder 2004). In healthy older adults also, sex modulates the effect of ApoE ε-4. In ε-4 carriers

(*n*=43), with no apparent neuropsychological deficits, *f*MRI (Functional Magnetic Resonance Imaging) demonstrated that women showed significantly reduced functional brain connectivity compared to *ε*-4 men and homozygous *ε*-3 women. In the same study, but using a separate sample of non-impaired 93 older adults, additional analyses demonstrated that spinal fluid levels of tau, a biomarker for prodromal AD were elevated in *ε*-4 women compared to men and other women who were homozygous for *ε*-3 (Damoiseaux et al., 2012).

These findings are complementary to those mentioned earlier of the relatively large heritability component in the cross-sectional variability found between people in level of cognitive ability. What is interesting is that although heritability studies have found little evidence of genetic contributions to variance in rates of cognitive decline, the ApoE *ε*-4 variant has been associated with decline in cognitively healthy populations[5] (Blair et al., 2005; Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Bunce, Fratiglioni, Small, Winblad, & Backman, 2004; Deary et al., 2002; Packard et al., 2007; Wilson, Schneider et al., 2002). In the LBC1921, cognitive performance on the domains of verbal memory, abstract reasoning, and verbal fluency was assessed at 79 years, and again at 83 and 87 years. Over the 8 year period, 27 people developed probable dementia (according to MMSE score < 24). In linear mixed models adjusted for demographic variables, vascular risk factors, and childhood mental ability, the ApoE *ε*-4 allele was associated with higher relative rate of cognitive decline over 8 years for verbal memory and abstract reasoning, although verbal fluency was not affected by ApoE *ε*-4 status (Schiepers et al., 2012).

[5]Schiepers et al., however, highlighted the important limitation in some studies that have investigated this association. Given the involvement of ApoE *ε*-4 allele in Alzheimer's disease, those who develop dementia over the course of the study need to be excluded. If this is not done then the association between ApoE status and non-pathological age-related decline may be over-estimated (Gow et al., 2012)

1.4.3 Environmental Factors

Multiple behavioural, social, and economic factors have been associated with differential cognitive ageing outcomes in observational studies but in a systematic review few had sufficient evidence from which to draw firm conclusions about their association with cognitive decline (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Nonetheless, dietary intake, educational attainment, and physical activity levels are three exposures for which there is some evidence of protective effects. The role of diet in cognitive ageing will be extensively reviewed in the following chapter, but evidence for educational attainment, physical activity, and cigarette smoking is presented below.

1.4.3.1 Education

The effect of educational achievement on cognitive decline is to some extent a proxy for prior ability. As discussed earlier, those of higher cognitive ability in early life are also likely to have gone on to attain higher levels of education. Unlike initial ability, however, the effect of education across life is likely to be cumulative with higher or lower education predicting multiple environmental factors such as economic prosperity and occupational complexity that may directly or indirectly impact on cognitive decline trajectories. Higher level of educational attainment is a robust predictor of better cognitive functioning throughout adulthood (Schaie, 2005), with low education associated with higher risk of developing dementia, particularly AD (Caamaño-Isorna, Corral, Montes-Martínez, & Takkouche, 2006). There are inconsistent findings, however, regarding whether educational attainment modifies the trajectory of age-related cognitive change. Differences in study methodologies, the abilities measured, and the populations assessed likely account for much of the variability in findings (Zahodne et al., 2011). In particular,

education may exert different effects on the trajectories of different cognitive domains. For example, Alley, Summins and Crimmins (2007) found that in a sample of 7,443 Americans aged 70 years and older that higher educational achievement attenuated seven year decline in overall cognition (as measured by the Telephone Interview for Cognitive Status), accelerated decline in verbal memory (assessed by immediate and delayed verbal recall), and was unrelated to working memory (assessed by the serial 7s test) (Alley et al., 2007).

Two other large scale longitudinal studies have assessed whether educational attainment predicted change over time in cognitively healthy older adults. In the Chicago Health and Aging Project (CHAP) (N = >6,000) brief single measures of immediate and delayed recall, the digit symbol modalities test (perceptual speed), and global cognition (the MMSE) were assessed. The results demonstrated that education was robustly associated with level of cognitive function but not with rate of cognitive decline over 14 years (Wilson et al., 2009).

Results from the Victoria Longitudinal Study (N=1014) supported the null findings of others for the effect of educational level on decline. Participants were aged between 54 and 95 years and were assessed over three year intervals for between 6 and 12 years. More extensive cognitive measures were used than in the previously mentioned studies; scores were based on confirmatory factor analysis of tests for verbal processing speed, working memory, and verbal fluency (Zahodne et al., 2011). These three longitudinal studies certainly demonstrated a role for educational attainment in older age cognitive performance, which is not unexpected, but there is very little evidence for its protective effects against decline.

1.4.3.2 Physical activity

The potential role of physical activity in ameliorating decline, or even improving cognitive functioning in older-age has been the focus of intense research efforts. Cross-sectional and prospective studies demonstrate robust associations between greater self-reported levels of physical activity and better cognitive functioning (Weuve et al., 2004), albeit a limited global or screening assessment of cognition (Miller, Taler, Davidson, & Messier, 2012), and a reduced likelihood of later impairment (Sattler, Erickson, Toro, & Schröder, 2011), or AD (Weih, Degirmenci, Kreil, & Kornhuber, 2010) [6].

Animal studies and findings from brain imaging studies have provided much of the continued impetus for research regarding the role of physical activity in cognitive ageing outcomes (Gregory, Parker, & Thompson, 2012; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). For example, it has been demonstrated in older mice that exercise on a running wheel enhances hippocampal neurogenesis and learning ability (van Praag, Shubert, Zhao, & Gage, 2005), and exercise-induced growth of new blood vessels has been linked to improved learning and memory (Pereira et al., 2007). In the human brain, greater physical activity in later adulthood has been associated with greater grey matter volume after a nine year follow-up (Erickson et al., 2010), increased hippocampal volume in an aerobic exercise intervention trial (Erickson et al., 2011), and exercise-induced functional efficiency and plasticity in neural networks after 12 months of walking (Voss et al., 2010).

Unlike the determinants of cognitive ageing variability discussed so far, physical activity is a lifestyle variable open to modification, and consequently

[6] Gregory (2012) provides a comprehensive review of physical activity in the context of cognitive status and decline/dementia prevention.

presents as a possible target for intervention with the aim of modifying the ageing trajectory. The majority of longitudinal studies of associations between physical activity and more comprehensive cognitive measures (as opposed to global measures of impairment) have been carried out within the intervention context. As usual, comparisons of results amongst these studies is problematic due to the differing study designs, intervention periods, types of activity, and the type of control group (if any) used (Gregory et al., 2012). For instance, in a group of 120 adults aged 55 to 80 years, over one year both a walking-three-days-a-week group and the control group (a stretching /toning group) improved on a spatial memory task (Erickson et al., 2011) but, in a group of women who over one year did either full-body resistance training or a balance-exercise program 2-times per week, performance on the Stroop test (an executive functioning task measuring selective attention and inhibition) improved in the training group, but declined in the balance exercise control group (Liu-Ambrose et al., 2010). Even in these two studies of similar duration, the results are difficult to compare due to the discrepant intensity level of the interventions and differing cognitive outcomes.

Although measuring the impact of exercise on cognitive ageing is fraught with methodological challenges (Miller et al., 2012), results from observational and intervention studies overall indicate a protective role for physical activity on older-age cognition.

1.4.3.3 Cigarette smoking

Two meta-analyses have demonstrated that cigarette smoking in older-age increased the risk for AD; specifically, a summary odds ratio of 1.59 (95% CI: 1.15, 2.20) from 28 longitudinal studies (Peters et al., 2008), and an increased relative risk of 1.70 (95% CI: 1.25, 2.31) from 21 case control and eight cohort studies

(Anstey, von Sanden, Salim, & O'Kearney, 2007). The two meta-analyses differed, however, in their findings regarding the association between current smoking and other forms of dementia and cognitive decline. Anstey et al. found that current smokers at baseline had greater risk for incident vascular dementia of 1.79 (95% CI: 1.28, 2.47) and 1.27 (95% CI: 1.02, 1.60) for any dementia, together with greater yearly decreases on the MMSE; β = - .07 (95% CI: - .18, -.08). Peters et al., however, found no associations between current smoking and increased risk of vascular or any other unspecified dementia, or cognitive decline. Only the Anstey et al. analyses fond an association between former smoking and rate of cognitive decline on the MMSE with no relationship demonstrated between being a former smoker and a greater risk of any kind of dementia.

Determining the relationship between cognition and smoking behaviour is complicated by a number of factors. Firstly, nicotine has plausible mechanisms for aiding cognitive function via its direct action on nicotinic receptors and on neurotransmitters that interact with the nicotinic receptor systems in the neural substrate of cognitive function. Improvements in attention and memory have been demonstrated in human non-smokers and experimental animals with some promise of being therapeutically useful for a variety of cognitive dysfunctions (Levin, McClernon, & Rezvani, 2006).

Such potentially beneficial effects of nicotine are overshadowed by the negative effects of smoking on cardiovascular disease risk, peripheral vascular disease, and lung disease (Ambrose & Barua, 2004; Ockene & Miller, 1997), all of which are associated with poorer cognitive outcomes in late life; as will be further addressed in sections 1.4.4.

In the English Longitudinal Study of Ageing (ELSA; N = 8,780), current smoking represented the most consistent vascular risk associated with cognitive decline, measured at baseline and 4 years later, across three measures assessing memory (immediate and delayed recall of 10 words), executive function (global score from a test of verbal fluency and a letter-cancelling test), and a cognitive index created by summing the z-scores on the memory and executive indexes (Dregan, Stewart, & Gulliford, 2013).

One of the issues with assessing the relationship between cognitive decline and smoking status in older populations is that associations may be attenuated by smokers relatively low rate of survival into old age (Richards, Jarvis, Thompson, & Wadsworth, 2003; Sabia, Elbaz, Dugravot, & et al., 2012). Cigarette smoking and cognitive decline was assessed in the British 1946 birth cohort when participants were aged between 43 and 53 years. Current smoking was associated with faster decline in verbal memory and slower visual search speed after controlling for a range of confounding variables, including previous cognitive ability at age 15 years. The participants were required to abstain from smoking during their assessment session and so it was possible that some smokers' cognitive performance was detrimentally affected by nicotine withdrawal over the 90 minutes of testing. In this sample, cardiovascular and respiratory functioning was explicitly controlled for in analyses and the authors raised the possibility of a direct effect of smoking on the central nervous system (Richards et al., 2003).

Preliminary evidence of smoking's direct effect on brain structure was found in a later small MRI study of younger adults that compared the brains of 22 smokers and 23 never-smokers. Significantly smaller grey matter volume and lower grey matter density were observed in the frontal regions, the occipital lobe,

and the temporal lobe in smokers compared to never-smokers, and magnitude of lifetime exposure to tobacco smoke (pack years) was inversely correlated with volume of frontal and temporal lobes and cerebellum (Gallinat et al., 2006).

Further evidence of the relationship between smoking and decline was found in the Whitehall II study (Sabia et al., 2012). Participants had an average age of 56 years at the first cognitive assessment and were followed up over two other assessments for 10 years. Cognitive functioning was assessed with five tests; memory, vocabulary, 3 tasks to measure executive functioning, and a global score summarising performance on all tests. In men only, greater pack-years of smoking and smoking over the 10 years of follow-up was associated with faster cognitive decline. Men who quit smoking in the 10 years preceding the study period were still at risk of greater cognitive decline, but longer-term ex-smokers did not show faster decline.

Assessing the relationship between ex-smoking status and cognitive decline is problematic because there are inconsistencies between studies in regard to the time since stopping and the level of smoking that had previously been usual. More consistent use of 'pack years' as a measure would allow for further exploration of this issue (Peters et al., 2008).

1.4.4 Health status

Advancing age is accompanied by increased risk for and prevalence of multiple diseases and widespread use of medications. Older people are frequently unaware of their health status and in the U.S over 25% of elderly people over 65 may have hypertension, diabetes, or high cholesterol (McDonald, Hertz, Unger, & Lustik, 2009). Given that older age and poorer health are so closely associated and that comprehensive assessment of health status in ageing studies is often limited, it

has been suggested that much of the variance between people in cognitive functioning that is attributed to age should actually attributed to health (Spiro & Brady, 2011).

Biological age and chronological age were examined in the Victoria Longitudinal Study of Aging (VLSA) as predictors of 12 year cognitive change over five domains in adults between 67 and 95 years of age. Biological age consisted of a number of biomarkers including peak expiratory flow, blood pressure, and BMI. Results showed that biological age predicted cognitive decline independently of chronological age. (MacDonald, Dixon, Cohen, & Hazlitt, 2004). Individual differences in health, therefore, are likely to account for much of the variability between people in cognitive ageing trajectories.

1.4.4.1 Vascular disease and cognition

Vascular disease is a well established risk for MCI and dementia, including AD (Duron & Hanon, 2008; Grodstein, 2007; Kerola, Kettunen, & Nieminen, 2011; Kivipelto et al., 2001; Launer, 2002; Whitmer, Sidney, Selby, Claiborne Johnston, & Yaffe, 2005; Zylberstein et al., 2011). Recently, the focus also has been on the impact of vascular health on cognitive performance in non-impaired populations; both older adults (>65 years) and those in midlife (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009), with the view of formulating possible intervention strategies to prevent vascular-related pathological cognitive ageing (Raz, Rodrigue, Kennedy, & Acker, 2007). In cross sectional studies, vascular risk factors, cardiovascular disease, and diabetes have predicted worse cognitive performance on a number cognitive domains (Aleman, Muller, de Haan, & van der Schouw, 2005; Singh-Manoux et al., 2008; Tamosiunas et al., 2012; van den Berg et al., 2009; Verhaeghen, Borchelt, & Smith, 2003). Relatively few longitudinal

studies, however, have tested associations between these factors and within person rate of change.

In the Whitehall II study of cognitive ageing (Marmot & Brunner, 2005), tests of reasoning, memory, verbal fluency, and vocabulary were administered at three time points over 10 years to 4,153 men and 1,657 women (mean age 55.6 years). Higher stroke risk (as defined by the Framingham Stroke Risk profile (FSR) (Wolf, D'Agostino, Belanger, & Kannel, 1991)) was associated with faster decline in verbal fluency, vocabulary, and global cognition; interestingly, no association was observed for memory and reasoning.

The ELSA had FSR data available for approximately 6,000 adults (mean age 66.9 years) assessed in 2004/2005. Associations were examined between FSR profiles and cognitive data collected four years later. The cognitive measures were: immediate and delayed recall (memory), attention, mental speed, and visual scanning (executive function), and a *z*-score measure of global cognition. In this cohort, the upper quartile of FSR scores negatively predicted all composite scores including memory. The 1998/2000 measures of individual vascular risk factors also predicted worse cognitive performance approximately five to six years later in 2004/2005 with higher blood pressure and smoking negatively associated with global cognition (Dregan et al., 2013).

In another large scale cohort study (the Atherosclerosis Risk in Communities cohort) cognitive assessments were administered to 10,963 individuals aged 47-70 years at two time points six years apart. Cognitive assessments included delayed word recall, delayed free word recall, digit symbol coding, and letter work fluency tasks. The presence of diabetes at baseline predicted decline on digit symbol coding and letter fluency across all age ranges

and hypertension was associated with decline on digit symbol coding only (Knopman, Mosley, Catellier, & Coker, 2009).

In summary, vascular risk factors predict decline across a number of cognitive domains with a meta-analysis demonstrating that the vascular factors of type 2 diabetes, hypertension, dyslipidemia (abnormal cholesterol levels), and obesity had moderate and consistent effects on cognitive speed, mental flexibility and memory (van den Berg et al., 2009).

1.4.4.2 Vascular determinants of brain ageing

Low levels of high density lipoprotein (HDL) and elevated low density lipoprotein (LDL) cholesterol, together with elevated triglycerides, and homocysteine levels contribute to arterial plaque deposition. This, in turn, leads to atherosclerosis and the risk of myocardial infarction and acute ischaemic stroke, or repeated, but often undetectable, silent brain infarcts (Fjell & Walhovd, 2011). The vascular system is also be compromised by chronic hypertension. Hypertension is one of the most prevalent diseases of older age affecting approximately 68% of adults between 65 and 74 years, and up to 75% of adults aged over 75 years (Australian Institute of Health & Welfare AIHW, 2010) The small delicate capillaries that supply the flow of blood throughout the brain are particularly susceptible to the damage caused by elevated blood pressure. Many of the risk factors for vascular disease also contribute to the definition of metabolic syndrome[7] which is a precursor of Type 2 diabetes.

[7] Since 2005, central obesity plus two of the following conditions are required to diagnose metabolic syndrome: Fasting glucose ≥100 mg/dl; Tryglcerides ≥ 150mg/dl; HDL cholesterol <50mg /dl (fasted); >130mm Hg systolic or >85 mmHg diastolic blood pressure. Up until 2005, insulin resistance was also a required criteria (Schiepers et al., 2012)

Recently, the contribution of vascular factors to cognitive ageing has been r elucidated further by the advances in brain imaging technology. A number of studies have demonstrated that markers of vascular health predict longitudinal changes in brain structure in cognitively healthy adults at midlife and older age; furthermore, that these brain changes are also associated with longitudinal cognitive decline (Debette et al., 2011; Nettiksimmons et al., 2013; Raz et al., 2007). Of particular interest are findings from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Nettiksimmons et al., 2013). An older subgroup of the rigorously screened cognitively normal control group of the study (normal 2s) was characterised by substantial brain atrophy and white matter hypertensities (WMH) as measured by MRI. This group had significantly higher BMI, Hachinski score (a clinical tool for defining vascular dementia (Hachinski, 2007)), triglycerides and blood glucose levels, and took significantly more medications for vascular disorders. After controlling for age and education, the 'normal 2' group showed greater decline on the Rey-Auditory Verbal Learning Test (RAVLT) 30 minute delay test, although there were no differences between groups on measures of executive functioning (Trail making B-A), the ADAS cognitive subscale, or the Wechsler test of Logical Memory. The authors highlighted the contribution of vascular disease to the heterogeneity of 'normal ageing' (Nettiksimmons et al.).

Associations between vascular disease variables (measured in midlife), and both brain damage and cognitive decline (assessed 10 years later) were demonstrated in a very large sample of 1,352 participants from the Framingham Offspring Cohort Study. Hypertension predicted accelerated WMH volume progression and worsening executive functioning, (measured by Trail making B-A) as did obesity. Mid-life diabetes and smoking were associated with more rapid

increase in temporal horn volume (a marker of hippocampal atrophy), and smoking also predicted a more marked decrease in total brain volume. Overall, longitudinal changes in brain structure were significantly correlated with decline in memory and executive function (Debette et al., 2011).

The two previous studies, although particularly informative regarding associations between vascular disease and brain damage, employed relatively limited measures of cognitive functioning. Raz, et al. (2007) examined the relationships between vascular health and five-year longitudinal changes in brain structure and comprehensive cognitive measures in a small sample of 46 adults (age range 45-75 years). The domains tested were verbal working memory (Computational Span and Listening Span), non-verbal working memory (Size Judgement Span), fluid intelligence (Catell Culture Fair Intelligence Test and Letter Sets Test), and verbal comprehension (Ekstrom et al. multiple choice vocabulary test). At both time points WMH and brain volume correlated with age but notably, over the five year period, the volume of WMH more than doubled in the vascular risk group but did not increase in the healthy participants, suggesting that WMH may not be as prevalent in healthy older adults as generally thought. In the vascular group systolic blood pressure at follow up correlated with WMH volume in the occipital lobes, a traditionally stable area not normally associated with ageing. In this sample, fluid intelligence correlated with WMH burden and declined with faster WMH progression but in the vascular group only (Raz et al., 2007).

1.4.4.2.1 The vascular hypotheses and cognitive speed

The 'vascular hypothesis' of cognitive ageing posits that vascular diseases and their risk factors impact on individual differences in the cognitive ageing trajectory via the pathological changes that occur in the brain's white matter (de la

Torre, 2002; Spiro & Brady, 2011). White matter is the brain region underlying the gray matter cortex. It is composed of neuronal fibres coated with electrical insulation called myelin. Myelin has multiple developmental and functional processes. Even in younger adults, myelin is vulnerable to the effects of elevated blood pressure and its integrity is critical for optimal mental performance and learning (Maillard et al., 2012).

Of particular relevance is the role of myelin in controlling the speed of impulse conduction through axons [8] (Fields, 2008). The contribution of mental speed to individual differences in cognitive ability measures has a long history in psychometric research (for a review see Danthiir, Roberts, Schultz, & Wilhelm (2005), and Nettelbeck (2011)). A general decline in processing speed has been hypothesised as a 'common cause' that underpins much of the apparent decline in the other cognitive functions when cross-sectional age differences are examined (Salthouse, 1996). Notwithstanding the methodological concerns inherent in this approach[9], decreases in mental speed due to white matter damage provides an *"attractively parsimonious"* (Rabbitt et al., 2007, p. 363) hypothesis of cognitive ageing.

A critique of this hypothesis was provided by Rabbitt et al. (2007) who highlighted how changes in the components of any complex system that are time-related will be correlated even if they are actually functionally independent.

[8] Interestingly, in the corpus collosum (the area responsible for signalling between the left and right hemispheres of the brain), approximately 30% of the axons in adults remain unmyelinated. The conduction time between the left and right hemispheres is 100-150ms through unmyelinated callosal fibres compared to only 30ms through myeliinated fibres (Fields, 2008).

[9] There has been an argument against the proposal that processing speed, or any particular 'common cause', accounts for age-related decline due to the theoretical foundations of the theory being grounded in cross-sectional analyses of age differences in cognitive functioning. (Alwin, 2009; Hofer & Piccinin, 2010; Hofer & Sliwinski, 2006) Nettelbeck and Rabbitt (1992) demonstrated that not all age-related changes are linked to processing speed.

Specifically, to determine the relationship between vascular factors, white matter pathology, and cognitive functioning it is necessary to establish how much of the common variance between them is due merely to synchronicity, and how much is due to functional dependence (Rabbitt et al.). In other words, this is a specific example of the 'correlation does not imply causation' caution.

This problem had been dealt with in an earlier study by Deary, Leaper, Murray, Staff, & Whalley (2003). They used a SEM framework to model the relationships between measures of WMLs (white matter lesions), history of hypertension, and general cognitive ability (represented by Raven's Matrices, the RAVLT, uses of Common Objects, and Digit Symbol sub-test of the WAIS), including early-life cognitive ability scores to control for the known effects of intelligence on health outcomes. MRI scans were performed on 83 of the participants when they were aged 78 years. WMLs contributed approximately 14% of the variance in older-age cognitive functioning. Hypertension accounted for significant variance in WMLs and contributed to variance in cognitive function both directly, and via its mediating effect on WML scores (Deary et al., 2003). This study therefore demonstrated a direct relationship between greater brain pathology and poorer performance.

1.5 Age-associated Brain Pathology and Cognitive Functioning

The aforementioned studies have demonstrated consistent relationships between vascular disease, quantity of white matter damage, and decline on cognitive measures. Intuitively, a linear relationship would be expected between greater brain pathology and poorer cognitive outcomes in older-age, but this association is a complex one (Raz & Rodrigue, 2006).

The following section will address brain pathology of the Alzheimer's type that may be present in cognitively normal older people. The quantity of such pathology accounts for only some of the variability between people on performance measures and additional mechanisms are likely to determine the extent of this relationship. The hypothetical construct of brain reserve (Stern, 2002) has been proposed to explain the inconsistent findings regarding brain pathology and older-age cognitive functioning. This hypothesis will be presented in order to provide the mechanistic rationale for the contributions to cognitive ageing made by the previously discussed genetic, environmental, and health factors.

1.5.1 Alzheimer's pathology and normal ageing

Alzheimer's pathology per-se is not necessarily associated with developing AD, or even with poorer performance. The cognitive trajectories of two groups of clinically normal elderly individuals were compared; one group had eventual neuropathology at autopsy, and one group did not, but there were no significant differences found between the cognitive trajectories of the two groups. In contrast, a group with MCI and eventual post mortem AD pathology showed steeper rates of cognitive decline in several aspects of cognitive functioning compared to those who were cognitively normal at baseline, regardless of whether those cognitively normal individuals' brains showed evidence of pathology at eventual autopsy (Driscoll et al., 2006)

Advances in amyloid imaging techniques have allowed beta-amyloid (the pre-cursor to plaque formation) to be studied in vivo and consequently provide information regarding the processes that may contribute to the continuum between normal ageing and AD. Carbon-labelled Pittsburgh Compound-B (C-PIB) is a substance that binds specifically to beta-amyloid. C-PIB can be used as a tracer

in positron emission tomography (PET) to examine relationships between amyloid deposition, brain structural changes, and cognitive functioning in cognitively normal individuals (Rabinovici & Jagust, 2009). The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing[10] performed C-PIB-PET scans in 177 healthy controls, 57 MCI participants, and 53 mild AD patients. Results demonstrated that 18% of rigorously screened healthy controls aged 60-69 years and 65% over those

over 80 years showed high cortical binding values levels of PIB (indicative of increased presence of amyloid deposits) (Rowe et al.). These findings support earlier post mortem studies that report Alzheimer's pathology in brains of the majority of cognitively normal elderly individuals over 80 years (Driscoll et al., 2006; Knopman et al., 2003; Price & Morris, 1999).

Given that age is the strongest predictor of increasing AD pathology, it could be expected that developing the eventual symptoms of AD would be inevitable if one lived long enough, but studies the oldest-old (those > 90 years) do not support this hypothesis. The associations between AD brain pathology and dementia symptoms have been found to be stronger in the younger old (75 years) and reduced in the oldest old (95 years) (Savva et al., 2009). Also, a post-mortem study of 58 individuals aged over 90 years without clinical symptoms of dementia found that both the high and low AD pathology groups had demonstrated modest improvement (consistent with learning effects) on repeated measures of global cognition and memory in the three years before death (Balasubramanian, Kawas,

[10] AIBL is a participant of ADNI ("World Wide Alzheimer's Disease Neuroimaging Initiative," 2013) that
a. Helps predict and monitor the onset on progression of AD,
b. Establish globally recognise standards to identify an diagnose AD,
c. Document cognitive changes linked to physical changes

Peltz, Brookmeyer, & Corrada, 2012). The presence of ApoE- $\varepsilon 2$ in the oldest-old is associated with increased AD neuropathology but reduced risk of dementia and has been hypothesised to confer protective effects on cognition independently of the formation of AD pathology (Berlau, Corrada, Head, & Kawas, 2009).

The inconsistent association between the presence of AD pathology and cognitive decline is puzzling, especially when the evidence is clear that a high proportion of individuals eventually diagnosed with AD post-mortem have marked pre-clinical deficits in measures of global cognitive ability, episodic memory, perceptual speed, and executive functioning (Bäckman, Jones, Berger, Laukka, & Small, 2005). An interpretation of data from the ADNI group suggests that it is the neurodegenerative component of AD rather than amyloid burden that determines the rate of cognitive decline. The authors proposed that there is a dissociation between the rate of amyloid deposition and the rate of neurodegeneration late in life, with amyloid deposition proceeding at a steady rate, while neurodegeneration accelerates. It is the neurodegeneration that both precedes and then parallels cognitive decline (Jack et al., 2009). Thus, as Satz (1993) suggests, there may be a threshold for neurodegenerative induced decline so it is only when this threshold is reached that the continuing amyloid deposition contributes to the consequently rapid deterioration seen in symptomatic AD.

1.6 Brain Reserve: A Heuristic for Cognitive Ageing

The structural deterioration that occurs in the brain is likely to account to some extent for the phenomenon of cognitive ageing but, as is apparent from the previous discussion, there is no universally applicable ratio of pathology to cognitive deficit. Rather, some individuals' brains appear to be more resilient than others to the effects of structural ageing. The brain reserve hypothesis was first

formally suggested by Satz (1993), but had been previously articulated by Katzman (1988) to explain post-mortem findings that a small number of people had enough AD pathology to be categorised as having the disease, yet prior to death had demonstrated that their functioning was as good, or better than, age matched controls. In this select group, better performance was also related to possession of greater number of neurons and higher brain weight. The 'reserve hypothesis' as it has become known, was subsequently defined in a seminal article by Yakov Stern (2002) with later applications of the concept to both AD (Stern, 2006), and general cognitive functioning and AD (Stern, 2009).

Stern proposed a 'passive' and an 'active' model of reserve. Passive reserve refers to the structural characteristics of the brain that can theoretically mediate between pathological damage and clinical manifestations of that damage. Concrete examples of brain reserve would include brain size, synapse count, dendritic branching, or white matter integrity. The active model of reserve suggests that the brain actively attempts to compensate for brain damage by either drawing upon additional brain networks or cognitive resources to maintain functioning, or recruiting brain structures and pathways not normally used by those with intact brains in order to compensate for brain damage (Stern, 2002) .

1.6.1 Brain reserve and cognitive reserve

Reserve was originally conceived as brain reserve and cognitive reserve. Brain reserve was synonymous with passive reserve, while cognitive reserve was conceived of as the mechanism or process by which the brain was actively able to compensate for structural damage. Initially, brain reserve and cognitive reserve were proposed as having separate antecedents. Brain reserve primarily was concerned with the anatomical status of the brain and was determined by those

factors that also determined initial brain integrity, such as pre-natal and early-life environmental exposures and ApoE carrier status. Cognitive reserve, on the other hand, was the encapsulation of higher educational and occupational attainment (predicted in turn by IQ), that would enable an individual to process tasks in a more efficient manner when brain resources were being undermined by damage or disease. In later descriptions of the reserve hypothesis, Stern acknowledged that the demarcation between brain reserve and cognitive reserve was not clear cut because many of the factors associated with cognitive reserve such as cognitively stimulating experiences, higher education, and greater physical activity also have a direct effect on the brain by contributing to neuronal plasticity and neurogenesis (Bartrés-Faz & Arenaza-Urquijo, 2011; Stern, 2009, 2012).

1.6.2 Testing the reserve hypothesis

The reserve hypothesis offers an intuitively appealing framework in which to integrate the biological and environmental determinants of individual differences in cognitive ageing outcomes. A critical question, however, for the study of reserve is quantification of what amounts to an abstract concept (Reed et al., 2010). The most common approach has been to demonstrate the influence of the individual variables hypothesised as markers of the construct on cognitive performance or cognitive decline. For instance, Staff et al. (2004) concluded that education and occupational complexity contributed to cerebral reserve because these measures predicted better cognitive function in old age, over and above what could be expected from prior ability measures. In a more recent study that investigated whether reserve predicted ten year cognitive decline in the Whitehall Two Cohort, education and occupation were also used as markers of cognitive reserve, with height included as a proxy for passive reserve. Although all measures

were associated with initial status, neither height or education were associated with declines in cognitive measures, and those with higher occupational level in fact declined more (Singh-Manoux et al., 2011).

The fundamental problem of using individual hypothesised markers of reserve as actual predictors of reserve is that such markers may contribute to cognitive functioning via processes that have nothing to do with a common mechanism of reserve, or at least not directly (Jones et al., 2011). Operationalising reserve as a latent factor goes some way to address this problem (Brickman et al., 2011), but latent variable models of reserve are nonetheless theoretically problematic. Jones, et al. (2011) presented an insightful discussion of this issue with their main point being that proxy indicators of reserve such as education and cognitive activity, or measures of brain structure tend to be formative (that is they form the variable of reserve). In formative models, very little insight can be gained into the validity of the hypothesised reserve concept because the observed variables are antecedent to the latent construct (Jones et al., 2011).

A novel approach to modelling reserve addressed the formative indicator conundrum by specifying reserve as the residual term in a model of episodic memory performance (Reed et al., 2010). Reed et al. applied a latent variable model to data from a longitudinal study of ageing and dementia in an educationally and ethnically diverse group of older adults > 60 years (N=162). They decomposed the variance in a measure of episodic memory into three components: one predicted by demographics (including education, ethnicity, sex[11]), one predicted

[11] Age was not included as a predictor in the model because previous work had indicated that the effects of age on cognition were entirely mediated through changes in brain volume, which was included in the MRI variables. This assumption was tested, however, and age did not contribute to the residual term (Reed et al. 2010).

by pathology (measured by MRI), and one predicted by a residual term which included all remaining variance and which was equated with reserve. The residual component was then tested as an operational measure of reserve. The results confirmed that this measure modified conversion from mild impairment to dementia, modified decline on executive function, and demonstrated that atrophy was more strongly associated with decline in low reserve than high reserve participants (Reed et al., 2010). This strategy appeared to offer an extremely promising approach to quantifying the abstract construct of reserve. The authors emphasise, however, that it eventually needs to be

> *replace(d) with a set of empirically based understandings of what specific factors - at what point in life, and by what mechanisms - increase the individual's capacity to mitigate the effects of brain disease on cognition* (Reed et al., 2010, p. 2207).

1.7 The Life Course Approach to Cognitive Ageing

Although modelling the actual components of reserve has been demonstrated as methodologically challenging, its protective effects accrue from exposures throughout the life time (Richards & Deary, 2005). Life course models of ageing attempt to integrate biological and psychosocial data to test not only the associations between early exposures with later outcomes, but also the cumulative effects of environmental factors on these outcomes. Such an approach acknowledges that the ageing process operates from the beginning of life, and that older age health is determined by a dynamic interplay between environmental and genetic factors operating across the whole of an individual's lifetime (Ben-Shlomo & Kuh, 2002; Kuh, 2007; Whalley, Dick, & McNeill, 2006). Additionally, genetic contributions to individual differences across the spectrum of ageing are not fixed but rather are modified by the physiological and environmental influences that act

to switch genes on or off (Ben-Shlomo & Kuh, 2002; Vasilopoulos et al., 2012). Within this framework, the existence of 'critical' or 'sensitive' periods for development or damage is also acknowledged. These are times when an exposure has potentially lifelong effects (Liu, Jones, & Glymour, 2010). A critical period is a limited time window for such effects to occur whereas a sensitive period is a time when an exposure has a stronger effect on outcomes than it would otherwise have had, but these effects are still open to modification (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003).

There are a number of inherent challenges to applying such an approach to the study of cognitive ageing however. Birth cohort studies are arguably the best method of studying the life course (Blane, 1996), but the collection of longitudinal cognitive data at multiple time points is not within the practical or scientific scope of original birth cohort designs (Wadsworth et al., 2003). Certainly, comprehensive longitudinal cognitive measures were the focus of adult intellectual development studies such as the SLS (Schaie, 2005) but, although the SLS has also gathered an impressive amount of health and socio-economic information from its cohorts, this study and others do have such measures spanning from the beginnings of life into early-adulthood; a potentially defining period for future health and disease outcomes (Hertzman, 1999; Power & Hertzman, 1997).

Gathering appropriate retrospective life course data from older participants offers a potential method to capture much necessary physiological, socioeconomic, and exposure information necessary to pursue investigations between longitudinal measures of decline and earlier-life exposures that would be otherwise unavailable. Blane, comments:

> *Central to this strategy is replacing the old blanket suspicion of retrospective data with research into the questions: Which items of information are recalled with greatest accuracy over what period of time? And which methods of retrospective data collection maximise accuracy and duration of recall* (Blane, Netuveli, & Sone, 2007, p. 36).

The collection of retrospective data will be utilised within the context of this thesis to enable the assessment of lifetime measures of dietary intake and this subject will be dealt with extensively in chapter three.

To conclude; an individual's trajectory of decline on measures of some cognitive abilities in older age may be determined by varying genetic, environmental, and health factors operating across the lifetime, and therefore many years before the symptoms of cognitive change and decline are apparent. The complex interactions between these factors impact on brain health and integrity which explains their relevance to older-age cognitive functioning.

One approach to reducing the increasing burden of cognitive ageing in society is to determine what, if any, environmental exposures are candidates for behavioural education or intervention in order to increase an individuals' chance of experiencing cognitive health rather than pathological decline during older age. Chapter 2 of this review provides a rationale for the focus on long-term dietary intake as one potentially modifiable source of differences in older people's cognitive outcomes.

Chapter 2 Nutrition and Cognition

2.1 Introduction

Nutrition is a modifiable environmental exposure that is critical for optimal brain development, thereby impacting upon the developmental trajectories that determine childhood cognitive ability. Childhood cognitive ability accounts for much of the variability in intellectual function between people in later life; potentially, therefore, the adequacy or otherwise of nutritional intake during early-life reverberates across the decades to impact on older-age functioning. Thus, the first part of this chapter examines nutritional contributions to early-life intellectual ability.

Nutrient mechanisms are also relevant to brain ageing, and underpin the hypothesised role for nutritional intake as a buffer against age-related decline. The nutritional influences on brain ageing will be discussed, focusing on intake of those nutrients that are hypothesised to have particular relevance, and the mechanisms that underpin their protective action. However, the majority of randomised controlled trials of these nutrients on normal age-related cognitive decline have shown no effect of supplementation on cognitive function. A number of methodological issues may account for these findings, but the temporal trajectory of the cognitive ageing process implicates dietary intake from life-periods prior to old age as being relevant to late-life cognitive health. For logistic reasons, very few studies have dietary data available for an older-age population prior to midlife, but the findings from those that have examined associations between midlife diet and older-age cognition are presented.

Dietary data from across the lifetime would more appropriately contribute to identifying the nutritional determinants of healthy cognitive functioning in older-age, and retrospective dietary recall is suggested as an alternative approach to gathering such data when dietary records are not available.

2.2 Nutrition and Childhood Cognitive Development

At birth, the infant brain morphologically resembles the adult brain (Georgieff, 2007), although brain growth and development continues throughout childhood and adolescence with myelination continuing to occur into the 3rd decade of life (de Graaf-Peters & Hadders-Algra, 2006). The first two years are a period of particularly rapid change with other peaks of growth at the ages of 3, 7, 12, and 15 years. Concurrently, there exist also 'sensitive periods' for the acquisition of particular skills such as language development and reasoning (Wachs, 2000). Such periods of rapid development need to be supported by appropriate nutritional intake, both to enable growth, and to promote optimal metabolic functioning. Nutritional deprivation during early-life, therefore, is likely to result in negative cognitive outcomes (Benton, 2008). The extent to which impairment can be reversed when deficiency occurs is still poorly understood and challenging to investigate.[12] This is in part due to the inherent plasticity of the brain during childhood and as Fuglestad et al. (2008) noted "*it is difficult to argue that the 'critical window' is ever 'closed' during childhood"(p. 635)*.

[12] However, it is established that damage to brain development in-utero caused by deficiencies of nutrients that exert their effects in a very narrow post-conceptual window cannot be remedied by later supplementation. These nutrients include selenium, folate, vitamin A (Fuglestad, Raghavendra, & Georgieff, 2008).

The impact of nutritional intake on early-life cognitive development in human populations has been examined by four approaches:

1. Assessing the intellectual functioning in children from impoverished communities (reviewed in Grantham-McGregor & Baker-Henningham (2005)).
2. The comparison of cognitive outcomes in infants (both pre-term and term) who have been fed various combinations of breast-milk, formula, or fortified formula, together with later life follow-up studies conducted to compare these same groups (Isaacs et al., 2010; Isaacs, Morley, & Lucas, 2009).
3. Randomised controlled trials of multivitamin supplementation on intelligence test scores in children from well-nourished populations (Reviewed in Frensham, Bryan, & Parletta, (2012)).
4. The evaluation of associations between childhood dietary patterns and either school performance or measures of IQ (Feinstein et al., 2008; Gale et al., 2009; Northstone, Joinson, Emmett, Ness, & Paus, 2011; Smithers et al., 2012).

An overview of study findings utilising these approaches is presented to highlight the crucial role of adequate and appropriate nutrition in establishing an individual's level of intellectual functioning.

2.2.1 Under-nutrition and cognitive development

The vast majority of children suffering from under-nutrition come from developing countries, and the deficiency in energy and protein that has led to their malnourished status is also likely to co-vary with deficiencies in a broad range of other nutrients (Wachs, 2000). The major challenge in identifying the effect of

under-nutrition on cognitive development in such populations is the confounding effect of socio-demographic factors such as poverty, poor health care, poor parental education and psychosocial functioning, and reduced school attendance (Grantham-McGregor & Baker-Henningham, 2005; Mendez & Adair, 1999).

The findings from early cross-sectional studies were generally consistent in the associations demonstrated between under-nutrition and poor cognitive development, but they were methodologically flawed due to the lack of control for demographic confounders. More conclusive results come from a group of studies examining the long term effects of differential supplemental feeding in children from birth to 7 years carried out in four Guatermalan villages from1969 until 1977, with follow-up periods extending over the next two decades (Fuglestad et al., 2008). Outcomes from these studies demonstrated that test scores in adolescence on knowledge, numeracy, reading, processing time, and vocabulary were significantly higher in those who received a protein-calorie supplement of 11.5 grams of protein/163kcal compared to a supplement of 59kcal, with no evidence of socio-demographic factors impacting on the differences observed (Pollitt, Gorman, Engle, Martorell, & Rivera, 1993).

Both the timing and severity of early-childhood nutritional deprivation are relevant to deficits in cognitive development. Mendez and Adair (1999) examined the stunting status of Filipino children (n=> 2,000) who were administered a test of fluid reasoning ability (The Philippines Non-Verbal Intelligence Test) and achievement tests of English reading, comprehension, and mathematics at ages 8 and11 years. Stunting at age 2 years was associated with significantly poorer test performance at 8 years compared to non-stunted children, but the unadjusted dose-response effect of the timing of stunting on later cognitive scores was

attenuated after adjusting for schooling; that is, some of the cognitive deficits in those who were stunted were accounted for by less exposure to schooling. Nonetheless, even after adjustment, severe stunting at age 2 years remained significantly associated with cognitive scores at age 11 suggesting that there may be a direct effect of severe chronic under-nutrition in early life on cognitive development in later childhood (Mendez & Adair).

2.2.2 Infant feeding studies

The importance of very early-life diet to cognitive development in childhood has been investigated by examining the associations between a pre-solids diet of breast-milk, formula, or supplemented formula, and tests of IQ in later childhood and early-adolescence.

2.2.2.1 Breast milk

Elucidating the role, if any, played by the particular nutrient profile of breast milk on childhood cognitive development has been the focus of intense research over the past decades. An early meta-analysis of 20 well-controlled observational concluded that breast feeding was associated with significantly higher cognitive test scores in later childhood than was formula feeding, and that these differences were stable across successive ages (Anderson, Johnstone, & Remley, 1999). Unfortunately, in breast feeding studies the beneficial effects of breast milk ascribed to nutrients cannot be separated from the potentially neurocognitive and developmental benefits resulting from the physical and/or emotional aspects of breast feeding (Kramer et al., 2008).

Findings from a pre-term infant feeding trial (Isaacs et al., 2010) demonstrated the lasting cognitive benefits of breast milk that are independent from the

potential confounding by the act of breast-feeding itself. In pre-term infants whose mothers elected to feed them with expressed breast milk but needed to supplement with formula, the percentage of expressed breast milk in the diet correlated significantly with adolescent verbal IQ. For boys it correlated with all IQ scores in addition to total brain volume, and white matter brain volume. No significant relationships were apparent in girls or with grey matter volume (Isaacs et al.). An important caveat to these findings is that the impact of early-life feeding in the pre-term cohort does not extend to term infants because the nutritional needs of full-term infants during the final weeks of gestation are met by maternal intake (Nyaradi, Jianghong, Hickling, Foster, & Oddy, 2013).

2.2.2.2 Long-chain polyunsaturated fatty acids (LC-PUFAs)

The candidate nutrients in breast milk particularly relevant to early-life cognitive functioning are the essential fatty acids n-3 and n-6 LC-PUFAs (Heird, 2001). The brain of formula fed infants accumulates approximately half the docosahexaenoic acid (DHA) compared to breast fed infants over the first 6 months of life (Cunnane, Francescutti, Brenna, & Crawford, 2000). Both n-3 and n-6 (arachidonic acid (AA)) PUFAs play important roles in neuronal growth, the synaptic processing of neuronal cell integration, and the expression of genes regulating cell differentiation (Uauy & Dangour, 2006). Essential fatty acids are also precursors for the mediators of inflammation and immune reaction processes (Nyaradi et al., 2013). During late gestation and early post-natal life the brain experiences a tremendous increase in growth, with brain weight increasing 60 fold from approximately 20g in the second trimester to nearly 1,200g by the age of 2 years (Dobbing & Sands, 1973). The content of DHA and AA increases in the

forebrain by nearly 30 fold during this time consequently requiring a considerable postnatal supply of LC-PUFAs (Martinez, 1992).

Follow-up studies of formula supplementation trials have demonstrated an indication of some positive effects in supplemented groups. At age 6 years, children whose formula had been supplemented for four months with DHA acid and AA showed they had faster mean response times for correct responses than the non-supplemented group, although no differences were seen in measures of IQ or speed of processing error scores between the groups (Willatts et al., 2013). No effect of supplementation of DHA alone during infancy was found in a group of 4 year olds, but a group supplemented with DHA and AA had similar IQ performance to a breast-fed group compared to the poorer performance of the control formula group or the group supplemented with DHA only (Birch et al., 2007).

2.2.3 Micronutrient supplementation of well-nourished school children

Although children in Western industrialised countries may on average meet the recommended daily intake requirements for nutrients, it is likely there are sub-groups of children within any sample whose intake of one or more nutrients is inadequate (Benton, 2001). There have been a large number of randomised controlled trials of various nutrients on children's cognitive functioning as assessed by both intelligence measures and school performance (Frensham et al., 2012). In the main, the nutrient interventions consisted of a cocktail of multiple vitamins and minerals because nutrients interact with each other and work synergistically to produce effects (Benton, 2010a). For example, vitamin C is given with iron to improve iron absorption (Bryan et al., 2004).

The majority of trials have found beneficial effects of supplementation; in particular on non-verbal or fluid measures of intelligence rather than on

crystallised measures of learning such as vocabulary or comprehension (Nyaradi et al., 2013). This finding is consistent with the theory that performance on tests of fluid ability are dependent upon the efficiency, or otherwise, of the biological substrates of intellectual functioning that may be directly impacted by nutritional intake on brain metabolism (Benton, 2001; Benton, 2012).

One trial that did demonstrate a significant positive effect of micronutrient supplementation on verbal learning and memory was conducted on 396 well-nourished Australian and 384 marginally-nourished Indonesian primary school aged children over 12 months (Osendarp et al., 2007). Supplementation with a drink containing a mix of micronutrients resulted in improved learning and memory tests across both countries, although effect sizes were small (*d*=.23; 95% CI .01, .46 in the Australian sample, and *d* =.32; 95% CI .10, .64 in the Indonesian sample). The addition of DHA and eicosapentaenoic acid (EPA) to the supplement made no significant contribution to outcomes (Osendarp et al.).

Evidence exists for a differential response to nutrient supplementation depending on whether there was a pre-existing condition of deficiency. The data suggest that positive findings for better performance on cognitive measures are driven by the minority of children who are micronutrient deficient. Studies that have collected pre- and post-supplementation blood samples can measure to what extent blood levels of micronutrient supplementation increased over the trial duration, with the assumption that stable levels indicated adequate nutrient status. A number of studies have demonstrated that IQ test scores improved only in those who were nutrient deficient (Benton, 2001; Benton, 2010a). Thus, performance on intelligence measures is not 'supercharged' by nutrient intake that is excess to requirements.

2.2.4 Dietary patterns in childhood and cognitive development

The relevance of overall diet to children's cognitive development in Western countries has only been investigated recently. Such studies are associational and so subject to the usual confounds, but of interest is that they identify patterns of intake that are potentially detrimental to cognitive development as well as those patterns that are associated with better performance.

Children's diets post-weaning that conform to dietary guidelines, and/or are high in home-made or nutrient-rich foods show small but significant positive associations with IQ scores in early childhood, even after adjustment for multiple socio-demographic confounders (Gale et al., 2009; Northstone et al., 2011; Smithers et al., 2012).

Consistent associations have been found also between higher scores on processed, high-fat and high-sugar dietary patterns across childhood, and lower IQ. In the Avalon Longitudinal Study of Parents and Children (ALSPAC) (Golding, Pembrey, & Jones, 2001), dietary patterns were assessed at 6, 15, and 24 months of age (Smithers et al., 2012), and at 3, 4, and 7 years of age (Northstone et al., 2011). IQ (assessed by the WISC-III) was tested at age 8.5 years. In this sample, after covariate adjustment, higher consumption of a 'processed' pattern at 3 years and a 'discretionary' pattern at 6, 15, and 24 months were negatively associated with IQ. Although these patterns were named differently, they included similar foods such as sweets, chocolate, fizzy drinks, biscuits, and crisps (Northstone & Emmett, 2008; Smithers et al., 2012).

These two sets of analyses of the same cohort using dietary patterns from different ages demonstrated the negative effects of a processed dietary pattern

consumed during early childhood on childhood IQ. A limitation of these studies, however, is that associations between both the earlier and later dietary patterns and IQ at 8.5 years did not adjust for all other repeated measures of dietary intake across the duration of the study. As a consequence, identifying if one time point was particularly relevant to IQ at age 8.5 years was not possible from these analyses.

2.2.5 Relevance of nutrition to early-life cognitive functioning: Summary

Ample evidence exists of the essential role of adequate and appropriate nutritional intake in early-life on the development of cognitive functions throughout childhood. Of particular relevance to cognitive development are adequate protein and calorie intake, the specific nutrient profile of breast milk (in particular, the LC-PUFAs DHA and AA), and adequate micronutrient intake with negative effects apparent for processed, high-fat and high-sugar diets.

It is now 25 years since one of the first micronutrient randomised controlled trials was performed in a developed country of nutrient supplementation in children (Benton & Roberts, 1988). At the time, the study met with incredulity and even hostility. Benton (2001) recalls the outrage of John Yudkin (a prominent British physiologist and nutritionist) who wrote *"This is the most scandalous paper I've seen printed in The Lancet. The study is ludicrous meaningless nonsense"* (p. 304). The understanding at the time was that adequate intake of micronutrients would naturally follow from being well fed. The argument developed by Benton, however, was that even low-level nutrient deficiencies in healthy populations would potentially impact on brain functioning. The brain is the most complex and metabolically active organ in the body and any behavioural

outcome represents the summation of millions of metabolic processes. Appropriate nutritional intake underpins these processes and it follows that even minor inefficiencies of metabolism, due to lack of optimal nutritional status, could create a cumulative adverse effect (Benton, 2008).

If nutrition has a critical role in promoting optimal brain development and subsequent cognitive development in early-life, then plausibly, it also impacts on the structural and functional changes that accompany ageing (Benton, 2010b; Gómez-Pinilla, 2008).

2.3 Nutrition in Brain Ageing and Later-Life Cognitive Functioning

Brain ageing is inherently complex, multifaceted, and poorly understood (Cole, Qiu-Lan, & Frautschy, 2010). During normal ageing, the brain suffers both morphological and functional changes affecting dendritic trees and synapses, neurotransmission, circulation, and metabolism that result in the alteration of motor, sensory, and cognitive systems (Mariani, Polidori, Cherubini, & Mecocci, 2005). While the brain can age successfully, its cells may face considerable adversity during the journey. Nutritional factors may buffer the brain against its vulnerability to the structural damage and compromised functioning that occur with increasing age (Mattson, Duan et al., 2002). Elucidating the contribution of nutritional intake to brain ageing has generated a vast and rapidly evolving inter-disciplinary body of research, much of which is based on *invitro* and *invivo* animal studies that model the complex bio-chemical and physiological pathways by which such influences may occur. The following section presents a non-technical account of the major nutritional factors relevant to brain ageing, and to the evolution of cognitive change and decline.

2.3.1 Antioxidants and oxidative stress

As in all other organs, the brain encounters a cumulative burden of oxidative and metabolic stress that may be a universal feature of the ageing process (Mattson, Chan, & Duan, 2002). Oxidative stress is commonly defined as an imbalance between reactive by-products known as reactive oxygen species (ROS) produced during oxygen metabolism, and the protective antioxidant system. ROS can attack proteins, lipids, and DNA, changing their structure and thus disrupting function. Unchecked oxidative stress ultimately leads to cell death (Pocernich, Butterfield, & Head, 2013).

The high metabolic rate of the brain makes it especially susceptible to oxidative stress; its weight represents only 2% of body mass yet utilizes 20% of total oxygen consumption, most likely due to its primary use of glucose as an energy source (Floyd & Hensley, 2002). Additionally, the brain has a high content of PUFAs which are especially vulnerable to peroxidation, together with high levels of iron and ascorbate which are key catalysts for membrane lipid peroxidation. Finally, the brain is not enriched in antioxidant protective defences and this adds to its potential for oxidative damage. Since the endogenous antioxidant defence systems in the brain are limited, it is plausible to suggest that nutritional antioxidants be exploited to combat the accumulation of oxidative stress over the life-span (Floyd & Hensley, 2002; Lau, Shukitt-Hale, & Joseph, 2005). Antioxidants offer protection on many different levels by preventing radical formation, neutralising free radicals, repairing oxidative damage, and eliminating damaged molecules (Pocernich et al., 2013).

2.3.1.1 Polyphenols

These protective compounds naturally occur in all plants and enhance the plant's survivability by combating oxidative stress and inflammation (Joseph, Cole, Head, & Ingram, 2009). Fruits and vegetables have elevated polyphenol content which is directly related to the plant's antioxidant potential (Pocernich et al., 2013). Pomegranate and berries, spinach, beets, red peppers, and broccoli have all been demonstrated to display particularly high levels of cellular antioxidant activity (Song et al., 2010; Wolfe et al., 2008). A large body of literature exists demonstrating the protective efficacy of polyphenols in rodent models of brain ageing, mainly via supplementation with grape, berry, or walnut compounds (Joseph et al., 1999; Joseph, Shukitt-Hale, & Casadesus, 2005; Shukitt-Hale, Carey, Simon, Mark, & Joseph, 2006) but human intervention studies are lacking[13]. A systematic review of nine well controlled cohort studies that had investigated the impact of fruit and vegetable consumption on the prevention of cognitive decline or dementia found that higher consumption of vegetables but not fruit was associated with a decreased risk of dementia or cognitive decline at follow up. Follow-up period ranged from 6 months to 31 years with a median of 6 years, and tests of cognitive decline, or risk of dementia, AD or MCI by intake of fruit and/or vegetables were specified as inclusion criteria (Loef & Walach, 2012).

2.3.1.2 Randomised controlled trials of antioxidant supplementation on older-age cognition

There have been six randomised controlled trials of antioxidant vitamin supplementation on older-age cognitive functioning including vitamin C, E, beta-

[13] A RCT of blueberry and omega-3 supplementation in age-related cognitive decline is currently underway in the United States: Clinical Trials Identifier:NCT01746303

carotene, zinc, and copper (Yaffe, Clemons, McBee, & Lindblad, 2004), vitamin E alone (Yaffe et al., 2004) , beta-carotene alone (Grodstein, Kang, Glynn, Cook, & Gaziano, 2007), vitamin C, E, and beta-carotene (Kang et al., 2009), a complex antioxidant blend of 34 elements (Summers, Martin, Cunningham, DeBoynton, & Marsh, 2010), and a combination of vitamins C, E, beta-carotene, selenium, and zinc (Kesse-Guyot, Fezeu et al., 2011). A positive effect was found for long-term (18 years) of beta-carotene supplementation on global cognition and a verbal memory score in older men (Grodstein et al.). Two of the trials that used a combination of antioxidants found protective effects on cognition (Kesse-Guyot, Fezeu et al., 2011; Summers et al., 2010). Both study samples included middle-aged participants. Summers et al. had 4 months of follow-up, while the follow-up in the Kesse-Guyot et al. trial was 6 years. Antioxidant supplementation has been shown to significantly improve scores on paired association and word recall tests (Summers et al.) and on tests of episodic memory (Kesse-Guyot, Fezeu et al.). However, a recent Cochrane systematic review of antioxidant supplementation (Bjelakovic, Nikolova, Gluud, Simonetti, & Gluud, 2012) warned against the use of antioxidant supplements in the general population and in those with various diseases. In particular beta-carotene and possibly vitamin E and vitamin A were associated with increased mortality. The authors applied the caveat that their findings should not be translated to potential effects of fruits and vegetables, only supplemental studies were included in their systematic review.

2.3.2 Fatty acids

Fatty acids impact on the ageing brain and its functioning via multiple mechanisms that also overlap and interact; these include vascular and inflammatory pathways, in addition to associations with beta-amyloid protein

accumulation, membrane fluidity, and apoptosis (Kalmijn, 2002). The following overview provides a general account of the role fat consumption plays in brain ageing and older-age cognitive functioning.

Fatty acids can be categorised into saturated fatty acids and unsaturated fatty acids depending on their structure. Chemically, a fatty acid is a chain of carbon atoms with pairs of hydrogen atoms attached. The number of carbon atoms varies from less than eight carbons (short chain fatty acids) to 16 or more carbons (long chain fatty acids) whereas fatty acids with more than 22 carbons are very long chain fatty acids. Saturated fatty acids are fully loaded with hydrogen atoms forming straight chains, and are typically solid at room temperature. They are present in foods such as meat, dairy products, pastries, biscuits, and processed snack foods. Unsaturated fatty acids have lost at least one of their pairs of hydrogen atoms from their carbon chain, in which case they are monosaturated fats and are found in olives and olive oil, avocados, and nuts (Kalmijn, 2002; Simopoulos, 1991). The PUFAs are missing more than one pair of hydrogen atoms. These fatty acids are especially relevant to brain structure and functioning, particularly the long chain n-3 PUFAs DHA, and the long chain n-6 PUFA AA. Both of these essential PUFAs are very inefficiently synthesised from their dietary precursors α-linolenic acid (ALA) for n-3, and linoleic acid (LA) for n-6. They are best obtained pre-formed from the diet; oily fish being the main source of the n-3 fatty acids (Tan et al., 2012).

2.3.2.1 Saturated and monosaturated fatty acids

A high intake of saturated fat is an established risk factor for vascular disease (Mente, de Koning, Shannon, & Anand, 2009; Reddy & Katan, 2004). Evidence was provided of the association between vascular diseases and poorer

older-age cognitive functioning in Chapter 1; thus, one mechanism by which saturated fat contributes to the risk of cognitive decline is by its contribution to vascular disease. Brain microvasculature has been estimated as having a surface area of 400ft ^{2} and any disruption to this structure by microvascular pathology induced by atherosclerosis or weakening of endothelial functions is likely to impact on functioning (Floyd & Hensley, 2002). Elevated serum cholesterol levels indicative of a high fat diet were associated with increased risk of MCI in a midlife Finnish sample followed up after 21 years with effects adjusted for age and BMI (Kivipelto et al., 2001). In animal models also, a high fat diet contributed to the accumulation of intra-neuronal beta-amyloid, reduced hippocampal neurogenesis, and increased oxidative stress (Freeman & Granholm, 2012)

Monosaturated fatty acids may favourably impact on brain ageing, largely again via to their impact on vascular health, but findings for monosaturated fatty acids are less conclusive than those for saturated fat (Vafeiadou et al., 2012), and the area is still a relatively new one. Very few studies specifically address the association between monosaturated fat intake and cognitive decline (Plourde, 2011). Higher monosaturated fatty acid intake was demonstrated to predict greater decline on the MMSE in the Italian Longitudinal Study on Aging (Solfrizzi et al., 2006; Solfrizzi et al., 1999), and with a more favourable cognitive trajectory over 4 years in the Women's Health Study (Okereke et al., 2012), but no effect of monosaturated fat on risk of dementia over 6 years was found in the Rotterdam study (Engelhart et al., 2002).

2.3.2.2 Long-chain PUFAs: n-6 and n-3

The brain contains large amounts of fatty acids, 50% of which are long-chain PUFAs; essentially, equal quantities of AA (n-6) and DHA (n-3) (Denis, Potier,

Vancassel, Heberden, & Lavialle, 2013). Western diets are typically high in n-6 fatty acids, particularly LA which is an AA precursor, and comparatively low in the n-3 fatty acids, ALA and the long-chain marine fatty acids, DHA and EPA (Cole et al., 2010). LA and ALA compete metabolically in their utilization of the enzyme delta6-desaturase to produce their longer-chain derivatives (n-6 and n-3). Without appropriate dietary intake of the pre-formed n-3 fatty acids (primarily from fatty fish), a net imbalance between n-6 and n-3 fatty acids will likely result (Bryan et al., 2004; Cole et al., 2010). The relevance to health outcomes, including cognitive functioning, of a high n-6 to n-3 fatty acid ratio is still relatively under-researched, but a recent review supports evidence of a positive association between a low n-3:high n-6 ratio and the risk of decline and incidence of dementia (Loef & Walach, 2013).

DHA is the primary n-3 fatty acid in the brain and represents between 12% and 16% of total fatty acids in gray matter lipids (Calon & Cole, 2007). It is also the predominant lipid in the most metabolically active brain areas including the cerebral cortex, synaptosomes and mitochondria (Morris, 2012). There are numerous DHA dependent mechanisms underpinning brain functioning that have been the focus of experimental research over the previous two decades, and that are particularly relevant to brain ageing (Cole et al., 2010). DHA is the main n-3 PUFA in brain cell membranes and has a vital role in regulating and maintaining the glutamatergic synapses that are responsible for memory formation. Glutamate is the major excitatory neurotransmitter in the brain, and glutamatergic synapses are particularly abundant in the hippocampus, the region mainly involved in memory processes. Insufficient brain DHA may contribute to the disruption of the homeostatis of the synaptic environment which contributes to age-related brain

damage and subsequent cognitive decline (Denis et al., 2013). DHA has also been demonstrated to provide neuroprotection via DHA-derived neuroprotectin D1. This endogenously derived lipid mediator protects against oxidative stress, apoptosis, and inflammation-triggered neuronal decline, while promoting brain cell survival and maximising cognitive function throughout the human life-span (Lukiw & Bazan, 2008).

The actions of n-3 PUFAs in enhancing vascular health also provide mechanisms for the potential beneficial effects of these essential fatty acids on cognitive health (Uauy & Dangour, 2006). N-3 PUFAs lower plasma triglyceride levels, decrease arrhythmias, lower blood pressure, impair platelet aggregation, and inhibit or block pro-inflammatory and other pathways associated with atherosclerosis (Sudheendran, Chang, & Deckelbaum, 2010).

The critical role for n-3 PUFAs in brain functioning could be expected to translate into associations between higher n-3 PUFA intake and preservation of cognitive functioning in older age (Cole et al., 2010). In prospective studies, incident dementia and cognitive decline have been consistently and negatively predicted by higher dietary intake of fish (Bégin, Plourde, Pifferi, & Cunnane, 2010; Huang, 2010), although the association between fish intake and older-age cognitive status is potentially confounded by other potentially protective nutrients apart from n-3 PUFAs present in fish, together with fish consumption co-varying with an overall healthy diet and lifestyle (Cunnane et al., 2009). Studies using biomarker indicators of n-3 fatty acid status are not as prevalent and are more difficult to interpret due to the variability between the biomarkers chosen; although interestingly, a recent investigation in cognitively normal adults of the relations between n-3 PUFAs in red blood cells and MRI measures of brain ageing found that

those in the lowest quartile of red blood cell DHA proportion had lower total brain volume after multivariate adjustment (Tan et al., 2012).

Despite the large body of epidemiological research that has attempted to establish positive associations between n-3 PUFA intake and cognitive health in older age, Huang, in reviewing the literature concluded that "*The variability in outcomes between human studies which are confounded by methodological differences, make it difficult for conclusions to be made at this time"* (Huang, 2010, p. 685).

2.3.2.2.1 n-3 PUFAs and interactions with ApoE status, sex, and age

Some of the variability in findings regarding the impact of n-3 PUFAs on cognition is likely due to genetically determined responses to n-3 PUFA intake (Schipper, 2011). In particular, ApoE ε 4 status has been demonstrated to differentially affect both plasma and lipid response to n-3 PUFA supplementation (Minihane et al., 2000; Plourde et al., 2009). This differential genetic response may also interact with sex. In the FINGEN study, it was reported that in the group as a whole, plasma triacylglycerol levels were lowered by n-3 PUFA supplementation, but that there were significant sex X treatment and sex X genotype X treatment interactions. Greater triacylglcerol-lowering responses were seen in men than women, and a doubling of the response was evident in ApoE-ε 4 men. In the same study, the impact of n-3 PUFA supplementation on antioxidant status was tested. There was little evidence of a response in the ε2 or ε4 participants, but higher levels of n-3 PUFAs were associated with higher antioxidant status in the ApoE-ε3 subgroup, but only in those who were older aged 60-70 years (Caslake et al., 2008). These findings are illustrative of the complexity inherent in determining the

plausible effects on cognitive functioning of n-3 PUFA intake, given the heterogeneity of physiological response in human beings to this intake.

2.3.2.3 Randomized controlled trials of n-3 PUFA supplementation on older-age cognition

There have been three completed large-scale randomized controlled trials of n-3 PUFAs on older-age cognitive functioning in cognitively healthy populations (Dangour et al., 2010; Geleijnse, Giltay, & Kromhout, 2012; van de Rest et al., 2008)[14], and one trial in a sample that were memory impaired (in comparison to younger adults) (Yurko-Mauro et al., 2010); supplementation periods ranged from 24 weeks (Yurko-Mauro et al.) to 40 months (Geleijnse et al.). One trial measured ApoE- ε 4 carrier status (van de Rest et al., 2008). The only positive outcome of supplementation was found in the memory impaired population (Yurko-Mauro et al.), with those receiving 900 mg a day of DHA plus antioxidants[15] demonstrating significantly less errors in a visuospatial learning and episodic memory test, and improved immediate and delayed verbal recognition memory scores compared to the placebo group.

2.3.3 The B vitamins

The B vitamins folate (B_9), B_{12}, and B_6 are required for the conversion of homocysteine to methionine and to cysteine (Herrmann & Obeid, 2011). Methionine is an essential amino acid found in protein-rich foods such as meats, seafood, dairy product, and eggs ("Homocysteine reduction," 2013). When methionine is metabolised, homocysteine is produced. Homocysteine is a sulphur containing amino acid that induces neurotoxicity, promotes apostosis, promotes

[14] In the trial by Geleijnse et al. (2012) the sample consisted of stable myocardial infarction patients.
[15] The placebo arm supplement also contained the same antioxidant content as the active supplement

vascular injury via inducing atherogenesis and platelet activation, which then contribute to the risk of ischaemic strokes (Garcia & Zanibbi, 2004). Both B_{12} and folate are required for the remethylation of homocysteine back to methionine. About 50% of homocysteine is remethylated; the remainder is transsulfurated to cysteine, which requires B_6 as a co-factor. Cysteine is then metabolised to make glutathione that protects cells from oxidative damage ("Homocysteine reduction," 2013). Dietary intake of the B vitamins therefore potentially impacts on cognitive health via both vascular and antioxidant pathways.

Dietary sources of vitamin B_6 and B_{12} are meats, fish, and dairy products, whole-grain breads and fortified cereals. Sources of folate include fortified cereals and whole-grain breads, dark leafy vegetables, and legumes (NHMRC, 2009). Despite the fortification of cereals with folate and the ready availability of vitamin B-rich foods, deficiency of vitamin B_{12} and folate is common in older people and increases with age. This is due in part to intestinal malfunctioning and increased use of antacid medications both of which interfere with absorption of food-derived vitamins. Age-related damage to the blood-brain barrier may also impede effective absorption (Clarke et al., 2004; Selhub, Troen, & Rosenberg, 2010).

Given the complexity of the mechanisms related to the metabolic relationship between multiple B vitamins and homocysteine levels, the relationship between B-vitamin status and subsequent cognitive function remains unclear, despite a plethora of observational studies (Raman et al., 2007). Two recent meta-analyses (Doets et al., 2013; Michelakos et al., 2013) and one systematic review (Raman et al., 2007) have examined these associations. Doets et al. only considered studies of B_{12} and cognitive function and included the results from two randomised controlled trials. They concluded that there were no

consistent associations between serum/plama vitamin B_{12} and either risk of dementia, global cognitive z-scores, or memory z-scores (Doets et al.). Michelakos et al. also reported no significant association between vitamin B_{12} and cognition but their meta-analysis did find that low-folate levels were significantly associated with cognitive impairment in older people (Michelakos et al.). The systematic review by Raman et al. assessed associations between cognitive function and folate, B_6 and B_{12}. The majority of the studies reviewed indicated that low blood folate concentrations were associated with poorer cognition and there was some evidence also for higher homocysteine concentrations predicting poorer cognitive function. The authors noted, however, the considerable heterogeneity between studies in terms of the B-vitamin-level thresholds and their comparisons, the data analytical techniques employed, and the assessment of cognitive functioning, all of which prevented conclusions being drawn (Raman et al.).

2.3.3.1 Randomised controlled trials of B vitamin supplementation on older-age cognition

There have been eight recent randomised controlled trials of B vitamins on older-age cognitive functioning within the last decade (Durga et al., 2007; Eussen et al., 2006; Ford et al., 2010; Hvas, Juul, Lauritzen, Nexø¸, & Ellegaardâœ 2004; Kang et al., 2008; Lewerin et al., 2005; McMahon et al., 2006; Walker et al., 2012). Two of these trials had very short follow-up periods of three (Hvas et al.) and four months (Lewerin et al.). Other follow-up periods ranged from two to eight years. Two trials found positive effect of supplementation: Folate supplementation for 3 years in participants with elevated serum homocysteine (50-70 years) was associated with improved performance on memory, sensorimotor speed, and information processing speed (Durga et al., 2007); and 2 years of folate and B_{12}

supplementation improved performance on the total score and the immediate and delayed memory scores from the Telephone Interview for Cognitive Status-Modified in older people (60-74 years) with depressive symptoms (Walker et al., 2012).

A RCT by Smith et al. (2010) of folic acid, B_{12} and B_6 on individuals over 70 years with MCI compared the rate of brain atrophy assessed by MRI in the treatment group compared to the placebo. They found tha that those in the treatment group with high baseline homocysteine levels showed a 53% slower rate of atrophy as than those in the placebo group and a greater rate if atrophy was also associated with lower final cognitve test scores.

2.3.4 The Mediterranean diet

The traditional Mediterranean diet (MeDi) is well established as promoting vascular health (de Lorgeril et al., 1999; Kastorini et al., 2011; Serra-Majem, Roman, & Estruch, 2006). Recently, the MeDi has been implicated in reducing the risk of AD and MCI, and higher adherence has been associated with less decline in normal ageing; for a current systematic review see Lourida et al. (2013). The majority of studies that have demonstrated protective effects of the MeDi on cognitive functioning in older people have been carried out in a single cohort prospectively followed over 6 years; the Washington Heights-Inwood Columbia Aging Project (WHICAP). These studies demonstrated that higher adherence to the MeDi was associated with reduced odds of MCI (Scarmeas, Stern et al., 2009) and AD (Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006), in addition to better cognitive performance (Gu, Luchsinger, Stern, & Scarmeas, 2010) and less cognitive decline (Scarmeus et al., 2006). Results from two other cohorts did not

support the protective effect of the MeDi against MCI (Roberts et al., 2010) or age-related decline (Cherbuin & Anstey, 2012).

The MeDi is characterised by high intake of vegetables, legumes, fruits, and cereal; high intake of unsaturated fatty acids (usually in the form of olive oil); a moderately high intake of fish; low to moderate consumption of dairy products (usually yogurt or cheese); low consumption of meat and poultry; and a regular, but moderate, amount of alcohol usually in the form of wine during meals.

The MeDi may exert effects on cognitive health via multiple pathways. Decreased oxidative stress (Dai et al., 2008) and markers of inflammation (Chrysohoou, Panagiotakos, Pitsavos, Das, & Stefanadis, 2004) have been demonstrated previously in those adhering to a MeDi, and its cardiovascular benefits have already been noted. Specifically, higher consumption of this dietary pattern negatively predicts a number of individual risk factors for vascular disease including obesity, diabetes, hypertension, and dyslipidemia (Scarmeas et al., 2011). The favourable impact of the MeDi on brain health was investigated *invivo* by examining the association between MeDi adherence and MRI of brain infarcts in a sample of 707 participants 65 years or older. In adjusted models, the high MeDi group had 36 % reduced odds of having an infarct. The strength, although not the significance, of this association remained for final model adjustment that included plasma tryglycerides, total cholesterol, HDL and LDL cholesterol (Scarmeas et al., 2011).

These promising observational findings and the mechanistic foundation for the MeDi's protective effects has led one reviewer to comment *"There is only one possible conclusion after reviewing the epidemiological literature on the MeDiet and age-related cognitive deterioration, AD, and stroke: we are in dire need of clinical*

trials" (Valls-Pedret & Ros, 2013, p. 505). Secondary neuropsychological outcomes are pending for the five year PREDIMED trial (Estruch et al., 2013), and at least one smaller scale trial is currently recruiting[16].

2.3.5 Summary of nutritional influences on brain ageing

The intake of antioxidants, B-group vitamins, and fatty acids is theoretically relevant to the evolution of older-age cognition via the role of these nutrients in brain metabolism and vascular health. Despite such relevance, very few positive findings were apparent in clinical trials of these nutrients on cognitive decline. Of the 18 identified trials of these relevant nutrients, only 6 had a positive effect, and these effects were on a variety of cognitive measures and included people with depressive symptoms (Walker et al., 2012) and impaired memory (Yurko-Mauro et al., 2010), so generalising from these findings is problematic.

The majority of trials were conducted in people ≥ 65 years of age, but as was discussed in Chapter 1, the mechanisms that underpin cognitive ageing operate across the lifetime, and by the time older-age has been reached many of the complex genetic and environmental interactions that determine older-age functioning have already had an impact. It is of note that the majority of positive trials of antioxidant supplementation (Grodstein et al., 2007; Kesse-Guyot, Fezeu et al., 2011; Summers et al., 2010) and folate supplementation (Durga et al., 2007) all included middle-aged older adults, that is, those who were in their 50s so potentially at a more malleable stage of brain ageing to those in more advanced old age.

[16] Recruiting for a 6 month RCT of the MeDi on cognition and cardiovascular health currently underway. Clinical trial number: ACTRN12613000602729.

Although randomised, placebo-controlled trials provide the 'gold standard' for testing causal relationships between variables (Daffner, 2010), such an approach presents a number of logistic difficulties when testing the potential nutrient effects on cognitive ageing (Benton, 2010b; Daffner, 2010). The primary problem is that the majority of follow-up periods are of relatively short duration ranging from a few months to a few years due to limitations imposed by the cost of such trials, and the burden of compliance they place upon participants[17]. Yet, such relatively short time periods may not reflect the prolonged period over which diet is influential (Benton, 2010b); for example, by its influence on prior vascular risk factors such as dyslipidemia, hypertension, and atherosclerosis. Indeed, the protective effects of the MeDi have been primarily demonstrated in cohort studies with long follow-up periods (Lourida et al., 2013).

2.3.6 Associations between prior intake and older-age cognition

The long term aetiology of cognitive ageing that was discussed in Chapter 1, together with the essential role of nutritional intake in maintaining optimal brain health, would suggest the relevance of dietary intake from life-periods prior to older age to late-life cognitive functioning, and the trajectory of cognitive change and decline. There is very little available evidence, however, regarding the association between dietary intake from earlier life-periods on older-age cognitive functioning within the context of non-clinical cognitive ageing outcomes. Table 2.1 (overleaf) provides an overview of studies that have assessed dietary variables from a period prior to older-age and tested their association with older-age

[17] An exception is Grodstein et al's. 2007 study of beta-carotene supplementation on older men which had a follow-up of 18 years. Interestingly, in a new group with only 1 year of supplementation no effect was found, but in the group with 18 years of supplementation, this study was one of the few to report a positive outcome.

cognition. These studies all assessed dietary intake in mid-life (at approximately 40-60 years). This is the life-period that is critical for the onset of chronic diseases, including vascular disease, and when lifestyle changes, including diet, are likely to modify the risk of disease development (Lambrinoudaki et al., 2013).

The studies presented demonstrate some evidence that diet in mid-life affects later-life cognitive functioning. Two studies evaluated the effect of dietary intake on cognitive ageing in the same cohort, the Nurses' Health Study. A better ageing trajectory was found in those with higher berry consumption (Devore, Kang, Breteler, & Grodstein, 2012), but in a separate study, no evidence was found of a protective effect over time from better adherence to the MeDi (Samieri, Okereke, Devore, & Grodstein, 2013). Another four studies were also carried out in the SU.VI.MAX 2 cohort, a follow-up cohort established from a randomised trial of antioxidants on cognition in a French middle-aged sample (Hercberg et al., 1998). Inconsistent findings were reported across three of these studies, and one had less relevance due to its use of self-reported cognitive difficulties as an outcome (Kesse-Guyot et al., 2010). Adherence to nutritional guidelines and a 'healthy' dietary pattern at midlife predicted better cognitive functioning 13 years later (Kesse-Guyot, Amieva et al., 2011; Kesse-Guyot et al., 2012), but there was no substantial effect of mid-life consumption of the MeDi (as calculated using the same dietary records as the other two studies) and later life cognitive functioning (Kesse-Guyot et al., 2013).

Table 2.1: Associations between dietary intake in mid-life and older-age cognitive functioning

Study author(s), year cohort name, design,	Population characteristics	Follow-up	Dietary exposure	Cognitive outcome	Results
White et al.(2000), Honolulu Aging Study; PC	Japanese/American men born 1900-1919. Baseline:1965, Cognitive functioning assessed 1991-1993: n=3734	26-28 yrs.	FFQ of either Japanese or Western-style diet at baseline & 6yrs.	The Cognitive Abilities Screening Instrument. Brain atrophy assessed with neuroimaging & at autopsy.	In adjusted models greater consumption of tofu in mid-life was associated with increasing cognitive impairment & low brain weight but not ventricular enlargement.
Laurin, Masaki, Foley, White, & Launer (2004), Honolulu Aging Study; PC	Population as above	25-33 yrs.	24 hr dietary recall and FFQ as above.	Incident dementia.	After adjustment no association between midlife dietary antioxidant intake and incidence of dementia in late life.
Kesse-Guyot et al.(2010), SU.VI.MAX; initially RCT, subsample as PC	Healthy participants 45-60 yrs; n=4527; analysed=3,294	13 yrs.	24 hr dietary record every 2mnths for 6mths used to calculate fish, EPA & DHA consumption.	MMSE. 5-word memory test, self-reported memory complaints using McNair's Cognitive Difficulties Scale	No association between n-3 PUFAs/fish with tests but higher n-3 PUFA consumption associated with less self-reported cognitive difficulties.
Kesse-Guyot et al.(2011), SU.VI.MAX; initially RCT, subsample as PC	Population as above: analysed= 2,135	13 yrs.	24 hr dietary record every 2mnths for 6mths.	Neuropsychological evaluation (6 tests) subject to PCA plus individual test scores examined.	After adjustment adherence to nutritional recommendations in midlife associated with better verbal memory 13 years later.

Table 2.*1 (continued)*

Study author(s), year cohort name, design,	Population characteristics	Follow-up	Dietary exposure	Cognitive outcome	Results
Kesse-Guyot et al.(2012), SU.VI.MAX; initially RCT, subsample as PC	Population as above; analysed	13 yrs.	Dietary patterns from 24 hr dietary record every 2mnths for 6mths.	As above but global cognitive score calculated from mean of standardised test scores.	A healthy dietary pattern in mid-life was associated with better global cognitive function 13 years later.
Kesse-Guyot et al.(2013) SU.VI.MAX; initially RCT, subsample as PC	Population as above	13 yrs.	MeDi score calculated from 24 hr dietary record every 2mnths for 6mths.	As above	No support found for beneficial effect of the MeDi consumed in mid-life on cognitive performance 13 yrs later, and no interaction with potential markers of cognitive reserve.
Devore et al.(2012), Nurses' Health Study; PC	Registered nurses 34-55 yrs in 1980; cognitive assessment in 1995-2001 of those ≥ 70 yrs, n=16,010	15-21 years; cognitive follow-up 2 times at 2 yr intervals.	61 item semi-quantitative FFQ administered in1980; 130 item semi-quantitative FFQ administered every 4 yrs from 1984. Berry and flavonoid consumption calculated across total exposure period.	Cognitive tests from the Telephone Interview of Cognitive Status (5 tests), plus the MMSE.	After adjustment, greater intake of flavonoids, particularly from berries, appears to reduce rates of cognitive decline in older women so that berry intake appears to delay cognitive ageing by 2.5 yrs.

Table 2.*1 (continued)*

Study author(s), year cohort name, design,	Population characteristics	Follow-up	Dietary exposure	Cognitive outcome	Results
Samieri et al. (2013), Nurses' Health Study; PC	As above	As above but cognitive assessment 3 times at 2 yr intervals.	130 item semi-quantitative FFQ administered every 4 yrs from 1984. MeDi adherence based on intake MeDi foods. Exposure estimated by averaging all 4 repeated measures of diet > 13 yrs.	As above	In primary analysis MeDi was not associated with decline in global cognition or verbal memory. Secondary analysis averaged the repeated measures of cognition and a higher MeDi consumption was associated with better multivariable-adjusted mean cognitive scores
Cadar et al. (2012),	British 1946 birth cohort: n = 3,004 at 43 years, n= 1,911 at 60 years	Lifestyle behaviours at 36 & 43; cognitive testing at 43 & 60 years	A 5-day diary at 36 and 43 years. Also a dietary choice score based on poorer (0)or healthier (1)choice	Memory and visual search speed decline over 20 years (2 time points)	Healthier dietary choice associated with less 20 year decline after covariate control
Akbarely et al.(2013), Whitehall 11; PC	London-based civil servants 35-55 yrs in 1985-1988. Baseline for dietary intake at 1991-1993; follow-up sample = ≥ 60yrs at 2007-2009; n=5,350	16 yrs.	127-item semi-quantitative FFQ subjected to PCA; 'healthy foods' pattern and 'Western-type' patterns extracted.	Good cognitive functioning defined as above median age & sex-standardised global scores from 5 cognitive tests.	Participants in the highest tertile of 'Western-type' diet were more likely to have poorer ageing outcomes with significant odds of having a below-median global test score.

Despite some limited support for the relevance of mid-life diet to later-life cognition, there are considerable methodological challenges in evaluating the results of these studies. When diet is only assessed during middle-age, and it is not assessed concurrently with the later-life cognitive measures, any influence of current diet or indeed diet from earlier periods cannot be controlled for in analyses. Therefore, although there are a number of theoretical pathways by which mid-life diet may impact on older-age cognitive functioning, it is not possible to determine the relevance of mid-life as a 'critical' period for dietary intake without controlling also for the potential impact of diet from other periods, an issue that will be dealt with in Chapter 5.

No studies have examined the impact of dietary intake over multiple life-periods because there are no prospective cohort studies that have gathered dietary data over a span of 60 or 70 years. Even the longest follow-up period of nearly 30 years in the Honolulu aging study is still relatively short in the scheme of a life-time's intake of food. It is clear that diet in early-life is crucial to cognitive development. Cognitive ability in childhood predicts one's intellectual ability, and educational attainment throughout life (Deary et al., 2000), and so may contribute to both passive and active brain reserve, thereby buffering the brain against the effects of ageing (Benton, 2010b; Daffner, 2010). Throughout adulthood, diet is likely to contribute to the aetiology of vascular disease, the symptoms of which become apparent in mid-life, and this is an alternate plausible pathway by which early life intake contributes to the cognitive ageing trajectory.

At the end of Chapter 1, it was acknowledged that a life-course approach to cognitive ageing would be an optimal method to uncover its determinants, but that the necessary measures, including diet, are not available even in the longest cohort

studies. But if, as Benton (2010b) states, "*this model of diet being influential throughout the entire lifespan is accurate, then it has substantial implications for the study of the topic*" (Benton, p. 59). Benton's comment was in the context of using established early biomarkers of decline (rather than the decline itself) as outcomes in nutritional intervention trials, but another approach is to use retrospective recall by cognitively healthy older adults of their dietary intake from earlier life-periods.

The next chapter, therefore, turns to the measurement of past diet and the methodological implications of using such an approach to gather life time dietary data.

Chapter 3 Past Diet Assessment

3.1 Introduction

Recall of dietary intake from across the lifetime provides dietary data that may be relevant to elucidating the influence of dietary factors on older-age cognitive health. Crucial to this undertaking is establishing the validity of past diet recall. A number of studies over the last 30 years have investigated relationships between dietary records and recall by participants of their diet during the past reference period, together with participants' current diet to determine the utility of long-term dietary memory in epidemiological studies. The nature of dietary memory in terms of its formation and retrieval places limits on the accuracy of both past and present dietary recall instruments such as food frequency questionnaires (FFQs). Although, on average, the reliability of past diet recall declines over longer periods, it has been consistently demonstrated to account for more of the variance in recorded past intake than peoples' current diet. This suggests that past dietary recall provides additional information regarding intake in the past over and above that provided by current intake. Despite a large body of research that has investigated the validity of past diet recall, there have been no studies as yet that have implemented its assessment.

3.2 Theoretical Background

In nutritional epidemiology, diet is assessed to determine its possible contribution to health or disease outcomes. Such a task is fraught with difficulties, and there are numerous factors that introduce error into the measurement of what is a universal human behaviour, food intake. Nelson and Bingham (1997) in the

following extract capture the methodological challenges that plague dietary assessment:

> *If the aim is to measure current diet then the Heisenberg uncertainty principle rears its head: as you stop something to measure it, you change its behaviour. If the aim is to measure past dietary exposure, then one is reliant on the memory, conceptual abilities, and ruthless honesty on the part of respondents...It would seem that no direct measure of what people eat will provide a true picture of their dietary intake (p. 123).*

Despite this rather pessimistic view of the validity of dietary measurement, researchers have not been deterred from the quest to uncover associations between dietary intake and a number of chronic diseases such as cancer (Key et al., 2004), cardiovascular disease (Lee et al., 2001), and more recently, cognitive decline and dementia (Morris, 2012).

Establishing the validity of dietary measures relevant to chronic diseases is particularly challenging because it is long-term dietary intake that is likely to be relevant rather than current diet (Riboli, 1989). Current dietary measures such as food diaries, checklists, or 24 hour recalls can be validated by testing various biological markers of intake, such as the 24-hour urine collection, to validate reported protein, sodium, and potassium intakes, or the doubly-labelled water technique to validate energy expenditure as calculated from the particular measure of dietary intake (Thompson & Subar, 2013). There are no validated biological measures of long-term diet, however. Long-term diet is measured by using self-report, or interviewer-administered FFQs that inquire about the usual frequency of food consumption over a particular time period which can range from a few months to a few years.

The assessment of past diet recall validity emerged as an area of inquiry during the early 1980s; specifically in the context of cancer research where the need was identified by a number of researchers to assess dietary intake from the distant past in case-control studies of cancer aetiology (Byers, Marshall, Anthony, Fielder, & Zielezny, 1987; Moore, Prestridge, & Newell, 1981; Rohan & Potter, 1984). At the time, such studies used measures of current diet as proxies for long-term diet because diet was considered to remain relatively stable over adulthood (Jensen, Wahrendorf, Rosenqvist, & Geser, 1984). It was demonstrated, however, when both records of current dietary intake and recalled past intake were compared with actual records of past intake, that the recalled measures were more highly correlated with the past dietary records than the measure of current diet (Byers et al., 1987). Therefore, as Byers et al. concluded " *the best estimate of diet from several years in the past may be derived directly from a retrospective dietary history which focuses on that past period of time*" (p. 999).

3.2.1 Validity of past diet recall

In recommending the measurement of past diet, Byers et al. (1987) themselves acknowledged the need for caution, particularly in the context of case-control studies of cancer incidence. It was possible, if not likely, that cancer diagnosis would bias long-term dietary recall so that cancer cases would under- or over-report a number of foods that had been associated anecdotally with cancer incidence (Riboli, 1989). Also, dietary changes made by those diagnosed with cancer may impact on their recall of past dietary intake, because recall of current diet is known to impact on recall of past diet (Persson, Ahlbom, & Norell, 1990). Apart from the validity problems of past diet recall specific to case-control studies, there were more general threats to the validity of long-term dietary recall in terms

of the accuracy of dietary memory over long time periods, and whether there was a limit on the length of time that dietary memory could be considered in any way representative of the period in question (Chavarro et al., 2009).

One approach used by a number of researchers to test the validity of dietary recall over lengthy time periods was to compare recall of past intake at a particular time with actual records of that intake gathered at the time in question. Friedenreich, Simani, and Riboli (1992) conducted the only review of study findings for the reliability of past diet recall. A summary of this early review is presented here because it forms much of the theoretical foundation for further progress in past diet measurement.

Three types of dietary measurement were considered: original diet was the diet reported at some time point in the past (time-point A), 'recalled' diet was the diet of time-point A reported at time-point B, and 'current' diet was the diet reported at, and referring to, time-point B. When dietary assessments were compared from at time-points A and B, the studies of retrospective dietary reporting could examine:

1. Whether dietary habits changed, by examining *original* and *current* measures.
2. Whether recalled diet accurately and reliably measured original diet by comparing *original* diet at time-point A with *recalled* diet at time-point B.
3. Whether current diet influenced the reporting of recalled diet by comparing *current* diet and *recalled* diet measurements versus *original* and *recalled* diet measurements (Friedenreich et al., 1992).

There were 17 studies identified that had assessed either the validity or the reliability[18] of past diet recall by using the above approach, although only nine included a measure of current diet. The period of time elapsed between original dietary records and recall of original diet ranged from just one year to 44 years but the median time was approximately 11.5 years. Study findings were compared by examining the correlation coefficients between the original, recalled, and current diet measurements which provided an assessment of individuals' relative rankings on these measures.

The key findings from this review were that on average, across studies, the highest correlations for nutrients were between current and recalled measurements (0.64). Next were correlations for original and recalled diets (0.5) and the lowest were for original and current diets (0.45). The same pattern was also observed for the food group variables with the highest average correlations for recalled and current diets (0.50), then original and recalled diets (0.44), and lowest for original and current diets (0.34). Thus, current diet appeared to influence the reporting of recalled diet, dietary habits seemed to change over time, and recalled diet provided a more reliable estimate of past diet than did current diet. Friedenreich et al. (1992) pointed out, however, that findings based on correlations between reported measures of intake should be interpreted with caution. Correlations are a function of the amount of variance shared by two measures, and in this case, a measure of the correspondence between two reports of diet. When examining the accuracy of recalled diet, the original estimation of diet is taken as being without error but, in reality, the correlation between the

[18] Validity was measured if different instruments were used to measure original versus recalled diet. (Friedenreich et al., 1992)

original and recalled measures is influenced by errors in recall, and by random and systematic errors in the original diet measurement (Friedenreich et al.).

3.2.1.1 Factors influencing recall

In the studies reviewed by Friedenreich a number of factors were identified that influenced the validity of dietary recall. Not unexpectedly, as the time interval between the original and recalled reports increased, the correlations decreased between diet records at time-point A, and diet recall at time-point B. Studies with time intervals ranging from one to ten years had average correlations of .5 to .75 (Byers et al., 1987; Friedenreich, Howe, & Miller, 1991; McKeown-Eyssen, Yeung, & Bright-See, 1986; Willett et al., 1988), and those with recall periods ranging from 10-15 years had average correlations from .35 to .55 (Sobell, Block, Koslowe, Tobin, & Andres, 1989; Thompson, Metzner, Lamphiear, & Hawthorn, 1990; Wu, Whittemore, & Jung, 1988). In contrast, recall from 40 years previously yielded a low average correlation of .16 between dietary records and recalled diet, although this recall was still a better predictor of historical intake than was current diet .

Some evidence was found for more reliable recall when interview rather than self-administered methods were employed, but in a study formerly investigating this question Sobell et al. (1989) noted that although self-administered questionnaires were not as adequately completed and resulted in lower correlations, the self-administered questionnaire option should not be discarded because good questionnaire design and adequate participant instruction could overcome the apparent disadvantages of self-administration.

In Friedenreich et al.'s 1992 review, more detailed, semi-quantitative or fully quantitative measures (i.e. those that assess quantities or portion-size rather than simple frequencies) were claimed to increase the correlation between

original and recalled diets. But on close inspection, these studies also spanned the lesser recall periods, with the periods spanning greater than 15 years using the non-quantitative FFQs, so it is not possible to determine if the higher correlations were due in fact to the detailed dietary assessment procedure or simply that the recall periods were shorter in these studies.

Participant age and sex were not consistently associated with past diet recall validity or reliability across studies, although higher education was associated with better recall ability and less recall errors in two studies with participants from the Aventist Health Study population (Kuzma & Lindsted, 1988, 1990).

A number of dietary factors were also shown to be relevant to past diet recall. Both the stability of diet and the consumption frequency of items impacted on recall accuracy. Persson et al. (1990) found that over 4 years, those with stable diets had high levels of agreement between original and retrospective information. For 84% of these participants the retrospective information agreed with the original information (Persson et al.). Over longer time periods (15 years) (Thompson et al., 1990) and 24 years (Kuzma & Lindsted, 1988), reproducibility was also positively related to diet stability which was particularly evident in vegetarian populations (Kuzma & Lindsted, 1988, 1990), and may be due to the influence of current eating patterns on retrospective reporting (Thompson et al., 1990). Foods that were rarely or never eaten were also recalled with good reliability (Thompson, Lamphiear, Metzner, Hawthorne, & Oh, 1987).

In all the early reliability and validity studies of past diet recall current diet affected recall of past diet, and this influence was independent of the method of dietary measurement, the order of administration of the current and recall diet

questionnaires, and the population under investigation (Friedenreich et al., 1992). Such a finding necessitates that any investigation of associations between past dietary intake and health outcomes simultaneously takes into account the impact of current diet on recall. Despite confounding by current diet, past dietary recall nonetheless provides information on past diet intake that is not available by using current diet as a proxy for past diet. The stronger association between past diet records and recalled past diet compared to past diet records and current diet records was a robust finding across studies (Friedenreich et al.). Therefore, *"recall of food intake in the distant past may be a sufficiently valid estimate of past intake to justify its collection"* (Dwyer et al., 1989).

3.2.1.2 Error in dietary recall

A study by Wu et al.(1988) also found correlation coefficients that showed closer agreement between recalled past diet and original past diet intake than between current and original intakes. They extended their analysis by partitioning the variation in recalled and original intakes into components due to interpersonal variation in true intakes, errors in recall, and residual reporting error; that is,. random variation that occurs when a person reports diet (whether past or present) on several occasions. They found that interpersonal variation accounted for only 20 – 37% of the variance in dietary intakes, with most of the balance due to residual reporting error. For comparison, they examined recalled and original reports of body size where interpersonal variation accounted for 70 – 85% of the variance in recalled and original reports of body size. They concluded that there was an unacceptable amount of error inherent in measures of dietary reporting, whether of present or past intake, and stressed the need for alternate designs in epidemiological studies (Wu et al.).

3.3. Past Dietary Recall and the Cognitive Science Perspective

The difficulties in recalling complex dietary information led to a focus during the mid to late 1990s by nutritional epidemiologists on the cognitive issues related to dietary survey methodology, and the cognitive processes that underpinned dietary recall (Friedenreich, 1994; Wirfält, 1998). Cognitive psychology presented a theoretical framework for how questionnaires are answered by respondents (Jobe & Mingay, 1991; Tourangeau, Rips, & Rasinski, 2000) and as such provided tools to improve the design and administration of dietary assessment with the aim of reducing error and increasing the validity of recall (Friedenreich). Of particular relevance to the reporting of past diet was the work by Smith (1991) and Smith, Jobe, and Mingay (1991) which related to the formation and retrieval of dietary memories, and the theory of autobiographical memory structure as proposed by Conway (1996).

3.3.1 Dietary memory

People eat a large variety of foods with dramatically different frequencies and generally they do not pay much attention to what they are eating. Any question about dietary intake, whether in the recent or distant past, concerns the recall of seemingly trivial knowledge. According to Smith, Jobe and Mingay (1991), these features make dietary recall an interesting memory problem. Smith and his colleagues conducted an experiment that compared survey reports of dietary intake over a two or four-week period with diaries the participants had maintained over the reference period. Findings from these studies indicated that even when questions were asked about food consumption within the specific reference period, the participants seemed to be reporting what they *usually* ate; that is. dietary report during one week matched diary entries for a different week about as

closely as they matched the entries for the reference week. Thus, although the information provided was inaccurate relative to the intake recorded for a specific period, it still characterised what respondents *typically* ate (Smith, 1991; Smith et al.).

The implication of these findings is that dietary recall is based on generic knowledge of one's diet rather than the report of specific dietary experiences. Recall of dietary intake for extended periods appears to be a task that people carry out quite inefficiently. Generic memory is a particular type of autobiographical memory that captures common features of many individual similar events (Conway, 1996). Cognitive scientists have instantiated this process as being analogous to a script. Scripts are mental representations of common-place action sequences. Eating is one such script, but potentially there are countless others such as shopping, going to the movies, driving to work, reading a book. Although there is some disagreement amongst researchers regarding the mental structure of these scripts, there is a general consensus that much autobiographical knowledge consists of information about general patterns stored at a relatively abstract level, and that information about the overall patterns is much more readily retrieved than information about specific details of the script components (Tourangeau et al., 2000).

Appreciating that long-term dietary memory is dependent on a generic 'script' of eating behaviour has implications for the type of information that can be reasonably expected to be extracted using dietary questionnaires. In particular, detailed frequency assessments or portion-size judgements are unlikely to be accurate. The underlying problem with the recall of portion size information is that a single portion size for any given food item does not exist. People have difficulty

relating pre-defined portion-size information to their habitual diet, and standard serving sizes are not generally encoded in memory (Smith, 1991).The demonstration by Smith of the generic nature of dietary recall lead him to recommend that *"If dietary reports are based substantially on generic memory, perhaps generic memory is what epidemiologists **should** ask about."* (p.290) (emphasis in original).

3.4 More Recent Studies of Past Diet Reliability and Validity

Despite the methodologically relevant findings from cognitive psychology regarding dietary recall (Thompson et al., 2002), there has been a relative dearth of studies that have pursued the topic since Friedenreich's 1992 review of past diet measurement. In the 10 years from 1980 to 1992, 17 studies investigated the utility of past diet measurement. Over the last 20 years, four studies have assessed the validity (Ambrosini, van Roosbroeck et al., 2003; Chavarro et al., 2009; Dwyer & Coleman, 1997; Eysteinsdottir et al., 2010; Fraser et al., 1998), and three studies the reliability (Frazier, Wilett, & Colditz, 1995; Maruti et al., 2005; Wolk, Bergstrom, Hansson, & Nyren, 1997) of recall[19], with only two studies (Fraser et al., 1998; Shatenstein, Payette, Nadon, & Gray-Donald, 2003) attempting to apply long-term dietary recall principles to developing a new instrument. Nonetheless, with the exception of one study (Ambrosini, van Roosbroeck et al., 2003), these more recent investigations spanned recall periods of approximately 20 years or more and in two studies, the recall period extended 40 years or more and provide informative data regarding very long-term dietary recall.

[19] Ambrosini et al. (2003) use the term 'reliability' to describe their study design. They had 28 day dietary records from participants in 1991 and then, in 2001, asked the same participants to recall their diet from 10 years previously using a FFQ. Other studies have defined such a design as a validity study because the past diet recall was being compared with actual dietary records rather than comparing two instances of recall but without actual records as reference data.

3.4.1 Reliability studies

Reliability studies required participants to recall their diet from a particular period, and then to recall it again a few months or years afterwards. Correlations or measures of agreement between the two recall measures were calculated to determine if the recalled diet was reproducible. In the Nurses' Health Study (Frazier et al., 1995), participants aged 42-65 years were asked to recall their diet and alcohol consumption during adolescence using a 24-item High School FFQ with nine frequency responses. Eight years later, participants used the same FFQ to record their diet from the same period. The average correlation between the two measures of past diet was 0.57 (range 0.38-0.74), which was higher than for the correlation between the first recall of past diet and current diet indicating that recalled diet was not merely reproducing current diet.

A second study reproducing the design of the previous study and in the same cohort was carried out 10 years later, but with only 4 years between the dietary recalls of adolescent diet (Maruti et al., 2005). The Spearman correlation between foods was slightly higher, 0.6 (range 0.37-0.77), but the difference in this study was that mothers of the participants also used the same 24-item High School FFQ and were asked to recall their daughters' diets during adolescence as an extra reliability measure. The association between daughters' recall and their mothers' recall for foods was 0.30. Not unexpectedly, there was much more variability in the range of the correlations between mothers' and daughters' recall of individual foods (0.1-0.61) given mothers would not necessarily be fully aware of their daughter's diet during adolescence.

One other reproducibility study of adolescent diet also used family member recall to test reliability (Wolk et al., 1997). As part of another long-term diet

reproducibility study, the adolescent diet of participants aged 41-81 years was assessed by interview using a 45-item FFQ with 9 frequency responses. Siblings of these participants completed the same questionnaire but in a self-administered format that referred to their adolescent diet also. Agreement between participant and sibling recall of individual foods was calculated to assess the consistency of long-term recall of adolescent diet from members of the same family. Correlations between participant and sibling recall of their respective diet in adolescence were generally ≤ 0.2 and for categorical variables agreement was 40%. Although siblings may share the same dietary environment they will not necessarily have the same food preference or intake, so weaker associations would be likely.

3.4.2 Validity studies

These studies had a recall period ranging from 18 to 48 years. All studies assessed correlation coefficients between original report and recall of individual foods with only one study reporting nutrient correlations (Chavarro et al., 2009). Current diet was only assessed in one study (Dwyer & Coleman, 1997), so the impact on past diet recall of the probable bias from current diet was not able to be quantified. The strength of the correlations between the two time-points varied considerably between foods across all studies, with some items yielding medium to high associations between original records and recall of the item(s) but others demonstrating little or no relationship or, in some cases, a negative relationship. Overall, three of these long-term validity studies reported a median correlation of 0.3 (Chavarro et al., 2009; Eysteinsdottir et al., 2010; Fraser et al., 1998).

Dwyer and Colman (1997) also measured the mean differences between past records and later recall to determine accuracy of recall rather than relative levels of association as reflected by the correlation coefficient. In this study some

foods were shown to have the same correlation co-efficient but quite discrepant levels of recall accuracy. The authors did, however, made the point that even if recall was not entirely accurate, it may be still useful in predicting a health outcome if the goal of a study is to show that groups with a relatively lower or higher previous intake are more like to develop a particular disease. Dwyer and Coleman's study was also the only one that had prior dietary records from three life periods; childhood, at 18 years and at 30 years, and current intake was assessed at age 55. As in previous studies, recalled past diet was shown to represent actual past dietary intake better than did current diet, and the comparison between past and current dietary records demonstrated dietary intake changed considerably over the life period. Of particular interest was the finding that although there was some evidence that median correlations for all foods decreased, there was not a consistent decline over time for individual foods; some food intake from earlier life had the same strength of association with recalled consumption as did foods from later periods (Dwyer & Coleman).

3.5 Past Diet Assessment: Summary and Implementation

Over the last 30 years the utility of past dietary recall has been investigated entirely within the context of reliability and validity studies. Results have demonstrated that for periods up to approximately 10 years the correlations between recall of past diet and past dietary records were between .5 and .75, which were similar in magnitude to the constitution of acceptable validity in current diet validity studies (Willett, 1998). Although associations between recall and past records were generally weaker beyond this period, it is important to incorporate the understandings of dietary memory imparted by cognitive psychology into the evaluation of dietary recall accuracy. Dietary memory draws

on generic 'scripts' for usual food consumption over particular periods of time rather than drawing on specific instances of eating that can then be recalled. The consequence of this is that even current diet recall is likely to be highly inaccurate in terms of absolute intake as demonstrated by Smith et al. (1991). Indeed, a validation study of a widely used Australian FFQ against four 7-day dietary records demonstrated that at the individual level there was poor agreement between the FFQ and dietary records when estimating absolute intakes, and the FFQ over- or under-estimated the dietary records by at least 50% (Ambrosini, Mackerras, de Klerk, & Musk, 2003).

It is evident from the investigations of past diet validity that current diet does not provide a reasonable estimate of past diet; there is some individual variability in past dietary intake that, although associated with current diet, is separate from it. Therefore, in terms of the impact diet from early life-periods may have on the aetiology of chronic disease, the incorporation of individuals' recall of past diet may provide worthwhile information.

One pilot study was located that had the clear aim of developing a long-term dietary recall FFQ in order to provide an instrument that could assess peoples' lifelong intake of functional foods that may be relevant to health and ageing outcomes (Shatenstein et al., 2003). Participants were a small sub-sample (n=51) of community-dwelling elderly people aged 70-86 years taking part in a larger semi-quantitative FFQ validation study. The past diet FFQ consisted of 33 food items and was either self-administered, interviewer administered, or telephone administered. Memory cues consisting of questions regarding personal circumstances and food preparation were used in the past diet pilot study prior to asking participants to recall their diets from ages 65, 45, 25, and 10 years. Such an

approach accords with the hypothesised underlying structure of autobiographical memory where lower level general memories can be primed by cues from personal histories (Conway, 1992). No attempt was made to quantify intake precisely; rather, three categories were used to describe consumption frequency: daily, regularly (defined as several times per month), and occasionally (either a few times per year, or never).

Participants were ranked on consumption of foods of interest and self-assessment of response quality was included as an internal reliability check. The study found that women consumed more functional foods at each of the target ages (70+, 65, 45, 25 and 10 years) than did men but that these means decreased for both sexes almost linearly with time; possibly as function of both recall ability and the increased availability of many foods in more recent times. Nonetheless, the study was sensitive to the probable difference between childhood and adult diet in that cruciferous vegetables were reported as being frequently eaten at 65 and 45 years compared to apples as being more frequent at 25 and 10 years. For functional foods eaten daily, fruit and vegetables were ranked first for all ages except 10 years when milk was in first place. The reliability of the past diet FFQ was tested in a sample of 20 people and in this small group showed good reproducibility with 73% of the participants' responses on all life-periods combined identical over the two occasions of testing. The mean reliability decreased by 10% from present age to age 10 years. Shatenstein et al. (2003) concluded that although the validity of reported past intake could not be verified, participants' responses showed an internal consistency and logical coherence from a temporal perspective, in particular that reports of diet consumed at the age of 10 were clearly indicative of a child's diet.

Shatenstein et al.'s (2003) pilot study of dietary recall from childhood to older-age in a community-dwelling sample has been described in some detail because it offers an approach to developing an instrument that assesses dietary intake from multiple life periods to enable the investigation of lifetime dietary impact on later-life cognitive health and functioning.

The LDQ is a non-quantitative FFQ that follows a similar approach to that of Shatenstein et al. (2003) and has been developed in the context of this thesis. In the following section, the reliability and validity of this measure will be tested.

SECTION B: RELIABILITY AND VALIDITY OF THE LIFETIME DIET QUESTIONNAIRE

Overview

Section B presents three studies. Studies one and two utilize inter-rater and test-retest designs respectively to test the reliability of dietary recall as assessed by the LDQ; study three tests the questionnaire's validity.

The inter-rater reliability study is an unpublished pilot study; the test-retest study and the validity study have been published respectively (Hosking & Danthiir, 2013; Hosking et al., 2011).

There is some duplication of material within this section, and in relation to the literature review, due to the inclusion of studies in their published format. Each published study is a 'stand alone' document so therefore includes the necessary information for interpretation and evaluation of the research within the context of a journal publication. The unpublished pilot study logically and temporally preceded the publications, so in this study in particular, information regarding the content of the LDQ is duplicated elsewhere.

The LDQ is designed to be used in older populations to provide a long-term dietary assessment instrument for the recall of dietary intake over a number of life-periods. The questionnaire is a new FFQ both in terms of the particular foods listed, and the frequency options given for recall. Before testing the reliability of the measure in the target older-age population, Study 1 (Chapter 4) tested the recall consistency for the foods and frequencies of the LDQ in a younger cohort. Participants' dietary intake was verified by their family members with both

participants and their family members using the LDQ to recall participants' diet. The precedence for such a design in past dietary reliability studies was demonstrated by Wolk et al. (1997) and Maruti et al. (2005) as described in Chapter 3 and tests the inter-rater reliability of the measure.

Study 2 (Chapter 5) evaluates the reproducibility of dietary recall across multiple life-periods in an older population by using a test-retest design. A similar approach was used by Cumming and Klineberg (1994) when they assessed the reproducibility of long-term recall over periods up to 82 years for a number of physical and lifestyle variables, including dietary intake of alcohol, coffee, tea, milk, cheese, and fruit.

The validity of past dietary recall as assessed by the LDQ was investigated in Chapter 6. As described in Chapter 3, the majority of studies assessing the validity of past dietary recall have done so by evaluating the relationship between records of dietary intake at a particular time-point, and recall of that intake using some form of FFQ at a later period. Unfortunately, no dietary records were available from the past to evaluate the validity of dietary memory as captured by the LDQ; therefore, the following approach was taken. Exploratory Factor Analysis (EFA) was applied to the frequency responses of the LDQ to extract dietary patterns from each life-period. Dietary patterns are increasingly used in nutritional epidemiology to investigate associations between dietary intake and both exposure and outcome variables (Mullie, Clarys, Hulens, & Vansant, 2010; Schwenke, 2010). If long-term dietary recall using the LDQ was valid, then some associations could be expected between participants' lifetime dietary patterns and the relevant demographic and health variables theoretically related to dietary patterns by prior research.

Chapter 4 Past Diet Recall Consistency

4.1 The Family Member Study (Study 1)

The objective of this study was to test the strength of associations between young adults' recall of earlier diet when they were 10 to 15 years, using the foods and their frequency options from the LDQ, and a family member's recall of the same individual's diet over the same period. This inter-rater approach to reliability evaluates the degree of consensus between two or more people in their assessment of a subjective behaviour (VandenBos, 2007), in this case past dietary intake.

4.1.1 Method

4.1.1.2 Participants and procedure

A sample of convenience was recruited from two sources: a register of interested staff members from CSIRO Animal Food and Health Sciences, and the undergraduate psychology course at the University of Adelaide. Students received course credit for participating. This cohort then recruited available family members to participate in the study. It is acknowledged that this sample, due to the process of recuitment, was of limited demographic variability.

Participants were asked to recall their diet from the time when they were 10-15 years old by using the food list and consumption frequencies of the LDQ. Participants' family members who had lived with the participant during this time also used the questionnaire to recall the participant's diet for the same period. Ethics approval for the study was granted by the University of Adelaide's Human Ethics Committee and all participants signed a consent form acknowledging their

agreement to take part in the study. Descriptive statistics for the whole sample are presented in Table 4.1

LDQ packs were distributed to participants for self-administration. These packs contained a copy of the questionnaire for the participant and up to three extra questionnaires for potential family members. Each participant could enrol any number of family members, with the proviso being that family members had to have co-habited with the participant during the time of recall. Information sheets about the purpose of the study were included, as were detailed instructions about completing the questionnaires. Particular emphasis was placed on the need for all parties to complete the questionnaires independently and without consultation with other family members. Cue questions regarding life circumstances, interests and occupations were included to help the participant and their family members recall the period when the participant was 10 to 15 years of age. Participants were assured that their responses to these questions were confidential and not part of the study; the questions were included only as memory prompts. The single life period from the LDQ used in the study together with the information sheet and consent form distributed to participants can be seen in Appendix A.

Table 4.1: Total sample of primary participants and their family members

Family-member group	mean age (SD) in	age range in yrs
primary participants n=203	19.6 (5.9)	15-59
female (n=160)		
male (n=40)		
sex not stated (n=3)		
mothers n=157	49.6 (5.8)	39-85
fathers n=54	53.4 (8.1)	41-85
brothers n=39	18.9 (3.2)	15-28
sisters n=32	18.4 (5.0)	15-31
Total sample N = 485		

4.1.1.3 Materials

The LDQ was designed to be self-administered to enable time and cost-efficient sampling. The full version of the LDQ consisted of four to five life-periods from childhood to older-age, but, for this preliminary reliability study in a younger age-group, only the childhood period was assessed.

The food groups in the LDQ were based on the core food groups from the Dietary Guidelines for Australian Adults (2003) and also included other relevant groupings such as beverages. The food groupings were vegetables, fruits, dairy products, cereals, takeaway food, protein-based food, seafood, sweets, snack-food, fats and oils, tea, coffee and alcohol[20]. Foods were listed under these food group headings as either single items, such as 'cow's milk' or 'eggs', or as composite items made up of similar foods; for example, the composite of 'oranges, lemons, grapefruit' was 'citrus fruit'. In total for the childhood period 74 foods were included in the questionnaire. The consumption frequency options given for various foods were 'daily', '2 to 3 times a week', '2 to 3 times a month' and 'rarely/never'.

4.1.1.4 Data screening

Data were screened for missing responses or multiple responses on the food frequency questions. In total 1.6% of the data were missing. Those 11 participants who did not include a family member questionnaire, or whose family member code was missing, were excluded from the analysis. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows graduate package (17.0.1.), and the Expectation Maximization (EM) procedure (Dempster, Laird, & Rubin, 1977) was used to estimate values for missing

[20] The rationale for the choice foods in the LDQ is elaborated upon in Chapter 5.

responses. The Chi Square statistic for each of the estimated data sets was not significant, suggesting the data were missing at random and that the EM procedure would not lead to systematic bias in subsequent analyses (Schafer & Graham, 2002).

4.1.2 Results

Polychoric correlations were calculated using the SPSS 17.0.1 HETCOR extension to assess the strength of the relationships between participants' diet recollections and their family members' recollection of that same diet. Polychoric correlations are appropriate when variables are ordinal or categorical but can be assumed to reflect an underlying continuous variable (Garson, 2008). Consumption frequency in this questionnaire was separated into four discrete categories; in reality, however, consumption of any food can be assumed to be a continual graduation from 'never eating it' to 'eating it very often'. Polychoric correlations capture this latent quality of consumption frequency and overcome the problem of attenuation that can occur when non-continuous dietary data are dealt with as being categorical (Uebersax, 2006).

The mean polychoric correlation coefficients between later childhood diet recalled by participants and their family members' recollection of that same diet are presented in Table 4.2, together with the 95% confidence intervals for these correlations[21].

[21] Significance levels for polychoric correlations are not calculated by the HETCOR program. The confidence interval for a correlation is normally calculated by standardizing the correlation to a Fisher's Z score then applying the formula; Z + or - [1/($\sqrt{n-3}$)*1.96; Z is then converted back to Pearson's r. Although Fisher's Z distribution is appropriate to standardize a Pearson's correlation, the distribution of the polychoric correlation is not necessarily the same as that of Pearson's r, therefore the null hypothesis (that the significance of the average polychoric correlations was 0) was tested via a permutation test implemented in the R program (Version 2.9.1 2009 The R Foundation for Statistical Computing) that randomly re-sampled the actual data 400 times. (Good, 2005). All family member correlations were significant at p <.001

To ensure the associations found between participant dietary recall and that of family members were not due to the possible homogeneity of dietary intake across the whole sample, participants were randomly paired with other participants' family members. This correlation coefficient of 0.33 demonstrated the weaker association between the diets of participants and non-family members' recall of random participant diets.

Table 4.2: Mean family member polychoric correlations

family relationship	correlation	95% CI
participant/mother n= 157	0.76	0.70, 0.81
participant/father n=51*	0.72	0.56, 0.83
participant/sibling n= 67*	0.76	0.63, 0.84
participant/non-family n=203	0.33	0.21, 0.44

*Three participant/father and four participant/sibling pairings were excluded from the analyses due to extreme violation of normality in their frequency distributions

The significance of differences between participants and family members' correlations compared to participants and random other family members was calculated by dividing the difference between the two correlation coefficients (converted to z-scores) by the standard error of the difference between them. If the z-score value for the difference was ≥ 1.96, the difference in the correlations was significant at the 0.05 level; if the difference was ≥ 2.58, it was significant at the 0.01 level, and if it was ≥ 3.95 it was significant at the 0.001 level.

participant/**mother** recall compared to participant/random recall: z-score = 5.98

participant/**father** recall compared to participant/random recall : z-score = 3.57

participant/**sibling** recall compared to participant/random recall : z-score = 4.71

The differences between participant and mother or sibling recall compared to participant and random family member were highly significant at $p < 0.001$ whereas the significance level was $p < .01$ for the differences between participant and father recall compared to participant and random family-member correlations.

Associations between the different family members' recall of individual food items were also examined. Those foods that were particularly strongly or weakly correlated are listed in Table 4.3 grouped by their corresponding family member pairing.

Table 4.3: Recall of specific foods by participants' family members

correlation < 0.3	correlation > 0.8	
participant & father	participant & father	participant & sibling
canola 0.21	chicken 0.92	vegemite 0.8
carrots 0.12	herb tea 0.91	spinach 0.8
melons 0.28	green tea 0.93	lentils 0.8
figs 0.20		black tea 0.83
		black coffee 0.86
lollies 0.28		
chocolate 0.02		
cakes 0.28		
soft drink 0.29		
brown rice 0.18		

4.1.3 Discussion

The LDQ demonstrated good inter-rater reliability. Moderately strong correlations were found between participants' recall of early adolescent diet and their family members' recollection of that same diet using the foods and frequency options of this questionnaire. Particularly high correlations were apparent between participants and both their siblings and fathers for tea, coffee and herbal tea consumption. These findings support those of Maruti et al.(2005). These authors found that beverages (iced tea and orange juice) had the highest correlations with family members' (in this case mothers') reports of adolescent diet. Generally, however, the two previous studies that used family members to verify adolescent diet found lower average correlations between participants' dietary recall than in the current study; .30 in the case of Maruti et al. (2005) and .29 in Wolk et al. (1997). For both these studies, however, the period of recall for participants was 25 and 50 years ago, respectively, compared to approximately a period spanning five to ten years in the current study, and it is known that more distant dietary memories are associated with lower correlations between dietary measures (Friedenreich et al., 1992).

The strength of the correlations found in the current study may be explained not only by the relatively short time elapsed since the target period of recall, but also by the non-quantitative design of the LDQ. Defining consumption by relatively few frequency options may be accessing generic, less detailed memories of intake that are likely to give more reliable results (Smith, 1993).

Given the non-quantitative nature of the questionnaire, and the limited demographic variability of the sample (university students of similar age range, and educational background) it is possible that dietary intake amongst participants

would be homogeneous. However, the significant differences found between participant and family member dietary recall compared to participant and non-family member dietary recall directly refutes this possibility, thereby demonstrating sensitivity to differing patterns of consumption as assessed by the food lists and frequency options of the LDQ.

Despite the strength of association found between participants' self-reported diet and the reports of their family members, it is not possible to gauge the validity of these dietary memories in terms of the actual period being recalled. Given the young age of the sample population, reported early adolescent diet may be equivalent to current diet, and it may be current diet that was being reported.

The relative correlations between dietary recall of participants and their different family members (mothers, fathers or siblings) are also of interest. Fair-to-good associations between participants dietary recall and that of their mothers was suggested given that there were no particularly low (< 0.3) food item correlations between these two groups. In contrast, although the overall correlation between participants and their fathers' recall was not significantly different compared to participants and mothers or participants and siblings, there was a greater proportion of low individual food item correlations (< 0.3) between participants and their fathers. In particular, participant and father correlations for what could be labeled 'treat food' or 'unhealthy food' were low.

If it is assumed in this population that mothers and fathers had traditional roles, then it could be expected that mothers would be more consistent in their recall accuracy of their child's diet than fathers, who would have been out of the home for longer periods and perhaps not be as aware of what their child was eating at times other than the main meal, such as after school when more snack

foods may have been consumed. Thus, although the primary purpose of testing the association between participant dietary recall and family member dietary recall using the LDQ was to test the reliability of the measure, the differential correlations between mothers' and fathers' reports of their children's diet also suggest some validity for dietary recall using the LDQ.

The recall period for foods and their consumption frequencies as assessed by the LDQ in this preliminary study equated to dietary memories from, on average, five to ten years in the past. It is encouraging that the correlations assessing the verification of individuals' dietary intake by their family members using the LDQ were also in the range of other studies assessing the reliability of past recall across a similar span of time (Friedenreich et al., 1992).

4.2 Preamble to Publication 1

There is general consensus that past dietary memory reliability measures will approximate the reliability of current diet up to 10 years in the past (Ambrosini, Mackerras et al., 2003; Willett, 1998), but over longer periods, recall may not be as reliable (Willett, 1998). The next study assesses the reliability of very long term dietary recall in the questionnaire's target population; older adults over 65 years. This is a reproducibility study utilizing the full version of the LDQ that encompasses up to five life-periods. The study is the first of the publications to be included in the thesis, and is presented as it was published with an abstract and an introduction that summarizes the rationale for assessing lifetime diet in the context of its plausible associations with later-life cognitive outcomes. Obviously, some of the material covered by this publication has been (or will be) duplicated elsewhere in the thesis, but, as previously mentioned in the section introduction, this is unavoidable when previously published works constitute some of the thesis content.

Chapter 5 Test-retest Reliability of Lifetime Diet Recall

"Assessing lifetime diet: Reproducibility of a self-administered non-quantitative FFQ"
(Hosking et al., 2011)

5.1 Abstract [Publication 1]

Objective: To demonstrate test-retest reliability (reproducibility) for a new self-administered lifetime diet questionnaire, with a focus on foods relevant to older age cognitive health.

Design: The reproducibility of dietary recall over 4-5 life periods was assessed by administering the questionnaire at 2 time points to an older cohort. The period between questionnaire administrations was 7 weeks. Polychoric correlations measured the association between recall at time 1 and time 2 and the weighted kappa statistic measured the level of recall agreement for food groups across the two administrations of the questionnaire.

Setting: Adelaide, South Australia.

Subjects: Fifty two cognitively healthy, older-age, community dwelling adults completed the LDQ; M = 81.8 (SD 4.4) years, range = 70 – 90 years

Results: The questionnaire showed very good reproducibility in this sample with a mean polychoric correlation co-efficient of 0.81 between administration at time 1 and time 2, and an average weighted kappa of 0.49 for the level of recall agreement between food groups.

Conclusions: The demonstrated reliability of this lifetime diet questionnaire makes it a useful tool to assess potential relationships between long term dietary intake and later age cognitive outcomes.

5.2 Lifetime diet assessment: Rationale

Possible relationships between diet and cognitive status in elderly people have been the focus of considerable study, with the aim of ameliorating the burden of dementia and decline within the ageing population. Although results are inconsistent between studies, there is a growing body of epidemiological evidence suggesting dietary factors contribute to cognitive health in old age via nutrient influence on brain metabolism (Calon & Cole, 2007; Fernandes, Mori, Ekuni, Oliveira, & Milani, 2008; Gillette-Guyonnet et al., 2007; Joseph et al., 1999; Morris et al., 2002), and indirectly via the dietary contribution to midlife vascular risk factors linked to later cognitive decline (Breteler, Claus, Grobbee, & Hofman, 1994; Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Knopman et al., 2001; Luchsinger, Tang, Shea, & Mayeux, 2002; Nash & Howard., 2006; Whitmer et al., 2005).

An important caveat, however, to the effectiveness of diet as a potential modifier of cognitive health, is the interaction between dietary intake and genetically determined responses to that intake. For instance, in a number of studies, significant associations between dietary intake and cognition have been found only in either the presence or absence of the ApoE-4 allele (Dai, Borenstein, Wu, Jackson, & Larson, 2006; Hu et al., 2006; Luchsinger et al., 2002; Whalley et al., 2008). In addition, genetic responses may also change with age, so there are times when an individual may be particularly susceptible to either damage or protection from dietary intake (Whalley et al., 2006).

The complex interactions across the lifespan between genetic and environmental factors suggests the importance of a life-course approach to cognitive ageing, yet most longitudinal studies of nutrition and cognition in the

elderly focus on relationships between cognitive performance and dietary intake after age 65, when many of these interactions that determine cognitive status have already occurred (Whalley et al., 2006). It follows that examining possible relationships between older age cognition and intake of cognitively relevant foods across the lifetime is a worthwhile, yet previously neglected, endeavour when attempting to elucidate the role of diet in cognitive maintenance and decline. Cohort studies over so many decades are not generally feasible and therefore the best option for gathering data from the distant past is usually by participants' recall (Cumming & Klineberg, 1994).

Long term dietary recall appears to rely largely on people's generic knowledge of their diet; individual episodes of eating particular foods are quickly lost from memory but often repeated instances of eating are superimposed upon one another so although details are lost, a general pattern or 'script' remains (Wirfält, 1998). In a series of experiments designed to explore the cognitive processes underlying dietary recall, Smith, Jobe and Mingay (1991) concluded that generic knowledge about one's habitual diet contributed significantly to reports of intake and that respondents could respond credibly about their average consumption frequencies, although precise estimates of dietary intakes for extended periods of time were unlikely to be accurate. This finding was supported by Fraser et al. (1998), who found better recall validity when non-quantitative methods of assessment were used (Fraser et al.).

Recall accuracy of long term diet has been shown as being improved by the inclusion of memory cues to 'locate' participants in the appropriate period. Episodic memories, memories of life experiences peculiarly relevant to the self, may serve as prompts to generic memories encoded during a particular time

(Conway, 1992). Therefore a number of questionnaires designed to assess dietary memory from the distant past have included autobiographical questions such as 'Where were you living?', 'What job did you have?', and 'Were you married? (Cumming & Klineberg, 1994; Fraser et al., 1998; Shatenstein et al., 2003). Lifetime diet assessment would appear then to be a plausible undertaking if informed by the cognitive processes underpinning long-term dietary recall.

The aim of the present study was to assess the reproducibility of a new, non-quantitative food frequency questionnaire designed to access long term dietary memory, with the focus on cognitively relevant foods. Demonstrating reproducibility is an important first step in validating a new dietary measure. Although high correlations or levels of agreement between the two time points do not imply validity, reliability is a necessary condition for validity and low reproducibility indicates that the questionnaire has little utility (Willett, 1998).

Very few studies have addressed the reproducibility of remote dietary recall. Cumming and Klineberg (1994) assessed the reproducibility of lifetime recall for a small number of foods in a sample of older people, aged between 65 and 100 years, with interviews one to three months apart; items assessed were beverages (including tea, coffee, alcohol and milk), cheese, and stewed fruit. Spearman rank-order correlations ranged from 0.47 for coffee consumed at 50 years, to 0.81 for tea consumed at age 20 years (Cumming & Klineberg). Hislop, Lamb, and Ng (1990) administered a past diet questionnaire to women, aged between 40 and 70 years, referring to four different age periods; childhood, teens, younger adulthood and older adulthood (over 40yrs). The questionnaire was administered at two time points four to six years apart. Overall, it was found that the weighted kappa statistics for individual food items were consistently in the

moderate range across all life periods. Interestingly, the food frequency questionnaire was found to be more reliable for specific food items from the distant past than the recent past (Hislop et al.). Finally, in a study that assessed the reproducibility of recalled adolescent diet from15 to 35 years in the past, the Spearman rank correlations for food groups ranged from 0.48 for breads/cereals/grains to 0.70 for beverages (Maruti et al., 2005). Unfortunately, results from these studies are not comparable given the disparity between their designs; however they all suggest the reproducibility of long-term dietary memories.

5.3 The Lifetime Diet Questionnaire

For the current study, a Lifetime Diet Questionnaire was developed as a self-administered instrument to enable time and cost-efficient sampling of large groups of participants. This questionnaire aimed to assess the intake of potentially cognitively relevant foods and beverages from childhood to older age, in older adults. The life period was divided into the following; childhood: 5 to18 years; early-adulthood: 19 to 30 years; adulthood: 31 to 45 years; middle-age: 46 to 60 years, and older-age: 61 to 75 years. At the beginning of each life-period section, autobiographical cue questions were included to help participants locate themselves in the appropriate period. The rationale for using these particular life periods was to capture the general (albeit not universally experienced) changing life circumstances that help delineate periods of time in people's memories.

Food groups rather than meals were used as the organising structure of the questionnaire. Although some studies have shown meal ordered rather than food-group ordered instruments are more accurate and reliable, eating customs have changed during the seventy years covered by this questionnaire (Fjellström, 2004)

so participants could find meal-based questions problematic. In addition, it has been shown that socio-demographic and lifestyle factors affect food choices throughout adulthood (Mishra, McNaughton, Bramwell, & Wadsworth, 2006), therefore, the food options given to assess lifetime diet needed to be general enough to capture these potentially different dietary patterns. The food groups used were based on the core food groups from the Dietary Guidelines for Australian Adults (2003), and included other relevant groupings such as beverages. The food-items were organised under the following broad food group headings: vegetables, fruits, dairy products, cereals, takeaway food, protein-based food, seafood, sweets, snack-food, fats and oils, tea, coffee, alcohol, and multivitamin supplements. Foods were listed under these headings as either items containing a single food, such as 'cow's milk' or 'eggs', or as items comprising a list of similar foods; for example, 'oranges, lemons, grapefruit' and 'lentils, dried peas/beans'. The food groups and their items were the same for each life period, with exceptions being food items that were unlikely to have been consumed during a particular life period; specifically, alcohol-related questions in childhood and lard for the later life periods. In total, 74 to 79 questionnaire items were included for each life period. Within each food group, specific foods were selected that had either been explicitly associated with cognitive health in the literature, such as cruciferous vegetables (Morris, Evans, Tangney, Bienias, & Wilson, 2006), berries (Galli, Bielinski, Szprengiel, Shukitt-Hale, & Joseph, 2006), and fish (Kalmijn, Feskins, Launer, & Kromhourt, 1997), or were considered deleterious, such as sweets and high-calorie foods (Gillette-Guyonnet & Vellas, 2008; Luchsinger et al., 2002). In addition, lists of fruit and vegetables high in antioxidants were consulted (Pellegrini et al., 2003; Szeto, Tomlinson, & Benzie, 2007) to guide foods included.

The consumption frequency options given for the foods were 'daily', '2 to 3 times a week', '2 to 3 times a month', and 'rarely/never'. It is important to emphasise that the LDQ was not intended as an instrument to comprehensively record long term dietary intake, but rather to differentiate between people on their general frequency of intake of foods that could potentially influence older-age cognitive status.

5.4 Method

5.4.1 Participants

Participants were recruited from the Ageing and Cognitive Change Study at the School of Psychology, University of Adelaide, South Australia.(Gregory et al., 2008). This was a 6-year study of cognitive ageing in older community-dwelling South Australians, screened for dementia at baseline; relevant ethical approval was gained for the current study from the University of Adelaide human ethics committee. Of the seventy-four people who agreed to participate, fifty-two completed the questionnaire at both time points, M = 81.8 (SD 4.4) years; range = 70.3 - 90.4 years. One person was excluded from the analyses because their second questionnaire was completed a month after all other questionnaires were returned. An acceptable level of association in a reproducibility study, as an indicator of reliability, is a correlation of 0.7 (Nunnally & Bernstein, 1994).With 51 participants, the power of the study to achieve a significance level of 0.01 was > 0.99 (Cohen, 1988).

5.4.2 Procedure

The LDQ, an information sheet, and completion instructions were posted to participants. They were requested to complete the questionnaire for each life

period in chronological order, one day at a time over five days to minimize memories from one life period intruding into another period. In addition, given that each life period covered up to15 years, participants were asked to recall their most representative diet and to report average consumption of seasonal foods. All participants completed the first four life periods; 'childhood', 'early-adulthood', 'adulthood, and 'middle-age'. The fifth life period, 'older-age' only applied to participants who were aged 80 years or over.

Five weeks after the completion date of their original questionnaire, each continuing participant was sent a repeat questionnaire with reminder information and instructions. The mean time between completion of the first and second administration of the questionnaire was approximately seven weeks; M = 50.4 (SD = 9.5) days.

5.5 Results

5.5.1 Missing data

Missing data in the LDQ were of two types; item non-response, and multiple consumption frequencies reported for a food item. Analyses were performed with SPSS for Windows (SPSS for Windows, Rel. 17.0.1. 2008 Chicago. SPSS Inc.). The Expectation Maximization (EM) procedure (Dempster et al., 1977) was used to estimate values for missing responses but convergence would not occur for Childhood on the first questionnaire or Adulthood on the second questionnaire. Due to the non-responses and the 'rarely/never' responses being matched at greater than chance rate across both administrations of the questionnaire, it was considered appropriate to recode non-responses as being equivalent to a food being eaten rarely/never and those missing data remaining (due to multiple responses to an item) were successfully estimated with the EM procedure. The Chi

Square statistic for each of the estimated data sets was not significant, suggesting the data were missing at random and that therefore the EM procedure would not lead to systematic bias in subsequent analyses (Schafer & Graham, 2002).

5.5.2 Analyses

Polychoric correlations were used to assess the strength of the relationships between participants' recall of their diet across the two administrations of the LDQ (SPSS 17.0.1 HETCOR extension). Polychoric correlations are appropriate when variables are ordinal or categorical but can be assumed to reflect an underlying continuous variable (Garson, 2008). Consumption frequency in this questionnaire was separated into discrete categories such as 'daily' or '2 to 3 times a week'; in reality, however, consumption of any food can be assumed to be a continual graduation from never eating it to eating it very often. Polychoric correlations capture this latent quality of consumption frequency and overcome the problem of attenuation that can occur when non-continuous dietary data are dealt with as being categorical (Uebersax, 2006) .

The average correlation between consumption frequencies of individual food items at each time point was calculated by person, and within life period. Table 5.1 shows the average correlations between individuals' recall of their total diet together with the 95% confidence intervals and the p-value as calculated by a permutation test for each life period. [22]

[22] Significance levels for polychoric correlations are not calculated by the HETCOR program. The confidence interval for a correlation is normally calculated by standardizing the correlation to a Fisher's Z score then applying the formula;

Z + or - [1/($\sqrt{n-3}$)*1.96; Z is then converted back to Pearson's r. Although Fisher's Z distribution is appropriate to standardize a Pearson's correlation, the distribution of the polychoric correlation is not necessarily the same as that of Pearson's r, therefore the null hypothesis (that the significance of the average polychoric correlations was 0) was

The test re-test correlations for each life-period are in the range considered good for a survey instrument and compare favourably to other reproducibility studies for dietary assessment questionnaires (Willett, 1998). It could be argued however, that the high correlations between the two administrations of the questionnaire were due to the same (or very similar), diet being recalled across

Table 5.1: Mean polychoric correlations between two administrations of the LDQ

Life period and # food items in questionnaire	Correlation between time 1 & time 2	95% CI
Childhood: n=74	0.86***	0.79, 0.91
Early-adulthood: n =79	0.81***	0.73, 0.88
Adulthood: n = 78	0.82***	0.72, 0.88
Middle-age: n = 78	0.79***	0.68, 0.86
Older-age: n = 78	0.80***	0.70, 0.87

*** $p < 0.001$ (as calculated by permutation test)

all life periods and at both administration time points; for example, if participants were simply recording their current diet for each period. Therefore, to examine whether the LDQ captured possible (and likely) change in dietary intake during the lifetime, paired samples t-tests compared the mean correlations between the first and second administration of the questionnaire (childhood, early-adulthood and adult periods only) to the mean correlations between each of these life periods and recall of middle-age diet at both time points; if the same diet was being recalled for all questionnaires, then it could be expected that there would be no significant difference between these mean correlations. However, if the LDQ was sensitive to

tested via a permutation test implemented in the R program (Version 2.9.1 2009 The R Foundation for Statistical Computing) that randomly re-sampled the actual data 400 times. (Good, 2005)

recalled dietary changes, then a significantly higher correlation could be expected for the same life period (at both administration time points) compared to the correlation for a particular earlier life period with the middle-age life period[23]. These correlation pairs and their differences are presented in Table 5.2.

Table 5.2: Mean differences in correlations for early-life diet recall at two time points compared to early-life diet recall and middle-age diet recall at two time points

	Correlation pairs	Correlation values	Difference in means (SD)	t value (DF)†	95% CI
Pair 1	CHD (T1/T2) and CHD (T1)/MAGE (T1)	0.86*** 0.58***	0.27 (0.18) ***	10.33 (48)	0.22, 0.32
Pair 2	EAD (T1/T2) and EAD (T1)/MAGE (T1)	0.83*** 0.71***	0.11 (0.16) ***	4.72 (47)	0.06, 0.16
Pair 3	AD (T1/T2) and AD (T1)/MAGE (T1)	0.82*** 0.81***	0.01 (0.14)	0.96 (47)	-0.03, 0.05
Pair 4	CHD (T1/T2) and CHD (T2)/MAGE (T2)	0.86*** 0.61***	0.24 (0.17)***	9.81 (48)	0.19, 0.29
Pair 5	EAD (T1/T2) and EAD (T2)/MAGE (T2)	0.83*** 0.73***	0.09 (0.16) ***	4.0 (47)	0.04, 0.14
Pair 6	AD (T1/T2) and AD (T2)/MAGE (T2)	0.82*** 0.81***	0.004 (0.11)	0.25 (48)	-0.02,0.03

CHD: childhood; EAD: early-adulthood; AD: adulthood; MAGE: middle-age;
T1, Time 1 administration T2, Time 2 administration
†One outlier was removed from each of the EAD (T1/T2) and AD (T1)/MAGE(T1) variables to improve normality; skewness and kurtosis values for all variables fell between -2/+2.
*** P ≤ 0.001

The mean correlations for dietary recall at time 1 and time 2 for childhood and early-adulthood were significantly higher than the mean correlations between these early periods and middle-age. There were no significant differences, however, in mean correlations between the two recalls of adult diet, and the mean

[23] The middle-age rather than the older-age life period was chosen for comparison because only 33 out of the 51 participants were over 80 years and eligible to complete the Older-age questionnaire

correlations for the recall of adult diet with middle-age diet. This would suggest that a different dietary intake was being recalled for earlier life periods compared to middle-age, indicating either a very plausible change in diet from these earlier periods to middle-age, or that the influence of current diet was exerting a greater influence on memory of these more relatively recent periods.

The level of agreement for memory of individual foods (as opposed to total diet) was assessed by the weighted kappa statistic; the distributions for most items were too far from bivariate normal for the polychoric correlation to be calculated. Weighted kappa takes into account the *degree* of agreement between items on an ordinal scale; items that are in perfect agreement are given a weight of 1 while different weights *wi* are assigned to items that differ by *i* categories. Thus if there are *k* categories the weights are calculated by $wi = 1 - \frac{i}{k-1}$; therefore, on a 4-point ordinal scale, disagreement by one category is weighted by 0 .67, disagreement by two categories is weighted by 0.33 and disagreement by 3 categories is given zero (Altman, 1991; Sim & Wright, 2005). Kappas thus range from 0 to 1, with 1 being the highest level of agreement. The weighted kappa averages for food groups within each life period are presented in Table 5.3.

With the exception of early-adulthood, the average weighted kappa for each life period was > 0.5 which indicated a moderate to good level of agreement between items in the two administrations of this reproducibility study (Altman, 1991). Weighted kappa ranged from 0.27 for fats & oils in Early-adulthood to 1.00 for soy products in childhood. There were no food groups that had consistently higher or lower levels of agreement across all life periods although tea/coffee and

soy products had the highest level of agreement, and other protein foods had the lowest level of agreement across two out of the five life periods.

Table 5.3: Average agreement for foods between the two administrations of the LDQ

Food group	Childhood	Early adulthood	Adulthood	Middle-age	Older-age
vegetables	0.53	0.33	0.46	0.47	0.51
dairy	0.51	0.45	0.46	0.54	0.55
fruit	0.51	0.34	0.48	0.44	0.48
cereals	0.54	0.31	0.47	0.49	0.52
meat	0.49	0.39	0.46	0.46	0.49
fish	0.57	0.24	0.57	0.50	0.42
soy products	1.00	0.34	0.61	0.70	0.74
other protein foods	0.53	0.42	0.52	0.38	0.34
snack food	0.53	0.34	0.49	0.40	0.51
fats/oils	0.63	0.27	0.49	0.45	0.57
vitamin	0.67	0.49	0.67	0.67	0.65
alcohol	n/a	0.45	0.60	0.58	0.58
tea/coffee	0.60	0.46	0.74	0.75	0.73
average weighted kappa all items	0.55	0.36	0.52	0.51	0.53

n/a, not applicable

For this sample, higher kappas were primarily associated with foods consumed rarely/never, or, to a much lesser extent, consumed daily; 81% of responses for items with a weighted kappa of over 0.6 had a mode of 1 (consumed rarely/never) and 17% had a mode of 4 (consumed daily), leaving only 2% of responses that had a mode of 2 to 3 times a week or 2 to 3 times a month.

5.6 Discussion

The LDQ demonstrated excellent reproducibility for all life periods in a group of cognitively healthy elderly people. This is in agreement with previous studies that demonstrated elderly people can recall dietary intake reliably, with

correlations between assessments equal to, or greater than, those of younger cohorts (Lazarus, Wilson, Gliksman, & Aiken, 1995). Nonetheless, it is acknowledged that reproducibility itself does not demonstrate the validity of dietary memories. The influence of current diet on past diet reporting has been well documented (Byers et al., 1987; Dwyer et al., 1989; Jensen et al., 1984; Wu et al., 1988) and in the case of the LDQ it could be argued that the questionnaire's reproducibility may be due to participants consistently reporting similar versions of their current dietary intake for all periods, and across both questionnaire time points. However, dietary patterns have been shown to change over time (Mishra et al., 2006; Prynne, Paul, Mishra, Greenberg, & Wadsworth, 2005; Shatenstein et al., 2003) so it could be expected that if the questionnaire was validly assessing lifetime memory, there would be stronger associations between two recalls of the same dietary period than between that life period and a later life period. Significantly higher reproducibility correlations were demonstrated for the early life periods (childhood and early-adulthood) compared to the mean correlation between these life periods and the middle-age period at both administrations of the questionnaire. Thus the LDQ appeared sensitive to temporal change in individuals' reported intake between early life and middle-age. The lack of a significant difference in the mean correlation between the two recalls of adult diet and that of middle-age was not surprising given that the largest changes in diet could be expected to occur in late adolescence and early adulthood as the transition is made from living with parents to the establishment of independent households and lifestyles (Lake et al., 2004). In addition, dietary choices have been shown to be associated with demographic factors such as income, occupation and life-circumstances (Mishra et al., 2006) which, for this older population, may have

been relatively stable from adulthood to middle age compared to earlier periods. The demonstrated success of the LDQ in discriminating between dietary intake across life periods may have been due, in part, to the non-quantitative and list-based approach used that utilised participants' generic dietary memory to successfully recall their typical diet for a given period (Smith, 1993).

It was noteworthy in this cohort that despite childhood being the most distant period, it was the period with highest reproducibility for diet recall. Autobiographical memory research has suggested that durable memories in childhood are formed by focused parental attention, guidance and interaction (Nelson, 1993; Pillemer, 1998). It is possible that meal times and food choices in childhood were particularly salient as a focus for these forms of close communication and so led to more vivid recall of diet during this period.

Unfortunately, no actual dietary records from the past were available for this elderly sample of participants to validate dietary memory using the LDQ. A number of studies have examined the validity of distant dietary memory by comparing recalled diet with dietary records from the relevant period. Generally, stronger correlations were seen in studies where the interval between the original records and the recall period was less than ten years (Willett, 1998). However, a study by Dwyer and Coleman (1997) showed that the memory of middle-aged people for food intake up to four decades earlier did not decline inevitably over time, rather, time-related memory loss varied from food to food. It was suggested that the pattern of consumption frequency may define memory accuracy so that foods eaten rarely, and those eaten every day, were more likely to be reported accurately. This is in accord with the relationship found between levels of agreement and consumption frequencies for food groups across the two

administrations of the LDQ; those foods with higher levels of agreement were those that were recalled as being eaten rarely/never or eaten daily. Although average weighted kappa for food groups generally fell within the moderate range, it was not possible to make a meaningful comparison between these results and those from other studies, given that the magnitude of kappa is dependent on the proportion of items in each category and the number of categories used; therefore two quite disparate values of kappa can be representative of the same absolute levels of agreement (Altman, 1991; Sim & Wright, 2005). Nonetheless, the moderate agreement between the two questionnaire administrations was consistent across all the summary food groups, and for all the five life periods, thus suggesting the LDQ effectively demonstrated long term dietary memories are reproducible for older adults.

5.7 Conclusion

Retrospective lifetime dietary recall is a new approach to evaluating the possible long-term contribution of dietary intake to age-related cognitive decline. The LDQ has been proposed as a self-administered instrument to assess dietary intake from the past in cognitively healthy older people without the necessity of actual dietary records, which are usually unavailable for elderly populations. When the questionnaire was administered at two time points to a group of cognitively healthy older community dwelling adults, the average reproducibility correlation coefficient was 0.81 for recall of dietary intake across five life periods, and the average weighted kappa for summary food groups was 0.49. Considering the length of period of recall we consider this a very good outcome. Although studies to assess the questionnaire's validity by comparing recalled intake with actual dietary records are desirable, the current results provide an encouraging first step

in demonstrating the reliability of the questionnaire and its potential utility in assessing long term dietary intake. Given the possible influence of lifetime diet on older-age cognitive functioning via its interaction in earlier life with biological and environmental factors, such an instrument is a valuable contribution to the investigation of temporal relationships between dietary intake and age-related cognitive decline.

5.8 Preamble to Publication 2

The following published study presents an approach to test the validity of the LDQ. The validity of new FFQs is usually tested by measuring its relative validity; that is, its relative association with an objective measure of dietary intake such as multiple food records (Willett, 1998). In the case of past dietary recall, especially when that recall is from the very distant past, such records are scarce; indeed, if there were such records readily available an assessment instrument such as the LDQ would not be necessary. An alternative approach to determining whether very long-term dietary recall has some validity is to test its predictive value and its divergent validity in terms of current diet. If the recall of past diet is associated with theoretically relevant demographic and health outcomes *after* accounting for the impact of current diet recall then some validity can be attributed to the recall of past diet.

The LDQ is a non-quantitative measure, so the relationships between nutrient intake and outcomes cannot be assessed. Dietary pattern analysis of the LDQ potentially provides information regarding individuals' relative intake of overall eating patterns rather than individual foods or nutrients at different life periods, and it is the relationships between these past dietary patterns, current dietary patterns, and relevant outcome variables that will be investigated in the next chapter.

Chapter 6 Validity of Lifetime Diet Recall

"Retrospective lifetime dietary patterns are associated with demographic and cardiovascular health variables in an older community-dwelling Australian population"

(Hosking & Danthiir, 2013)

6.1 Abstract [Publication 2]

Dietary patterns derived from factor analytic procedures have been demonstrated to predict demographic and health outcomes across a wide range of populations. To examine the potential validity of long-term dietary recall, we examined associations between dietary patterns from across the lifespan with demographic and later-life cardiovascular-related health variables, using the LDQ. The LDQ is a self-administered, non-quantitative, retrospective food frequency questionnaire designed to assess dietary intake from childhood to older-age. Participants (n = 352) from the EPOCH trial, aged 65-91 years, completed the LDQ. EFA was conducted on the LDQ and plausible dietary patterns were derived. Three patterns were extracted from each life-period, with five distinct patterns overall; these were 'traditional Australian' and 'non-traditional Australian', high sugar and fat, vegetable, and fruit and vegetable patterns. In separate adjusted regression models, age, sex, education, income, parental background, and childhood physical activity all significantly predicted dietary patterns across the lifetime. A 'traditional Australian' pattern in childhood predicted higher HDL cholesterol levels and lower odds of cholesterol medication use; lower HDL was predicted by the adult 'processed, high-sugar and high-fat pattern', and higher intake of a non-traditional Australian pattern also in adulthood predicted lower odds of using cardiac medications. Lifetime dietary recall, as instantiated by the LDQ, provides a hitherto

untapped source of long-term dietary information in older adults that may contribute to greater understanding of the impact exerted by early-life and cumulative dietary choices on later-life health.

6.2 Introduction

As lifespan increases, healthy ageing has become a public health priority. The World Health Organization's 2002 Active Ageing Report recommended a life-course approach to older-age health and well-being (WHO, 2002)that acknowledges the critical periods throughout life when an individual may be particularly vulnerable to environmental exposures, and the cumulative effect of these environmental influences which may interact with genetic propensity to health or disease (Ben-Shlomo & Kuh, 2002; Darnton-Hill, Nishida, & James, 2004).

Dietary intake has been identified as one of the readily modifiable environmental factors that influence health; in particular, intake levels of antioxidant vitamins and minerals and nutrients such as folate, vitamin B12, omega-3 fats, and dietary fibre (NHMRC, 2009). Recently, there has been increasing interest in analysing dietary intake in terms of whole dietary patterns given that individual nutrients or even foods are not eaten in isolation and may act in a synergistic manner to influence (Hu, 2002; Kant, 2004). Dietary patterns may be defined by two general approaches. Dietary indexes or scores group foods and nutrients together that have been associated with health or other outcomes (Newby & Tucker, 2004). Diets are assessed for the presence or absence of the relevant foods/nutrients and the score indicates the level of adherence to the *a priori* defined dietary pattern (Kant, 2004); for example, the Healthy Eating Index developed by the US Department of Agriculture (Kennedy, Ohls, Carlson, & Fleming, 1995) and the Mediterranean Diet Score (Trichopoulou, Costacou, Bamia,

& Trichopoulos, 2003). The second approach is driven by the statistical relationships between dietary variables, and is not dependent on pre-existing definitions of diet quality, although theoretical interpretability is an important consideration when evaluating the patterns that emerge from the data (Newby & Tucker). These methods generally derive dietary patterns that are specific to a particular population; nonetheless, the common patterns of a 'healthy',' traditional', 'sweets', and 'Western' patterns have emerged consistently across studies (Moeller et al., 2007). Cluster analysis, factor analysis, and principal component analysis all fall into this category of data driven methodology (Newby & Tucker).

Although there is some theoretical and methodological debate surrounding the objectivity and reproducibility of dietary patterns (Kant, 2004; Martínez, Marshall, & Sechrest, 1998; Schulze & Hoffmann, 2006), the approach is nonetheless considered a valuable exploratory tool in nutritional epidemiology (Slattery & Boucher, 1998). Instantiations of both healthy and unhealthy dietary patterns have been associated with older-age disease risk factors such as hypertension, cholesterol levels, and BMI measurements(van Dam, Grievink, Ocke, & Feskens, 2003; Weikert et al., 2005), and with the risk of developing cardiovascular disease (Tourlouki, Matalas, & Panagiotakos, 2009), cancer (Murtaugh et al., 2008), diabetes(Kim, Park, Grandinetti, Holck, & Waslien, 2008; Schulze et al., 2005), Alzheimer's disease, cognitive decline(Akbaraly, Singh-Manoux, Marmot, & Brunner, 2009; Barberger-Gateau et al., 2007), as well as with all-cause mortality(Brunner et al., 2008; Heroux et al., 2010; Huijbregts et al., 1997; Trichopoulos & Lagiou, 2001). Furthermore, it has been recognised that dietary patterns are determined within the context of the broader socio-

demographic environments of the population under consideration; age, sex, ethnicity, education, and occupation have all been shown to influence consumption of particular dietary patterns. Such information can enable the identification of those groups who would benefit from public health initiatives regarding dietary intake (Darmon & Drewnowski, 2008; Mishra, Ball, Arbuckle, & Crawford, 2002; Mishra et al., 2010; Park et al., 2005).

Given the demonstrated relationships between dietary patterns and disease risk, together with the salience of a life-course perspective on healthy ageing (Ben-Shlomo & Kuh, 2002; Whalley et al., 2006), assessing dietary patterns from across the life-span could contribute valuably to understanding of long-term dietary influence on older-age health outcomes. However, accruing actual lifetime dietary data requires longitudinal cohort studies and these are relatively rare; in those that do exist, the comprehensive biological and psychosocial data necessary to life-course research were not always collected, or even available(Ben-Shlomo & Kuh, 2002; Wadsworth et al., 2003). Thus, despite the plausible influence of earlier-life dietary intake on later-life health, dietary assessment across multiple life periods remains a considerable research challenge. An alternative approach to logistically complex and costly longitudinal cohort studies, when investigating the contribution of lifetime diet on older-age outcomes, is to use the recall of lifetime diet from cognitively healthy older adults (Hosking et al., 2011).

Although measurement error is inherent in past diet recall, it nonetheless may have some utility in dietary epidemiology (Dwyer & Coleman, 1997; Friedenreich et al., 1992), in particular, on a group level when reported intake level, either low or high, is used to predict disease outcomes (Dwyer & Coleman, 1997). Recently, the LDQ, a non-quantitative retrospective lifetime FFQ, was

proposed as an instrument to assess lifetime diet in older people. It was shown to have excellent test-retest reliability in an older cognitively healthy sample, with an average reproducibility correlation co-efficient of 0.81 for recall of dietary intake across five life periods (Hosking et al., 2011). One method of examining the potential utility of the LDQ as an instrument to examine relationships between older-age health outcomes and dietary intake from across the life period is to first extract plausible dietary patterns from the LDQ, and then relate these to outcomes. To this end, the current study conducted an exploratory factor analysis of the items from the LDQ. Subsequently, associations were investigated between these LDQ factors and current demographic and cardiovascular health variables.

6.3 Method

6.3.1 Participants

Participants were drawn from the EPOCH cohort, an 18-month randomized controlled trial of omega-3 fish oil on cognitive functioning in a cognitively healthy, community dwelling population of older adults in Adelaide, South Australia (Danthiir, V. et al., 2011). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the CSIRO Human Ethics Committee. Written informed consent was obtained from all subjects. A total of 352 people (53.7% female) completed the LDQ, with an age-range of 65-91 years (M =73.12; SD = 5.47). 26.4% of men and 37.6% of women completed schooling to year 10 and 22.7% of men and 21.8% of women completed schooling to year 12. A bachelor degree or higher was held by 8.2% of the sample. Median gross household income accorded with the national median for individuals aged 65yrs and above (AIHW, 2007). For 95% of participants, English was their first language but 13% had at least one parent

from a non-Anglo background. Baseline Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) mean score for the LDQ cohort was 28.71 (SD=1.32).

Mann-Whitney non-parametric tests demonstrated there were no significant differences between LDQ participants and non-participants from the EPOCH cohort in age, level of education, and baseline MMSE score.

6.3.2 Lifetime diet assessment

The LDQ is a self-report non-quantitative food frequency questionnaire that divides the life into periods of 15 years from childhood until older-age. The questionnaire has been described previously (Hosking et al., 2011) but a brief overview follows: Participants recalled their average consumption frequency of various food items on a four-point frequency scale ranging from 'rarely/never' to 'daily'. The food groups and their items were the same for each life period, with exceptions being food items that were unlikely to have been consumed during a particular life period; specifically, alcohol-related questions in childhood and lard for the later life periods. The number of items for each life period ranged from 74 in childhood to 79 in early-adulthood, with adulthood and middle-age each having 78 items. Questions assessing physical activity levels were also asked as a proxy measure for energy expenditure across each life period. One question was asked in each life-period regarding the frequency per week of vigorous, moderate and light physical activity. One additional question (for all periods except childhood) was included to determine the physical activity level ('little, some, frequent, or heavy & frequent') associated with occupation. Recall across life periods was aided by a series of autobiographical cue questions that were completed prior to the period-

specific dietary recall questions; these related to family and working lives at the time as well as important world or personal events that may have occurred.

The LDQ has been showed to have good reproducibility in an older population with test-retest correlations for each of the life-period questionnaires of 0.86 in childhood, 0.81 for early-adulthood, 0.82 in adulthood, 0.79 in middle-age and 0.80 in older-age. The average weighted kappa statistics for food items between the two administrations of the questionnaire were for 0.55 for childhood, 0.36 for early-adulthood, 0.52 for adulthood, .051 for middle-age and 0.53 for older-age (Hosking et al., 2011).

6.3.3 Current diet

Current diet was assessed by the Victorian Cancer Council Food Frequency Questionnaire (CCFFQ) (Giles & Ireland, 1996) ; an 84 item assessment of dietary intake over the previous 12 months. Response frequencies ranged from 1 ('never') to 10 ('3 or more times a day') with the exception of eggs (number per week), and bread, milk, and sugar where responses were defined as units per day.

Reported current intake was used in subsequent analyses to control for the known influence of current diet recall on past diet recall (Dwyer et al., 1989). To ensure current intake was represented in a manner commensurate with past intake, foods that were assessed by the CCFFQ but not by the LDQ were excluded (18 items). In addition, consumption frequencies of the relevant items were converted to equivalent times per week and composite items were made from some individual foods to represent the food groupings in the LDQ; for example, the items cabbage, broccoli, and cauliflower on the CCFFQ were combined into the single item 'cruciferous vegetables' and bacon, ham, sausages, and salami on the CCFFQ were combined to form 'processed meats', as represented in the LDQ.

6.3.4 Demographic and cardiovascular health variables

An extensive range of health and demographic information was collected from the EPOCH cohort which has been fully described in the study protocol (Danthiir, V. et al., 2011). The variables included in the current analyses were: age, sex, years of education (including schooling and post-schooling), parental birth country and parental income, current income level, pack years of smoking, and both current and past physical activity levels. Indicators of cardiovascular health were measured by BMI, systolic blood pressure, diastolic blood pressure, concentrations of LDL, HDL cholesterol levels, total cholesterol, and triglycerides. Medication use was also assessed for hypertension, high cholesterol, and cardiac conditions. Descriptive statistics for these variables are presented in Table 6.1

6.3.5 Procedure

All EPOCH participants were given the opportunity to participate in the Lifetime Diet Assessment. The study was described to participants individually during a study visit at CSIRO Animal Food and Health Sciences (the study centre). On providing written informed consent, they were given the self-administered LDQ to complete at home, and provided with detailed verbal and written instructions as to the study requirements. The questionnaire for each life period was completed in chronological order, one day at a time, over five days to minimize memories from one life period intruding into another period. In addition, given that each life period covered up to 15 years, participants were asked to recall their most representative diet and to report average consumption of seasonal foods. All participants completed the first four life periods: 'childhood', 'early adulthood', 'adulthood, and 'middle-age'. The fifth life period, 'older-age' only applied to participants who were aged 80 years or over, of which there were 30.

Table 6.1: Descriptive statistics for the LDQ sub-sample of the EPOCH cohort

Variable	Mean	SD
Age	73.12	5.47
Years of education	12.91	4.16
Smoking history, *pack years**	9.83	17.77
BMI, *kg/m2*	27.27	4.29
Systolic blood pressure, *mmHg*	136.83	16.48
Diastolic blood pressure, *mmHg*	76.62	9.75
HDL cholesterol, *mmol/L*	1.39	0.36
LDL cholesterol, *mmol/L*	3.16	0.86
Total cholesterol *mmol/L*	5.23	1.00
Triglycerides *mmol/L*	1.48	0.64
Medication use	% of sample	
Cardiac medication	26.4	
Cholesterol medication	25.9	
Hypertensive medication	42.3	
Sex (female)	53.7	
Current income (> Australian median for 65 yrs +)	44.4	
Early-life socio-demographics		
Parents with non-Anglo heritage	13.4	
Parents' income		
Low	21.0	
Medium/high	73.3	
Missing	5.7	

6.4 Statistical analyses

6.4.1 Missing data

Participants who had whole life periods (n=9) or > 80% of responses missing across any life periods (n=3) were excluded from the following missing value analyses.

The remaining missing data in the LDQ were of two types; item non-response (mean per person = 6.43; SD = 10.79) and multiple consumption

frequencies reported for a food item (mean per person = 1.06; SD = 0.55). Fatigue may cause elderly participants to skip foods not eaten (Fraser et al., 2009; Michels & Willett, 2009), so for this population, it was assumed that null responses generally equated to the 'rarely/never' consumption frequency. It has been shown that the greater the proportion of initially missing items, the greater the probability that these missing responses are likely to be true zeros (where zero equals non-consumption) but this probability declines when a threshold is reached of greater than 25 out of 80 item responses being missed (approximately 30%) (Fraser et al., 2009).Thus, missing responses herein were equated with a food being 'rarely/never' eaten (mean n for all life periods = 58; SD = 3.65) except when a participant had less than the average number of non-responses (mean n for all life periods = 184.25; SD = 10.84) or a large number (> 30%) of non-responses (mean n for all life periods = 30; SD = 5.88) to items in each life-period. These items, in addition to those with multiple responses, were missing at random and estimated with the Missing Value Analysis in SPSS for Windows statistical package version 17.0.1 (SPSS Inc., Chicago, IL, USA).

6.4.2 Dietary patterns

Exploratory Factor Analysis was conducted separately on each of the life periods from the LDQ [24], using M-plus Statistical Analysis with Latent Variables version 5.1 (Muthén LK, and Muthén BO, Los Angeles), The Weighted Least Squares Matrix (WLSM) estimator was used as estimates are based on polychoric correlations as opposed to the more commonly used Pearson's product moment correlation coefficient. Polychoric correlations are appropriate when variables are

[24] EFA could not be conducted on the questionnaire data from the older age period (> 75 years) because only 30 participants fell within this age-range.

ordinal or categorical but can be assumed to represent a latent continuous construct, in this case, consumption frequency. Thus, the strength of linear relationships between ordinal variables that would be otherwise attenuated, due the limited range of response frequencies, is better represented by a polychoric correlation coefficient rather than Pearson's (Uebersax, 2006).

The consumption frequency of all items was checked prior to analyses. It is feasible that relationships between foods that were either never or rarely consumed by the majority of participants may still define dietary patterns; however any subsequent associations between such a factor and other measures would be driven by a very small proportion of the overall sample. Consequently, items that had 70% or greater of 'rarely/never' responses were excluded from the EFA. The number of foods excluded and the number entered for each life-period are as follows: childhood - 17 foods excluded, 57 foods entered; early-adulthood - 10 foods excluded, 69 foods entered; adulthood - 7 foods excluded, 71 foods entered; middle-age - 4 foods excluded, 74 foods entered.

A range of two to ten factors were extracted and an oblique rotation was specified (Oblimin) to allow factors to correlate. All factor correlations were below 0.3 so the orthogonal rotation Varimax was subsequently chosen to promote simple structure of the rotated solution and therefore aid in factor interpretability (Kline, 1994).

An important decision when conducting factor analysis is how many factors to retain. There is an extensive literature on the processes available to determine factor retention, and their relative strengths and weaknesses, although theoretical plausibility is the overarching criterion (Fabrigar, Wegener, MacCallum, & Strahan, 1999; Stellefson, Hanik, Chaney, & Chaney, 2009). In these analyses, the factor

retention decision was guided by the break point in the scree plot (Costello & Osborne, 2005), interpretability, and having a clear factor structure (Kline, 1994). Participants received a score on each factor extracted from the LDQ by weighting all food items by their factor loadings then summing the items (DiStefano, Zhu, & Mîndrilă, 2009).

EFA was also conducted on the abbreviated (47 items) CCFFQ in M-Plus, following a similar procedure as for the LDQ, and using frequency of intake as the input variables. There were no missing data and responses had a frequency range from 1 (rarely/never) to 10 (three or more times a day) so data were treated as continuous. Bread, milk, sugar, and eggs were exceptions; these were assessed as units per day (so number of slices of bread etc.) and re-coded as binary values representing consumption versus non-consumption, except for eggs where the response frequency was number per week and this original coding was retained. M-plus can conduct EFA simultaneously on both binary and continuous variables and factors were extracted using the Maximum Likelihood estimator.

6.4.3 Current diet and demographic variables as predictors of LDQ dietary patterns

Regression models were carried out using IBM SPSS for Windows statistical package version 20 (IBM Corporation, New York, U.S.A) with each past dietary pattern being the outcome variable in separate models. Firstly, current dietary patterns were used as predictors of each of the LDQ patterns across all life periods to determine the influence of current dietary intake on past diet recall; the average R^2 value for each life period indicated the average percentage of variance in recalled past diet that was accounted for by current diet. Next, demographic

variables were entered to demonstrate relevant associations between these variables and past dietary intake as assessed by the LDQ.

The LDQ factor scores were normally distributed, and regression diagnostics showed no influential cases or serious violations of assumptions. Models were adjusted for current diet, physical activity (past and present), and the other past dietary factors; the study was powered at 0.8 to detect a medium effect size with alpha (two-tailed) at 0.05 (Green, 1991).

In preliminary analyses, a number of the LDQ factors showed higher than acceptable Variance Inflation Factor (VIF) values in the regression models, indicating multicollinearity amongst the LDQ factors. This would be problematic in further analyses when individual LDQ patterns were to be the predictors of model outcomes; when predictors are highly related, their shared variance makes it impossible to reliably identify the individual contribution of any one of them (Myers, 1990). One method to deal with multicollinearity amongst predictors is to compute principal components and use these components instead of the original variables in analyses (Tabachnick & Fidell, 2007); therefore, for each LDQ factor, a set of four unrelated principal components was created that accounted for approximately 80% of the shared variance amongst all the other past dietary patterns. Subsequently, these LDQ principal components, rather than the original LDQ factors were entered as covariates in the models.

6.4.4 LDQ dietary patterns as predictors of cardiovascular risk factors

In separate analyses, cardiovascular risk factors were outcomes in regression models with the individual LDQ factors as predictors. Multiple regression was used to test associations with the continuous variables of BMI, blood pressure, and lipid measurements. The variables for BMI and triglycerides

were log10 transformed, and those for systolic and diastolic blood pressure were square root transformed to normalise the distributions (Tabachnick & Fidell, 2007). Covariates were entered simultaneously into the models. They included age, sex, number of years of education, smoking history (pack years), income (parents' income for childhood and early-adulthood; current income for adulthood and middle-age), life period-specific physical activity, current physical activity, medication use, current dietary factors, and the four principal components representing the other past dietary factors.

Three dichotomous variables (use/do not use medication) represented medication use for managing hypertension, cholesterol levels, or cardiac conditions. Logistic regression was employed for models using these variables. Restrictions were imposed by sample size on the number of covariates possible to include in the logistic regressions (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996) compared to the previous multiple regressions. These models were adjusted for age, sex, the relevant life-period physical activity variable, current physical activity, and current diet; the number of 'events per variable' for precluded the entry of the other LDQ principal component scores as covariates.

6.5 Results

Three factors were retained for each life period from the EFA. These factors and the food items with a loading of 0.3 and above are presented in Tables 6.2 to 6.5.

Table 6.2: Dietary patterns for childhood

CHILDHOOD					
Factor 1 (variance 9.65%) vegetable & non-processed		**Factor 2** (variance 17.70%) traditional Australian		**Factor 3*** (variance 8.35%) coffee & high-sugar, high-fat extras	
Food item	Loading	Food item	Loading	Food item	Loading
Parsnip	0.677	White grapes	0.908	Sweet coffee	0.943
Cruciferous vegetables	0.630	Red grapes	0.847	White coffee	0.905
Rhubarb	0.584	Apricot/peaches	0.793	Snack food	0.515
Beetroot	0.550	Citrus fruit	0.733	Soft drink	0.501
Carrots	0.527	Vegemite	0.707	Chocolate	0.496
Plums	0.473	Melon	0.704	Nuts	0.408
Lentils/bean	0.458	Pumpkin	0.667	Cherries	0.403
Oats	0.451	Bananas	0.649	Chicken	0.399
Pears	0.450	Butter	0.615	Ice cream	0.390
Berries	0.447	Cream	0.569	Parsley	0.317
Lettuce	0.442	Lettuce	0.568	Bananas	0.308
Parsley	0.440	Figs	0.566	Fish (other)	0.305
Green beans	0.429	High fibre cereal	0.515		
Tomatoes	0.403	Nuts	0.515		
Cherries	0.376	Plums	0.507		
White rice	0.375	Red meat	0.465		
Vegetable soup	0.361	Ice cream	0.455		
Oily fish	0.355	Tomatoes	0.442		
Potatoes	0.350	Apples	0.436		
Onions	0.323	Spinach	0.414		
White tea	0.305	Pears	0.402		
		Eggs	0.393		
		Beetroot	0.390		
		Desserts	0.386		
		Parsley	0.340		
		Cheese	0.331		
		Sweet tea	-0.365		
		White tea	-0.372		

* Item loadings on this factor were initially all negative so the sign has been reversed on all loadings and in subsequent associations for ease of interpretation

Table 6.3: Dietary patterns for early-adulthood

EARLY ADULTHOOD					
Factor 1 (variance 10.83%) vegetable		**Factor 2** (variance 12.24%) traditional Australian		**Factor 3** (variance 8.80%) non-traditional Australian	
Food item	Loading	Food item	Loading	Food item	Loading
Carrots	0.721	White grapes	0.817	Multi-grain bread	0.677
Green beans	0.663	Red grapes	0.750	Whole-grain bread	0.643
Tomatoes	0.646	Apricot/peaches	0.653	Red wine	0.618
Beetroot	0.609	Ice cream	0.610	Herbs	0.598
Lettuce	0.582	Soft drink	0.598	Margarine (unspecified)	0.597
Potatoes	0.554	Melon	0.575	Parsley	0.505
Cruciferous vegetables	0.546	Citrus fruit	0.518	Other wine	0.486
Parsnip	0.543	Nuts	0.510	Chicken	0.381
Rhubarb	0.509	Snack food	0.502	Vegetable oil	0.367
Pumpkin	0.457	Bananas	0.489	White rice	0.352
Onions	0.456	Cherries	0.479	Black tea	0.332
Spinach	0.452	Chocolate	0.475	Oily fish	0.326
Parsley	0.443	Other wine	0.449	Melon	0.314
Cow milk	0.397	Vegemite	0.436	Sweet tea	- 0.312
Plums	0.394	Sweet coffee	0.431	Desserts	- 0.355
Citrus	0.378	Red wine	0.421	Butter	- 0.617
Apples	0.369	Pears	0.404	White bread	- 0.749
Cheese	0.354	Berries	0.403		
Vegetable soup	0.349	White coffee	0.394		
Oats	0.332	Take away food	0.377		
Herbs	0.319	Pumpkin	0.368		
Pears	0.303	Chicken	0.363		
		Lettuce	0.361		
		Parsley	0.359		
		Vegetable oil	0.358		
		High fibre cereal	0.346		
		Cream	0.331		
		Plums	0.330		
		Apples	0.327		
		Fish (other than oily or shellfish)	0.318		
		Desserts	0.318		

Table 6.4: Dietary patterns for adulthood

ADULTHOOD					
Factor 1 (variance 10.26%) fruit & vegetable		**Factor 2** (variance 10.31%) non-traditional Australian		**Factor 3** (variance 6.36%) processed, high-sugar & high-fat	
Food item	Loading	Food item	Loading	Food item	Loading
Carrots	0.578	Herbs	0.673	Soft drink	0.654
Apples	0.575	Peppers	0.635	Take-away food	0.581
Plums	0.553	Red wine	0.595	Ice cream	0.569
Beetroot	0.539	Parsley	0.579	White bread	0.566
Apricot/peaches	0.529	Olive oil	0.537	Sweet coffee	0.549
Citrus fruit	0.516	Yoghurt	0.522	Sweet tea	0.539
Tomatoes	0.510	Seafood	0.508	Snack food	0.469
Green beans	0.508	Other wine	0.508	Chocolate	0.451
Bananas	0.499	Red grapes	0.502	Sausage	0.428
White grapes	0.486	Chicken	0.470	Desserts	0.377
Parsley	0.478	Multi-grain bread	0.459	Cow's milk	0.352
Lettuce	0.477	Whole-grain bread	0.442	White coffee	0.342
Red grapes	0.457	Brown rice	0.442	Cream	0.310
Pears	0.453	Nuts	0.427	Whole-grain bread	-0.395
Rhubarb	0.450	Melon	0.417		
Cruciferous vegetables	0.417	White grapes	0.392		
Pumpkin	0.404	White rice	0.385		
Cheese	0.394	Cherries	0.366		
Parsnip	0.386	Lentils/beans	0.366		
Herbs	0.384	Margarine (unspecified)	0.358		
Cherries	0.374	Vegetable oil	0.348		
Spinach	0.371	Berries	0.327		
Vegetable soup	0.363	Fish (other)	0.327		
Potatoes	0.346	Take-away food	0.313		
Oats	0.344	Butter	-0.329		
Berries	0.324	Red meat	-0.342		
Onions	0.320	White bread	-0.428		
Melon	0.319	Potatoes	-0.512		
High fibre cereal	0.316				
Vegemite	0.313				
Brown rice	0.305				

Table 6.5: Dietary patterns for middle-age

MIDDLE-AGE					
Factor 1 (variance 12.33%) fruit, vegetable & non-processed		**Factor 2** (variance 7.33%) non-traditional Australian		**Factor 3** (variance 6.46%) processed, high-sugar & high-fat	
Food item	Loading	Food item	Loading	Food item	Loading
Apricot/peaches	0.724	Herbs	0.697	Soft drink	0.635
Plums	0.670	Olives	0.662	Ice cream	0.589
Cherries	0.625	Parsley	0.563	Desserts	0.583
Pears	0.597	Seafood	0.529	Snack food	0.529
Apples	0.583	Olive oil	0.520	Sausage	0.520
Citrus fruit	0.574	Red wine	0.491	White bread	0.504
Lettuce	0.537	Peppers	0.443	Cream	0.485
White grapes	0.533	Onions	0.440	Takeaway food	0.456
Bananas	0.516	Other wine	0.435	Chocolate	0.456
Berries	0.511	Red grapes	0.425	Red meat	0.402
Tomatoes	0.505	Mangos	0.409	Sweet tea	0.397
Parsley	0.504	Nuts	0.394	Sweet coffee	0.390
Rhubarb	0.503	Fish (other)	0.364	Cow's milk	0.332
Cruciferous vegetables	0.487	Melon	0.339	Vegemite	0.328
Beetroot	0.485	White grapes	0.330	Green beans	0.313
Red grapes	0.483	Potatoes	-0.406		
Carrots	0.481				
Brown rice	0.456				
Parsnip	0.440				
Peppers	0.420				
Melon	0.419				
Green beans	0.418				
Whole-grain bread	0.413				
Spinach	0.412				
Yogurt	0.402				
Herbs	0.398				
Oats	0.381				
Lentil/beans	0.365				
Vegetable soup	0.351				
Oily fish	0.345				
Mangos	0.315				
Onions	0.314				
Pumpkin	0.303				

No single factor was common to all periods although there was considerable consistency in the factors found across periods. They were 'traditional Australian' and 'non-traditional Australian' patterns, a version of a

processed fat and sweets pattern, and a vegetable, or a fruit and vegetable pattern. The 'traditional Australian' pattern was only evident in the two early-life periods of childhood and early adulthood; however, a 'non-traditional Australian' pattern was present in all periods except childhood and a processed, fat and sweets pattern was common across all periods except early adulthood. The total percentage of variance accounted for by the factors in all the items of the LDQ for each life period was 35.7% in childhood, 31.87 % in early adulthood, 26.93% in adulthood, and 26.12% in middle-age.

Three similar factors to those extracted from the LDQ were extracted from the abbreviated CCFFQ using EFA, based on the same criteria. Loadings on each factor > 0.3 and the variance accounted for in the items are presented in Table 6.6. Item loadings for the current dietary factors were generally lower than those for the LDQ with the highest loading value of 0.53 for processed meat on factor 2. Consequently, the extracted factors for current diet accounted for much less item variance than those for past diet.

Table 6.6: Current dietary factors extracted from the CCFFQ

CURRENT DIET*					
Factor 1 (variance 9.37%) health aware		**Factor 2** (variance 4.53%) processed		**Factor 3** (variance 3.11%) traditional vegetables	
Food item	Loading	Food item	Loading	Food item	Loading
Peppers	0.568	Processed meat	0.530	Carrots	0.490
Beans (chick peas/lentils etc.	0.560	Ice cream	0.445	Cruciferous vegetables	0.456
Mango	0.487	Takeaway	0.444	Pumpkin	0.356
Apples	0.466	Bread	0.432	Beans/peas	0.341
Spinach	0.461	Sweets	0.406	Spirits	- 0.390
Onions/garli	0.460	Snack food	0.401		
Green salad	0.454	Red meat	0.350		
Yogurt	0.446				
Pears	0.438				
Strawberries	0.436				
Melon	0.434				
Stone fruit	0.428				
Nuts	0.390				
Bananas	0.368				
Cruciferous vegetables	0.364				
Carrots	0.363				
Tomatoes	0.327				
Fish (tinned)	0.324				
Citrus fruit	0.320				

*Only intake frequency of foods common to LDQ and CCFFQ assessed.

Each of the past dietary patterns was significantly predicted by the three current dietary patterns, as shown by the highly significant F values in Table 6.7. However, the percentage of variance accounted for by current diet in the past dietary factors from each life period increased incrementally over the life-course. In childhood, current diet contributed 7.6 % of the variance in dietary patterns for this period while by middle-age current diet contributed 41.5% of the variance in these later patterns.

Table 6.7: The contribution of current diet to the variance in past dietary factors

	Past dietary pattern	R^2	F (*df*)	Average R^2 for each lifetime period
Current dietary patterns entered simultaneously into each model as predictors of each past dietary pattern	CHD F1	0.092	11.73(3,348)***	0.076
	CHD F2	0.070	8.70 (3,348)***	
	CHD F3	0.066	8.21 (3,348)***	
	EAD F1	0.133	17.78 (3,348)***	0.158
	EAD F2	0.124	16.42 (3,348)***	
	EAD F3	0.217	32.11 (3,348)***	
	AD F1	0.284	45.92 (3,348)***	0.279
	AD F2	0.279	44.87 (3,348)***	
	AD F3	0.273	43.65 (3,348)***	
	MAGE F1	0.400	77.18 (3,348)***	0.416
	MAGE F2	0.452	97.45 (3,348)***	
	MAGE F3	0.393	75.24 (3,348)***	

CHD: childhood; EAD: early adulthood: AD, adulthood; MAGE, middle-age
*** $p < .001$

Demographic and cardiovascular health variables were significantly associated with lifetime dietary patterns after controlling for current dietary intake in this sample of older Australians. The standardized Beta weights for the relationships between the LDQ patterns and the demographic variables are presented in Table 6.8.

Age was the most robust predictor of the dietary patterns with one association found in every life period and two in early adulthood and adulthood. Age positively predicted 'vegetable' or 'fruit and vegetable' patterns in childhood, early -adulthood, and adulthood. It also negatively predicted 'non-traditional Australian' patterns (early-adulthood and middle-age), and a 'processed, high-sugar and high-fat' patterns in adulthood. Being female predicted higher scores on the 'vegetable' pattern in early adulthood, and men scored higher on the 'processed, high-sugar and high-fat' pattern in mid-life.

Table 6.8: Demographic predictors of lifetime dietary patterns

	Age		Sex		Education		Anglo parents		Income†		Pack years		Life-period physical activity	
Dietary pattern	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value
CHD vegetable & non-processed	0.092	0.047	0.028	0.546	- 0.055	0.213	0.004	0.934	- 0.012	0.784	0.018	0.682	0.146	0.001
CHD traditional Australian	0.000	0.987	0.022	0.639	0.026	0.556	0.039	0.371	- 0.005	0.910	- 0.016	0.718	- 0.055	0.195
CHD coffee & high-sugar, high-fat extras	0.093	0.060	0.058	0.250	- 0.037	0.440	0.090	0.058	0.015	0.750	- 0.001	0.991	- 0.027	0.570
EAD vegetable	0.097	0.024	0.118	0.007	- 0.055	0.187	0.061	0.145	0.051	0.208	- 0.032	0.443	0.078	0.052
EAD traditional Australian	- 0.064	0.083	- 0.066	0.080	- 0.023	0.513	- 0 .050	0.157	0.012	0.725	- 0 .006	0.857	- 0.066	0.056
EAD non-traditional Australian	- 0.113	0.013	- 0.091	0.050	- 0.079	0.071	- 0.118	0.007	0.083	0.048	- 0.025	0.573	- 0.045	0.281
AD fruit & vegetable	0.081	0.011	0.048	0.143	0.037	0.224	0.039	0.197	- 0.010	0.746	- 0.016	0.606	0.008	0.782
AD non-traditional Australian	- 0.008	0.795	- 0.034	0.291	0.084	0.005	- 0.007	0.828	0.046	0.130	- 0.043	0.160	- 0.016	0.585
AD processed, high-sugar, & high-fat	- 0.169	< 0.001	- 0.027	0.536	- 0.051	0.195	0.021	0.596	- 0.003	0.935	0.008	0.849	0.052	0.184
MAGE fruit, vegetable, & non-processed	0.015	0.652	0.062	0.069	0.000	0.988	0.006	0.838	0.007	0.833	- 0.018	0.577	0.010	0.746
MAGE non-traditional Australian	- 0.082	0.012	- 0.026	0.443	- 0..021	0.495	0.008	0.793	0.006	0.849	0.036	0.255	- 0.018	0.572
MAGE processed, high sugar, & high fat	0.076	0.053	- 0.100	0.013	- 0.016	0.660	- 0.026	0.477	- 0.014	0.712	- 0.003	0.930	- 0.061	0.105

CHD, Childhood; EAD, Early adulthood; AD, Adulthood; MAGE, Middle-age; Standard, Standardised
* Models additionally adjusted for current dietary intake, current physical activity, and other LDQ dietary patterns.
†Parents' income level (low vs medium/high) for the life-periods of childhood and early-adulthood; current income as proxy for income in adulthood and middle-age.

Table 6.9: Lifetime dietary patterns as predictors of cardiovascular outcomes

	BMI *kg/m2*		Systolic BP *mmHg*		Diastolic BP *mmHg*		HDL cholesterol *mmol/L*		LDL cholesterol *mmol/L*		TOTAL cholesterol *mmol/L*		Triglycerides *mmol/L*	
Dietary pattern	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value	Standard. β weight	*P* value
CHD vegetable & non-processed	0 .040	0.589	- 0.064	0.391	- 0.050	0.497	0.000	0.998	- 0.015	0.819	- 0.034	0.608	- 0.060	0.422
CHD traditional Australian	- 0.101	0.176	- 0.149	0.050	- 0.062	0.416	0.143	0.049	0.096	0.148	0.108	0.114	- 0.057	0.453
CHD coffee & high-sugar, high-fat extras	- 0.066	0.327	0.029	0.672	0.011	0.874	0.045	0.498	- 0.006	0.916	- 0.007	0.904	- 0.065	0.344
EAD vegetable	0.115	0.136	0.109	0.159	0.151	0.052	- 0.093	0.214	- 0.064	0.348	- 0.086	0.224	0.084	0.287
EAD traditional Australian	0.053	0.560	0.018	0.840	0.113	0.217	0.033	0.703	- 0.045	0.577	0.002	0.983	0.005	0.957
EAD non-traditional Australian	0.140	0.053	- 0.032	0.667	0.130	0.076	- 0.023	0.742	- 0.008	0.900	0.015	0.824	0.074	0.318
AD fruit & vegetable	0.003	0.973	- 0.040	0.692	- 0.138	0.168	- 0.146	0.127	- 0.030	0.737	- 0.050	0.580	0.065	0.533
AD non-traditional Australian	0.010	0.918	0.095	0.350	0.006	0.950	- 0.172	0.075	0.061	0.499	0.010	0.918	0.065	0.535
AD processed, high-sugar, & high-fat	0.020	0.788	- 0.013	0.867	- 0.121	0.113	- 0.178	0.015	0.016	0.811	- 0.038	0.586	0.062	0.439
MAGE fruit, vegetable, & non-processed	- 0.031	0.749	0.137	0.160	0.013	0.896	0.069	0.460	0.026	0.766	0.033	0.714	- 0.038	0.713
MAGE non-traditional Australian	- 0.067	0.483	- 0.077	0.430	- 0.189	0.053	0.087	0.352	0.015	0.863	0.013	0.886	- 0.033	0.746
MAGE processed, high sugar, & high fat	0.055	0.497	0.057	0.485	0.130	0.114	- 0.044	0.577	- 0.023	0.756	- 0.026	0.726	0.047	0.585

CHD, childhood; EAD, early adulthood; AD, adulthood; MAGE, middle-age; BP, Blood Pressure; Standard, Standardised
*Models adjusted for age, sex, education, smoking history, income, life-period physical activity, current dietary intake, other past dietary factors, and medication use. BMI: log10 transformed, Systolic BP and Diastolic BP: square root transformed, Triglycerides: log10 transformed.

In adulthood, a greater number of years spent in formal education was associated with higher scores on the 'non-traditional Australian' pattern. Having one or both parents from a non-Anglo background strongly predicted a higher score on the 'non-traditional Australian' dietary pattern in early-adulthood, which also positively predicted income. Childhood was the only life-period where physical activity was associated with a dietary pattern; it positively predicted the 'vegetable and non-processed' pattern.

Results did not substantially change when current dietary factors or the LDQ principal components were excluded from the models; the exception was for associations between the LDQ patterns and smoking history. In the primary models, when the variance from other past periods was controlled for, smoking did not predict any dietary pattern, but when the LDQ components were excluded, smoking history negatively predicted dietary patterns that had high loadings of vegetables, fruit, and were non-processed, or the healthful non-traditional Australian patterns.

One lifetime dietary pattern from childhood and two from adulthood significantly predicted markers of current cardiovascular health in the sample. Table 6.9 presents multiple regression models for the continuous outcomes, and Table 6.10 presents logistic regression models for the dichotomous outcomes.

Higher scores on the childhood 'traditional Australian' pattern predicted higher HDL cholesterol and a 3.6% reduced chance of using cholesterol medication. In adulthood, the 'processed, high-sugar and high-fat' pattern negatively predicted HDL cholesterol, and the non-traditional Australian pattern predicted a 6.2% reduced chance of cardiac medication use in later life.

Table 6.10: Lifetime dietary patterns as predictors of cardiovascular medication use

	Cardiac medications†		Cholesterol medications†		Hypertensive medications†	
Dietary pattern	OR	95% CI	OR	95% CI	OR	95% CI
CHD vegetable & non-processed	1.022	0.958,1.090	0.996	0.934, 1.061	0.958	0.903, 1.017
CHD traditional Australian	0.994	0.960,1.029	0.964	0.931, 0.998	0.978	0.949, 1.009
CHD coffee & high-sugar, high-fat extras	1.070	0.993,1.153	0.983	0.916,1.054	1.038	0.972, 1.107
EAD vegetable	1.005	0.951,1.062	1.022	0.968, 1.079	0.980	0.934, 1.029
EAD traditional Australian	0.973	0.930, 1.019	0.989	0.945, 1.034	1.003	0.963, 1.044
EAD non-traditional Australian	0.960	0.901, 1.024	0.997	0.938,1.059	1.002	0.949, 1.059
AD fruit & vegetable	0.970	0.913,1.030	1.031	0.973,1.093	1.014	0.963, 1.069
AD non-traditional Australian	0.938	0.886,0.993	0.995	0.943, 1.049	1.011	0.963, 1.062
AD processed, high-sugar, & high-fat	1.019	0.940,1.104	1.024	0.947, 1.107	1.001	0.933, 1.075
MAGE fruit, vegetable, & non-processed	0.989	0.941, 1.039	1.038	0.988,1.091	0.978	0.936, 1.023
MAGE non-traditional Australian	0.965	0.896, 1.039	1.020	0.948,1.096	1.026	0.960,1.096
MAGE processed, high-sugar, & high-fat	0.995	0.915, 1.081	0.975	0.898, 1.058	0.986	0.915, 1.062

Abbreviations: CHD, childhood; EAD, early adulthood; AD, adulthood; MAGE, middle-age
OR, Odds Ratio
* Logistic regression models adjusted for age, sex, current dietary intake, current physical activity, life-period physical activity.
†Medication use coded as 1.

For the medication outcomes, associations were not adjusted for possible shared variance with the other lifetime dietary patterns due to the limited number of covariates able to be included to ensure adequate power, but in each case, no more than one pattern was a significant predictor. It was reasonable to assume therefore that controlling for the other dietary patterns would not change the results.

6.6 Discussion

Lifetime dietary intake is a potentially modifiable environmental contribution to health and wellbeing in older age. The LDQ provides a possible means of assessing this intake in older cognitively healthy people, with dietary patterns extracted for each life period of the questionnaire proving to be a useful method of representing this intake.

Similar patterns to those extracted from the LDQ have been found in other studies across a variety of populations. A version of the sweets or desserts pattern has been found to be the most reproducible (Newby, Weismayer, Akesson, Tucker, & Wolk, 2006) and was present for all life periods of the LDQ except in early adulthood. The 'non-traditional Australian' pattern that emerged in three out of the four periods of the LDQ was comprised of many foods that have been associated in other studies with a 'prudent' style or healthful diet such as whole-grains, herbs, chicken and fish, fruit, olives and olive oil, red wine and grapes (Newby & Tucker, 2004); it was named 'non-traditional' in the current study to differentiate it from the 'traditional Australian' pattern. The 'traditional Australian' pattern also had high loadings from particular vegetables and fruits (such as lettuce, pumpkin, beetroot, grapes, and pears) but, in combination with other items such as ice-cream, vegemite (a yeast extract spread), butter, cream, and red meat, this pattern represented dietary intake that was more specific to an Australian population with a predominantly Anglo-Saxon heritage, particularly in the period when participants were children or young adults (Truswell & Wahlqvist, 1988) . The fruit and vegetable patterns found in both adulthood and middle-age are also common across multiple populations when dietary pattern analysis is applied to FFQs. Patterns dominated by fruit and vegetable intake are often also known as

'health aware' or 'healthful', to differentiate them from patterns high in processed foods or sweets (Newby & Tucker).

It is well established that dietary intake changes over time (Lake et al., 2004; Mishra et al., 2006; Weismayer, Anderson, & Wolk, 2006) and that these changes are determined by changes in individuals' social and demographic circumstances (Lake et al., 2004; Mishra, Prynne, Paul, Greenberg, & Bolton-Smith, 2004). The LDQ has been previously demonstrated to capture change in dietary intake over the life period (Hosking et al., 2011) thereby giving some validity to the long-term dietary recall process. Th**es**e findings have been strengthened by the results of the current study. When current diet was used to predict each of the past dietary patterns, the percentage of variance accounted for by current diet incrementally increased from childhood, where current diet only accounted for 7.6% of variance, to middle-age where current diet accounted for 41.5% of the variance in recalled intake for this later life period.

Age, sex, and markers of socio-economic status are robust predictors of dietary intake across a wide spectrum of populations (Kant, 2004; Pryer et al., 2001). These variables also predicted patterns from the LDQ after controlling for the influence of both current diet and other past dietary patterns; however, interpretation of these associations in the context of previous findings is challenging, given that no studies have followed the eating patterns of individuals over their whole lifetime. Dietary choices across life are determined by direct cohort effects, for example, the imposed frugality during World War II, and within-person effects, such as having greater disposable income at various life stages, or particular health concerns that necessitate dietary modifications (Wendt & Kinsey, 2007). In this cohort it was evident that participants' diet, as captured by the

dietary patterns of the LDQ, particularly reflected the influence of the cultural and social determinants of dietary intake across the various life periods.

A catalyst for change in Australian eating habits was the post-war influx of European migrants and the introduction of many previously unavailable foods and meal choices (Truswell & Wahlqvist, 1988). Accordingly, in this sample, having non-Anglo parents strongly predicted a non-traditional Australian diet in early adulthood. In this period also, being of older age negatively predicted this non-Australian pattern. Early-adulthood for the older participants would have spanned the late 1940s to the beginning of the 1960s and it is possible that the impact of European immigration had yet to be assimilated into mainstream dietary practices, which may explain the negative association.

Changes in food availability in Australia were also reflected by the older members' early life dietary patterns. Higher consumption of the 'vegetable & non-processed' pattern in childhood, and a 'vegetable' pattern in early-adulthood were predicted by older age; these were frugal eating patterns defined by high loadings from garden-grown vegetables and represents a diet common to the war and pre-war years in Australia (Truswell & Wahlqvist, 1988). For these older participants, the higher consumption of dietary patterns high in vegetables continued into adulthood also, with older age positively predicting the adult 'fruit and vegetable' pattern, and in middle-age, this more conservative diet was reflected by the negative association between age and the 'non-traditional Australian' dietary pattern.

Sex predicted dietary patterns in early-adulthood and middle-age. Differences in dietary patterns consumed by men and women are a robust finding in the dietary pattern literature and in general, women have been found to follow

healthier dietary patterns than men (Park et al., 2005; Villegas, Salim, Collins, Flynn, & Perry, 2004). This finding was replicated to some extent for the patterns from the LDQ; the exception was the higher consumption by males of the healthful 'non-traditional Australian' pattern in early-adulthood. This border-line association was unexpected and it is possible there were other unassessed socio-demographic variables confounding the relationship.

The relationship between higher educational attainment and healthy dietary choices has been well established (De Irala-Estévez et al., 2000; Mullie et al., 2010; Vlismas, Stavrinos, & Panagiotakos, 2009) . It is unknown however if this association is also historically relevant; although others did find that higher education positively predicted increased consumption of an ethnic foods and alcohol pattern during adulthood in the decade from 1989 to 1999 (Mishra et al., 2006). The adulthood 'non-traditional Australian' dietary pattern (which could be considered 'ethnic' during the relevant time period) had high loadings from herbs, peppers, all wine, olive oil, yogurt, seafood, whole grains, chicken and nuts; with negative loadings from butter, meat, bread and potatoes. This pattern was strongly and positively predicted by years of formal schooling. Formal education (including individuals' highest level of post-school qualification) would have been completed for the majority of people by adulthood; it is appropriate then that the association between higher education and a healthful diet emerged in this life-period.

Interestingly, the relationship did not carry through into mid-life. Given the relatively high amount of shared variance that was demonstrated between current dietary intake and diet in middle-age, it is theoretically possible that controlling for current diet in the model suppressed the association; however, supplementary analyses that excluded the current and other past dietary factors failed to reveal

any association between years of education, and healthy dietary choices in middle-age. It appears that for this life-period, there were other more influential factors that determined dietary intake.

Childhood was the only period in which physical activity specific to the life period was associated with a dietary pattern from the LDQ with higher levels of activity predicting the non-processed vegetable pattern. This is consistent with other findings of a positive relationship between healthier patterns of intake and higher levels of physical activity (Park et al., 2005; van Dam et al., 2003). In recent years the synergistic interaction of dietary choice and physical activity has been a widely promoted public health message (2004), with the aim of reducing the risk and incidence of disease in society. During the earlier years of the six decades covered by the LDQ however, physical activity and dietary choices may not have always been so closely related, which could explain the overall lack of associations between dietary patterns from the LDQ and historical levels of physical activity. Alternatively, the lack of associations between the lifetime dietary patterns and lifetime physical activity could be explained by some systematic error in long-term recall on both measures.

In fully adjusted models, smoking history was not associated with any of the dietary patterns during any lifetime period. This could be considered unexpected given that the relationship between smoking and dietary choices is a robust one in the literature (La Vecchia, Negri, Franceschi, Parazzini, & Decarli, 1992; O'Doherty et al., 2011; Whichelow & Prevost, 1996), however, when the influence of other lifetime patterns was not controlled for, smoking history significantly predicted dietary patterns. This finding suggests that lifetime smoking habits are not related

to variance specific to a particular life-period pattern, but are related to general dietary pattern variance that is common across life periods.

Given that lifetime exposures, including diet, contribute to older-age health outcomes, it was also of interest, for exploratory purposes, to investigate the associations between recalled lifetime dietary patterns and the specific markers of cardiovascular health that were measured in this cohort. Although it is well established that dietary intake impacts on cardiovascular outcomes in later life (Mente et al., 2009; Tourlouki et al., 2009), there is only scant evidence from longitudinal cohort studies as to the contribution of earlier life dietary influences on long-term outcomes. In the Boyd Orr cohort (Martin, Gunnell, Pemberton, Frankel, & Davey Smith, 2005), the association was examined between household diet during childhood, and cardiovascular-induced death post-30 and -50 years of age. Higher consumption of fruit and vegetables but lower consumption of fish was associated with lower stroke risk. These authors did not propose a mechanism for the fruit and vegetable association with later stroke risk but suggest the finding may have been due to confounding and should be reproduced (Ness et al., 2005). Higher HDL is protective against risk of stroke (Boden-Albala et al., 2008), and healthy levels are partly determined by dietary intake of fruit and vegetables (Bertsias, Linardakis, Mammas, & Kafatos, 2005). The childhood 'traditional Australian' pattern in the current study predicted HDL levels, and is a pattern primarily defined by higher loadings from both fruit and vegetables. It is possible that frequent consumption of these items during childhood may determine a life-time of habitual intake; thereby lowering the risk of unfavourable vascular outcomes via HDL maintenance.

Consumption of this childhood 'traditional Australian' pattern was also associated (at border-line significance (p = 0.05) with participants having lower systolic blood pressure. This finding adds support to the increasing evidence that early-life factors, including childhood diet, are important determinants of later-life hypertensive outcomes (Lawlor & Smith, 2005). The pattern is defined by factor loadings from spinach, tomatoes, pumpkin, nuts, and eggs; all of which are high in Vitamin E ("United States Department of Agriculture National Nutrient Database for Standard Reference, Release 24," 2011) . Relationships between Vitamin E intake from food in childhood, and cardiovascular health in mid-life were examined in the 1946 British birth cohort (Mishra, Malik, Paul, Wadsworth, & Bolton-Smith, 2003). No associations were found for the effect of intake during either childhood or middle-age alone, but lowest consumers of vitamin E in childhood, together with low intake at 43 years, were more likely to be hypertensive (Mishra et al., 2003). An additional explanation for the protective effect of the childhood 'traditional Australian' diet on later-life blood pressure measurement is via the potassium content of other higher loading foods such as apricots, bananas, citrus, melon, figs, nuts, tomatoes, and pears (He & Whelton, 1997; "United States Department of Agriculture National Nutrient Database for Standard Reference, Release 24," 2011).

Border-line significance (p = 0.05) was also found for the prediction of higher diastolic blood pressure by greater consumption of the 'vegetable' pattern in the early-adulthood period. The association between diastolic blood pressure and cardiovascular risk is not clear-cut in older adults and there is some evidence that higher diastolic blood pressure may actually be protective in this age group(Okayama, Kadowaki, Okamura, Hayakawa, & Ueshima, 2006) .

In contrast to the protective effects of the fruit and vegetable-based diets, those high in trans-fats or in foods with a high glycemic index are detrimental to cardiovascular health. The 20-year follow-up of the Nurses' Study cohort (Oh, Hu, Manson, Stampfer, & Willett, 2005) demonstrated that in 78,778 women free of coronary heart disease in 1980, trans fat intake significantly increased the odds of disease development particularly in younger or overweight women. In the current study, higher consumption of such a pattern (processed, high-sugar & high-fat) in adulthood was associated with lower levels of HDL cholesterol in older-age. Just as high HDL levels are protective, lower HDL is considered a risk factor for cardiovascular disease via its contribution to the atherosclerotic process, which, from early onset, takes many decades to develop the lesions that result in heart disease (Basile, 2004; Hansson, Robertson, & Söderberg-Nauclér, 2006).

One other lifetime dietary pattern predicted cardiovascular health in the EPOCH cohort. Current cardiac medication use was negatively associated with the non-traditional Australian pattern in adulthood; a similar pattern in many respects to a Mediterranean-style diet. It is defined by herbs, parsley, red and white wine, yoghurt, olive oil, seafood, chicken, and whole-grains. Given the empirical findings regarding the protective effect of such a diet in adulthood on later cardiac health (Willett, 2006), the association between this recalled dietary pattern, and the non-use of medications for cardiac conditions further contributes to establishing the validity of the LDQ.

6.7 Conclusions

This is the first known study to extract retrospective dietary patterns from across periods comprising an individual's whole life. Although precise estimates of intake over such a timeframe are impossible, the current exploratory analyses

have demonstrated the utility of a simplified, non-quantitative approach to gathering long-term food frequency data from older cognitively healthy people.

Building on these findings by replication is desirable. Doing so potentially provides valuable public health information regarding dietary modifications that are possible in earlier life periods so as to increase the odds of a healthier older age. Although it is acknowledged that error in recalled historical diet is an inevitable outcome of such an approach, as is some confounding by unmeasured environmental factors, it nonetheless offers a valuable and hitherto untapped contribution to unravelling the influence of early-life dietary choices on older-age health when long-term dietary information is otherwise not available.

SECTION C: LIFETIME DIET AND COGNIITIVE FUNCTIONING

Overview

The two studies presented in this section address the central objective of the thesis; to investigate whether lifetime dietary intake is associated with individual differences in healthy older adults' cognitive functioning. The first study is a submitted publication and reports the cross-sectional associations between the lifetime dietary patterns extracted from four life-periods of the LDQ and baseline cognitive functioning of the EPOCH cohort who contributed lifetime dietary data. The concluding study examines whether differential consumption of these same lifetime dietary patterns predicted cognitive change over 18-months of the EPOCH trial.

The cognitive outcomes of these two studies were factor scores on ten cognitive constructs. These constructs were derived from the Confirmatory Factor Analysis (CFA) of the 26 individual tests that formed the EPOCH test battery. The scope of the thesis does not include the design and analysis of the test battery, and these details have been published in the trial protocol (Danthiir, V. et al., 2011)[25]. An extract from a submitted publication (Danthiir et al., 2013) is included for reference as Appendix C and presents further detail regarding the derivation of the factor scores.

The cross-sectional and longitudinal associations between the LDQ dietary patterns and the cognitive constructs could have been examined simultaneously

[25] Link to EPOCH Protocol paper: http://www.nutritionj.com/content/10/1/117

using Linear Mixed Models and reported within the one publication. This approach was not applied because at the time of writing, the primary outcome of the EPOCH trial, (i.e. the impact of 18-months supplementation with Omega-3 fish oil on rate of cognitive change) had not been published.

The final chapter of Section C presents a concluding discussion of the thesis findings and implications, and identifies the challenges and directions for future research

Chapter 7 Lifetime Diet and Cognition: Cross-sectional Analyses

"Retrospective lifetime dietary patterns and cognitive performance in community-dwelling older Australians"

(Hosking, Nettelbeck, Wilson, & Danthiir, 2013).

7.1 Abstract [Publication 3]

Dietary intake is a modifiable exposure that may impact on cognitive outcomes in older age. The long-term aetiology of cognitive decline and dementia, however, suggests the relevance of dietary intake extends across the lifetime. We tested whether retrospective dietary patterns from the life-periods of childhood, early-adulthood, adulthood, and middle-age predicted cognitive performance in a cognitively healthy sample of 352 older Australian adults > 65 years. Participants completed the LDQ and a battery of cognitive tests designed to comprehensively assess multiple cognitive domains. In separate regression models, lifetime dietary patterns were the predictors of factor scores representing ten constructs derived by confirmatory factor analysis of the cognitive test battery. All regression models were progressively adjusted for the potential confounders of current diet, age, sex, educational attainment, English as native language, smoking history, income level, ApoE e4 status, past and present physical activity, other past dietary patterns, and relevant health variables. Lifetime dietary patterns predicted cognitive performance in this sample of older adults. In models additionally adjusted for intake from the other life-periods and mechanistic variables, dietary patterns from the childhood period alone reached significance. Higher consumption of the 'coffee & high-sugar, high-fat extras' pattern predicted poorer performance on Simple/Choice reaction-time, Working memory, Retrieval fluency, Short-term

memory, and Reasoning. The 'vegetable & non-processed' pattern negatively predicted Simple/Choice-reaction time, and the 'traditional Australian pattern' positively predicted Perceptual speed and Retrieval fluency. Identifying early-life dietary antecedents of older-age cognitive performance contributes to formulating strategies for delaying or preventing cognitive decline.

7.2 Introduction

Lifestyle approaches to delay cognitive decline and the incidence of dementia are of considerable interest; delaying disease onset and progression by one year would result in approximately 9.2 million fewer cases world-wide by 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Dietary intake is a modifiable exposure that potentially influences cognitive status in older-age via nutritional mechanisms that contribute to brain health and functioning (Gómez-Pinilla, 2008). Dietary intake is also implicated in the aetiologies of cardiovascular disease, diabetes, and stroke, all of which are risk factors for unfavorable later-life cognitive outcomes (Spiro & Brady, 2011).

Substantial evidence is accruing for both protective and detrimental effects of dietary patterns on older-age cognition (Gu & Scarmeas, 2011). The MeDi, together with patterns that share a similar profile (so those rich in vegetables, fruits, grains, and fish) are protective against risk of dementia and decline (Barberger-Gateau et al., 2007; Gu, Nieves, Stern, Luchsinger, & Scarmeas, 2010; Scarmeas, Stern et al., 2009; Scarmeas et al., 2006; Tangney et al., 2011; Wengreen, Neilson, Munger, & Corcoran, 2009), and in cross-sectional studies have been associated with better cognitive performance (Akbaraly et al., 2009; Nurk et al., 2010; Samieri et al., 2008; Samieri et al., 2013; Valls-Pedret et al., 2012; Wengreen

et al., 2009). Conversely, dietary patterns defined by processed foods high in saturated fats and sugar predict poorer cognitive functioning (Akbaraly et al., 2009; Torres et al., 2012).

A major challenge when determining dietary strategies for the maintenance of cognitive health is the appropriate timing of any intervention. A large portion of the intellectual variability that exists between older people is present by childhood (Deary et al., 2004), and cognitive ageing itself begins during early-adulthood (Salthouse, 2009). The brain pathology that underpins dementia accumulates over many years before clinical symptoms become apparent (Sperling et al., 2011), and is evident in mid-life for those that are genetically pre-disposed to Alzheimer's disease (Xiong C & et al., 2011). Therefore, the impact of diet on older-age cognition is likely to be a function of intake over the lifetime, with possible sensitive periods when dietary exposures are particularly salient (Benton, 2010b).

Only one known study has examined dietary patterns from an earlier life-period as predictors of older-age cognitive function. In the SU.VI.MAX 2 (Kesse-Guyot, Amieva et al., 2011) study, a 'healthy' pattern consumed at mid-life, defined by fruit, whole-grains, vegetables, and negatively correlated with meat and poultry, was associated with better cognitive scores thirteen years later (Kesse-Guyot et al., 2012). Currently, however, there are no cohort studies with comprehensive dietary data over multiple decades to assess the 'life course approach' to cognitive ageing (Richards & Deary, 2005) in the context of dietary intake.

Cognitively-healthy older people can recall general consumption frequencies for individual foods, and food groups, over multiple life-periods with reasonable reliability (Hosking et al., 2011). Additionally, dietary recall of earlier

intake has been demonstrated to capture dietary change, and to be associated with relevant

demographic and health outcomes (Hosking & Danthiir, 2013). Life-time dietary recall therefore offers a novel and practical solution to examining dietary intake and older-age cognition within a life-course framework.

The current study examined recalled dietary patterns from childhood, early-adulthood, adulthood, and middle-age as predictors of comprehensively measured cognitive outcomes in an older sample of cognitively healthy adults.

7.3 Methods

7.3.1 Design and participants

Participants were a sub-sample of the EPOCH trial; an 18-month double-blind, randomized, controlled trial of omega-3 fish oil on cognitive functioning in a community-dwelling population of older adults in Adelaide, South Australia (Danthiir, V. et al., 2011). Recruitment commenced in June 2007 and baseline data collection was completed by April 2008. A detailed account of the study's design and measures can be found in the study protocol (Danthiir, et al.). Participants were older adults aged 65-90 years, who had a score > 22/27 on a modified telephone administered Mini Mental State Examination (Newkirk et al., 2004), and lived in the greater metropolitan area of Adelaide, South Australia. Of the 390 eligible EPOCH trial members, 352 (90%) contributed lifetime dietary data. The study was conducted in compliance with the Declaration of Helsinki and followed Good Clinical Research Practice Guidelines. All experimental procedures were approved by the Human Research Ethics Committee of CSIRO Animal, Food, and Health Sciences. Informed consent was obtained from all participants. The current

study reports the cross-sectional relationships between dietary patterns, assessed by recall of dietary intake across the lifetime, and baseline cognitive measures from the EPOCH trial. All analyses were adjusted for demographic, lifestyle, and physiological variables.

7.3.2 Procedure

Participants completed multiple questionnaires to assess demographic, lifestyle, health, and wellbeing factors prior to the cognitive testing sessions held at the study centre (CSIRO Animal, Food and Health Sciences). Sessions were conducted in groups of up to seven people. A fasted venous blood sample was collected at baseline, together with measurements of height, weight, and blood pressure. After consuming a standardised breakfast, participants undertook the cognitive test battery that was administered by two trained research staff. The battery was divided into computer-based tasks and pencil and paper-based tasks, and took approximately four hours to complete, with 10 minute breaks given every hour.

Three months post-baseline assessment, participants collected their quarterly supply of study capsules (omega-3 fish oil or placebo) from the study centre and provided notification of any medication changes. During this visit, they were given the opportunity to complete the self-administered LDQ at home and return it to the study centre by post.

7.3.3 Lifetime diet

Lifetime diet was assessed by the LDQ, a measure of historical dietary intake covering all life periods from childhood to older age. The questionnaire's rationale and design have been detailed previously, together with its

reproducibility in an equivalent population (Hosking et al., 2011). Although the LDQ has not been validated against dietary records, support for the questionnaire's validity was demonstrated by the plausible associations found between earlier-life dietary intake as measured by the LDQ, and both demographic and late-life cardiovascular outcomes (Hosking & Danthiir, 2013). A brief description of the instrument follows. The questionnaire distinguishes between the life-periods of childhood (5-18 years), early-adulthood (19-30 years), adulthood (31-45 years), and middle-age (46-60 years) and uses a non-quantitative approach; response options are on a four-point scale: 'rarely/never', 'two-three times a month', 'two-three times a week' and 'daily'. The food groups and their items remain the same for each life period with exceptions being food items that were unlikely to have been consumed during a given period. The number of items ranged from 74 in childhood to 79 in early-adulthood, with adulthood and middle-age each having 78 items. Physical activity levels across all life-periods were also assessed as a proxy measure for energy expenditure. Level of physical activity associated with occupation was categorized as 'little', 'some', 'frequent', or 'heavy & frequent'. All other physical activity was assessed as frequency per week of (any or all) vigorous, moderate and light physical activity.

The variables representing lifetime dietary intake in the current study were dietary pattern factor scores from each distinct life-period of the LDQ. The dietary pattern analysis of the LDQ has been fully described elsewhere (Hosking & Danthiir, 2013) so is only briefly described in the following. Exploratory factor analysis (EFA) for ordinal variables was used to extract dietary factors from each life-period of the LDQ using M-plus (Muthén & Muthén, 2007). Each factor was

defined by the individual food items with the highest loadings on it (Hu, 2002), and these factors explained the following percentages of the shared variance amongst the questionnaire items for each life-period; 31.6% in childhood, 31.87% in early adulthood, 26.93% in adulthood, and 26.12% in middle-age. The extracted factors are listed below; the individual food items with loadings > 0.3 have been reported previously (Hosking & Danthiir, 2013).

Childhood: Factor 1 – 'vegetable & non-processed', Factor 2 – 'traditional Australian', Factor 3 – 'coffee & high-sugar, high-fat extras'.

Early-adulthood: Factor 1 – 'vegetable', Factor 2 – 'traditional Australian', Factor 3 – 'non-traditional Australian'.

Adulthood: Factor 1 – 'fruit & vegetable', Factor 2 – 'non-traditional Australian', Factor 3 – 'processed, high-sugar & high-fat'.

Middle-age: Factor 1 – 'fruit, vegetable & non-processed', Factor 2 – 'non-traditional Australian', Factor 3 – 'processed, high-sugar & high-fat'.

The naming of the dietary factors indicated the foods, or types of foods that defined the factor or (in the case of 'traditional' or 'non-traditional Australian') differentiated between types of diet based on their social determinants (Newby & Tucker, 2004). Dietary pattern scores were calculated by weighting individuals' frequency of consumption for each item by its loading on each of the dietary patterns and then summing the items (Moeller et al., 2007); these scores were used as predictor variables in the current study; a higher dietary pattern score equated to greater consumption with the exception of the childhood 'coffee & high-sugar, high-fat extras' pattern. For this pattern, all item loadings were negative, so its dietary pattern score was reverse-coded.

7.3.4 Cognitive outcomes

The cognitive test battery used in the EPOCH trial took a comprehensive approach to cognitive functioning with the inclusion of tasks to assess multiple cognitive domains. In particular, a number of the tests were chosen as indicators of cognitive speed constructs (Danthiir, Wilhelm, & Roberts, 2011), given that cognitive speed is a sensitive indicator, vulnerable to the effects of ageing, and arguably fundamental to higher-order abilities (Salthouse, 1996). The design, composition, and statistical analyses of this test battery have been fully described and reported in the EPOCH trial protocol (Danthiir, V. et al., 2011; Danthiir et al., 2013)[26]. Six speed-based and four accuracy-based cognitive constructs were derived from two confirmatory factor analytical (CFA) models of twenty-eight tests in total. In addition, a vocabulary task was used as a marker of crystallised knowledge. These constructs were found to be empirically distinct and the tests that defined them are listed below:

Speed constructs:

- Perceptual speed (Finding As, Number Comparison, Digit-symbol Coding)
- Simple/Choice-reaction time (simple, 2-choice, 4-choice)
- Speed of memory-scanning (Number and Letter Memory Scanning)
- Reasoning Speed (Number and Letter Odd-man-out)
- Inhibition (Simon task, Spatial and Colour Stroop)
- Psychomotor Speed (Simple, Up, and Diagonal Movement Tasks)

Accuracy constructs:

- Working memory (Operation Span, Counting Span)
- Retrieval Fluency (Word Endings, Categories)

[26] Included as Appendix C

- Short-term memory (Face Recognition, Word List Recall, Paired Associates)
- Reasoning (Raven's Standard Progressive Matrices, Letters Sets, Everyday Problem Solving)

Constructs derived by CFA exclude error variance and test-specific variance, and so represent only the shared variance between the two or more tests that define them. Construct validity and the reliability of assessment is thereby increased (Danthiir, V. et al., 2011). Factor scores were estimated for the cognitive constructs in the same manner as for the dietary patterns; scores on each of the cognitive test variables were weighted by their loading on the relevant factor and then summed.

7.3.5 Other variables

The acknowledged correlates of older-age cognitive status were assessed, in addition to lifestyle or health and well-being outcomes that could plausibly be related to lifetime dietary patterns. These measures were obtained during the course of the EPOCH trial. The full details for these measures are described in the trial protocol (Danthiir, V. et al., 2011), but listed below are the variables used in the current analyses.

Demographic variables: age, sex, years of education (school, tertiary and vocational), native language (a dichotomised variable representing English or other), a four-level parental income variable (constructed from parental occupation), and current income level (a 19- category variable following the Australian census 2006).

Health/lifestyle variables: years of smoking (calculated as pack years), BMI (kg/m2), systolic blood pressure, depressive symptoms (assessed by the Centre for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977)), medication use

for cardiac conditions, hypertension, and cholesterol levels (dichotomous variables representing usage or non-usage), and past physical activity (assessed by the LDQ), current physical activity (assessed by the Yale Physical Activity Scale (YPAS) (Dipietro, Caspersen, Ostfeld, & Nadel, 1993)).

Blood-based markers: ApoE geneotype (dichotomised as the presence or absence of the ApoE e4 allele), plasma homocysteine, LDL, HDL

Present and past dietary covariates: Recall of past dietary intake is known to be confounded and biased by current dietary measures (Friedenreich et al., 1992), therefore three EFA-derived pattern scores from the baseline response frequencies of the CCFFQ (Giles & Ireland, 1996) were included as covariates. In addition, all 12 past dietary factors were interdependent, so in order to allow the identification of any unique contribution by a past dietary pattern, principal component analyses were employed to create a set of four unrelated past dietary variables that accounted for the shared variance amongst all the other past dietary patterns (not including the pattern focused on as the main predictor in each model). Details of both the present and past dietary pattern analyses have been previously reported (Hosking & Danthiir, 2013).

7.3.6 Missing data

For the LDQ, those who had whole life periods (n=9) or > 80% of responses missing across any life periods (n=3) were excluded from missing value analysis. The remaining missing data in the LDQ were of two types: item non-response (mean per person = 6.43; SD = 10.79) and multiple consumption frequencies reported for a food item (mean per person = 1.06; SD = 0.55). The explanation and rationale for the treatment of missing data in the LDQ have been previously

(Hosking & Danthiir, 2013); all missing responses were imputed using EM (Dempster et al., 1977) implemented with Missing Value Analysis in SPSS for Windows statistical package version 17.0.1. There were minimal missing values for the cognitive data but these were estimated by Full Information Maximum Likelihood as part of the CFA of the test battery (Danthiir, V. et al., 2011). The small proportion of values missing on the continuous covariate data was estimated using the EM procedure; categorical data with missing values were dealt with by pair-wise deletion in analyses.

7.3.7 Regression models

Multiple linear regression models were used to examine the prediction of baseline cognitive performance by individual dietary patterns extracted from the life-periods of the LDQ. Separate models were performed with each cognitive factor score as the outcome variable predicted by each of the dietary pattern scores separately. Models were progressively adjusted for the following three blocks of covariate entries:

- Block 1: Age, sex, years of education, smoking history, income level (parents' income for the two earlier life-periods and current income for the two later life-periods), English as native language, presence of the Apoe e4 allele, and current dietary intake.
- Block 2: The four component scores representing past dietary intake excluding the predictor period of interest.
- Block 3: Systolic blood pressure, HDL cholesterol, LDL cholesterol, homocysteine, CES-D score, medication usage for cardiac conditions, hypertension, cholesterol levels, and depression. Variables in this block

were considered as potential mechanisms for associations between lifetime dietary patterns and cognitive outcomes.

In total, there were 24 predictors in each model. With a total sample size of 352 and, α = 0.05 (two-tailed), there was power of 0.8 to detect an f^2 effect size of 0.023 for the contribution of a single predictor (i.e. the dietary pattern) (Faul, Erdfelder, Lang, & Buchner, 2007).

Examination of the regression diagnostics in preliminary models demonstrated no violation of assumptions; in particular, high multicollinearity was not apparent amongst the dietary predictors (past and present) so the contribution of individual dietary patterns could be feasibly evaluated.

Alternate analyses were carried out without adjusting for current dietary intake; previous findings had indicated that current dietary patterns accounted for incrementally increasing amounts of variance in past dietary patterns across the lifetime (Hosking & Danthiir, 2013) so in later life-periods it was possible that past dietary effects were being confounded by current dietary intake.

7.4 Results

Descriptive statistics for the sample are presented in Table 7.1.

A total of 352 people (53.7% female) completed the LDQ, with an age-range of 65-91 years (M =73.12; SD = 5.47). 26.4% of men and 37.6% of women completed schooling to year 10 and 22.7% of men and 21.8% of women completed schooling to year 12. A bachelor degree was held by 8.2% of the sample.

Table 7.1: Descriptive statistics for the EPOCH sample who undertook the LDQ

Variable (*number missing*)	Mean	SD
Age	73.12	5.47
Years of education	12.91	4.16
Smoking history *pack years*[1] (*2*)	9.83	17.77
BMI, *kg/m²*	27.27	4.29
Systolic blood pressure, *mmHg* (1)	136.83	16.48
HDL cholesterol, *mmol/L* (*2*)	1.39	0.36
LDL cholesterol, *mmol/L* (*2*)	3.16	0.86
plasma homocysteine, *µmol/L* (*5*)	10.66	3.23
Medication use	% of sample	
Cardiac medication	26.4	
Cholesterol medication	25.9	
Hypertensive medication	42.3	
Depressive medication	6.5	
Sex (female)	53.7	
Apoe e4 allele carrier (*1*)	24.8	
Current income > Australian median for 65 yrs + (*24*)	44.4	
English speaking	95.7	
Parents' income (*20*)		
Low	21	
Medium/high	73.3	

[1]Pack years = (cigarettes/dayXyears of smoking)/20

Mann-Whitney non-parametric tests demonstrated there were no significant differences between LDQ participants and non-participants from the EPOCH cohort on any of the 10 cognitive constructs or in age (U = 6714.00, p = 0.823), level of education (U = 6378.00, p = 0.454), or baseline MMSE score (U = 6582.50, p = 0.891).

Table 7.2 and Table 7.3 present the standardised regression weights and their p-values for the relationships between each lifetime dietary pattern and the cognitive factors. After adjustment for current dietary intake, demographic and

lifestyle variables, in addition to the presence of the Apoe e4 allele (Model 1), the childhood 'vegetable & non-processed' pattern negatively predicted Perceptual speed, Simple/Choice reaction time, and Working memory. The childhood 'coffee, high-sugar, high-fat extras' negatively predicted Simple/Choice reaction time, and strongly and significantly negatively predicted all accuracy constructs. The remainder of significant associations for Model 1 were for the accuracy-based rather than the speed-based constructs. Working memory was negatively predicted by the early-adulthood 'vegetable' and 'non-traditional' patterns, the middle-age 'fruit, vegetable and non-processed' pattern, and positively predicted by the 'processed high-sugar and high-fat' pattern in adulthood. Short-term memory was negatively predicted by the 'non-traditional Australian' pattern in both early-adulthood and adulthood, When current dietary patterns were excluded as covariates, no additional associations were found between any of the life-periods and the cognitive outcomes (results not tabled).

Model 2 additionally controlled for the variance shared between the dietary pattern of interest and the other lifetime patterns. Significant negative associations remained between the 'childhood vegetable & non-processed' pattern and Simple/Choice-reaction time, and between the childhood coffee & high-sugar, high-fat extras' and all accuracy constructs. In this model, two additional relationships reached significance; the childhood 'traditional Australian pattern' positively predicted Perceptual speed and Retrieval fluency. As a final step (Model 3)the mechanistic variables were included in all models. The childhood 'traditional Australian' pattern remained positively associated with Retrieval fluency and the childhood 'coffee & high-sugar, high-fat extras' pattern remained negatively

associated with all the accuracy based constructs, and reached significance for Simple/Choice reaction time. The strength of significant associations between model 2 and model 3 changed very little. No other associations remained significant or reached significance.

Table 7.2: Lifetime dietary factors as predictors of the speed-based constructs [1]

Life time dietary pattern		Perceptual speed		Psychomotor speed		Inhibition[2]		Simple/Choice reaction time		Reasoning speed		Memory scanning	
		β weight	P value	β weight	P value	β weight	P value	β weight	P value	β weight	P value	β weight	P value
[3]CHD 'vegetable & non-processed'	Model 1	- 0.126	0.023*	- 0.093	0.098	- 0.090	0.123	- 0.124	0.028*	- 0.027	0.627	- 0.032	0.581
	Model 2	- 0.137	0.057	- 0.111	0.130	- 0.103	0.172	- 0.152	0.037*	- 0.029	0.696	- 0.061	0.414
	Model 3	- 0.091	0.205	- 0.061	0.411	- 0.096	0.212	- 0.122	0.104	- 0.017	0.827	- 0.019	0.806
CHD 'traditional Australian'	Model 1	0.015	0.784	- 0.012	0.824	- 0.076	0.181	0.014	0.807	- 0.005	0.933	0.057	0.318
	Model 2	0.151	0.038*	0.044	0.551	- 0.086	0.263	0.138	0.062	0.025	0.741	0.138	0.069
	Model 3	0.142	0.053	0.035	0.645	- 0.088	0.264	0.122	0.109	- 0.018	0.818	0.125	0.114
CHD 'coffee & high sugar, high fat extras'	Model 1	- 0.050	0.362	0.010	0.857	- 0.022	0.706	- 0.111	0.046*	- 0.063	0.251	- 0.019	0.741
	Model 2	- 0.011	0.866	0.067	0.325	- 0.002	0.978	- 0.132	0.055	- 0.097	0.156	- 0.028	0.688
	Model 3	- 0.033	0.619	0.044	0.514	- 0.010	0.887	- 0.150	0.030*	- 0.099	0.155	- 0.046	0.522
[4]EAD 'vegetable'	Model 1	- 0.098	0.092	- 0.045	0.446	- 0.044	0.474	- 0.033	0.579	- 0.001	0.983	- 0.021	0.733
	Model 2	- 0.071	0.356	- 0.011	0.892	- 0.032	0.685	0.015	0.853	0.009	0.909	- 0.045	0.429
	Model 3	- 0.062	0.414	0.003	0.973	- 0.031	0.702	0.029	0.714	0.020	0.801	- 0.031	0.701
EAD 'traditional Australian'	Model 1	- 0.040	0.486	- 0.058	0.303	0.035	0.556	- 0.020	0.729	0.010	0.863	- 0.006	0.918
	Model 2	0.051	0.563	- 0.076	0.391	0.128	0.166	0.062	0.494	0.046	0.607	- 0.025	0.788
	Model 3	0.015	0.866	- 0.121	0.178	0.110	0.237	0.026	0.775	0.013	0.892	- 0.067	0.478
EAD 'non-traditional Australian'	Model 1	- 0.125	0.040*	- 0.094	0.122	- 0.018	0.714	- 0.103	0.096	- 0.018	0.772	- 0.030	0.630
	Model 2	- 0.104	0.152	- 0.091	0.211	0.004	0.958	- 0.082	0.267	- 0.006	0.936	- 0.056	0.458
	Model 3	- 0.052	0.466	- 0.057	0.440	0.033	0.667	- 0.038	0.612	0.012	0.869	- 0.021	0.781

[1] Model 1 adjusted for current diet, socio-demographic variables, and Apoe- ε4 allele; Model 2 adjusted for other past dietary patterns; Model 3 adjusted for mechanistic health-related variables. *p < 0.05; **p < 0.01.[2] Reversed β sign for Inhibition, so a higher score equals better performance.[3]CHD: childhood; [4]EAD: early adulthood

Table 7.2 *(continued)*

Life time dietary pattern		Perceptual speed		Psychomotor speed		Inhibition[2]		Simple/Choice reaction time		Reasoning speed		Memory scanning	
		β weight	P value	β weight	P value	β weight	P value	β weight	P value	β weight	P value	β weight	P value
[3]AD 'fruit & vegetable'	Model 1	-0.072	0.232	- 0.038	0.537	- 0.020	0.757	- 0.015	0.809	0.015	0.808	0.007	0.913
	Model 2	0.004	0.968	0.020	0.839	- 0.068	0.502	0.001	0.993	- 0.002	0.980	- 0.005	0.958
	Model 3	- 0.015	0.878	- 0.004	0.967	- 0.067	0.508	- 0.005	0.933	0.013	0.899	- 0.020	0.842
AD 'non-traditional Australian'	Model 1	- 0.046	0.448	- 0.025	0.684	0.033	0.612	- 0.041	0.510	- 0.014	0.817	0.061	0.337
	Model 2	0.106	0.278	0.056	0.571	0.061	0.551	0.047	0.636	- 0.033	0.743	0.173	0.090
	Model 3	0.083	0.386	0.013	0.899	0.059	0.566	0.035	0.726	- 0.035	0.732	0.159	0.124
AD 'processed, high sugar & high fat'	Model 1	0.038	0.532	0.039	0.522	0.113	0.075	0.046	0.455	0.011	0.855	- 0.001	0.982
	Model 2	0.031	0.673	0.027	0.716	0.132	0.091	0.005	0.947	- 0.030	0.690	- 0.019	0.808
	Model 3	0.031	0.670	0.031	0.683	0.133	0.089	0.017	0.826	- 0.006	0.939	- 0.009	0.910
[4]MAGE 'fruit, vegetable & non-processed'	Model 1	- 0. 104	0.116	- 0.057	0.396	- 0.024	0.730	- 0.033	0.625	- 0.006	0.925	- 0.010	0.884
	Model 2	- 0.048	0.540	- 0.016	0.870	- 0.046	0.643	- 0.014	0.884	- 0.037	0.698	- 0.044	0.654
	Model 3	- 0.074	0.425	-0.015	0.873	- 0.067	0.501	- 0.027	0.783	- 0.040	0.678	- 0.047	0.640
MAGE 'non-traditional Australian'	Model 1	- 0.089	0.201	- 0.017	0.807	0.007	0.919	- 0.037	0.605	0.027	0.702	0.034	0.635
	Model 2	- 0.004	0.966	0.079	0.415	0.038	0.705	0.014	0.884	0.053	0.580	0.059	0.551
	Model 3	- 0.024	0.800	0.065	0.497	0.018	0.856	- 0.004	0.964	0.048	0.621	0.038	0.713
MAGE 'processed, high sugar & high fat'	Model 1	- 0.005	0.944	0.034	0.606	0.032	0.639	0.054	0.421	0.071	0.286	0.012	0.860
	Model 2	- 0.059	0.462	0.016	0.840	- 0.034	0.683	0.031	0.707	0.104	0.197	0.008	0.921
	Model 3	- 0.030	0.698	0.033	0.680	- 0.019	0.816	0.056	0.490	0.115	0.156	0.031	0.712

[1] Model 1 adjusted for current diet, socio-demographic variables, and Apoe- ε4 allele; Model 2 adjusted for other past dietary patterns; Model 3 adjusted for mechanistic health-related variables. *p < 0.05; **p < 0.01. [2] Reversed β sign for Inhibition, so a higher score equals better performance. [3]AD: adulthood; [4]MAGE: middle-age

Table 7.3: Lifetime dietary factors as predictors of the accuracy-based constructs[1]

Life time dietary pattern		Working memory		Retrieval fluency		Short-term memory		Reasoning	
		β weight	P value	β weight	P value	β weight	P value	β weight	P value
[2]CHD 'vegetable & non-processed'	Model 1	- 0.109	0.037*	- 0.096	0.056	- 0.096	0.054	- 0.090	0.077
	Model 2	- 0.038	0.575	- 0.068	0.292	- 0.041	0.527	- 0.020	0.756
	Model 3	0.014	0.833	- 0.044	0.513	0.003	0.965	0.016	0.808
CHD 'traditional Australian'	Model 1	- 0.042	0.415	0.011	0.830	- 0.023	0.647	- 0.046	0.352
	Model 2	0.092	0.175	0.165	0.012*	0.110	0.089	0.068	0.304
	Model 3	0.052	0.455	0.139	0.040*	0.076	0.252	0.033	0.631
CHD 'coffee & high sugar, high fat extras'	Model 1	- 0.144	0.005*	- 0.139	0.004*	- 0.163	0.001**	- 0.137	0.006**
	Model 2	- 0.128	0.043*	- 0.152	0.012*	- 0.179	0.003**	- 0.125	0.042*
	Model 3	- 0.131	0.038*	- 0.154	0.012*	- 0.180	0.003**	- 0.130	0.036*
[3]EAD 'vegetable	Model 1	- 0.121	0.028*	- 0.079	0.130	- 0.081	0.123	- 0.094	0.077
	Model 2	- 0.067	0.353	- 0.041	0.551	- 0.014	0.844	- 0.034	0.627
	Model 3	- 0.057	0.432	- 0.032	0.643	- 0.004	0.954	- 0.024	0.731
EAD 'traditional Australian'	Model 1	- 0.102	0.056	- 0.062	0.221	- 0.072	0.160	- 0.093	0.071
	Model 2	- 0.044	0.595	0.020	0.799	0.031	0.699	- 0.029	0.716
	Model 3	- 1.00	0.231	- 0.019	0.815	- 0.019	0.810	- 0.075	0.361
EAD 'non-traditional Australian'	Model 1	-0.150	0.009*	- 0.089	0.103	- 0.141	0.010*	- 0.106	0.056
	Model 2	- 0.091	0.182	- 0.048	0.467	- 0.088	0.175	- 0.050	0.434
	Model 3	- 0.066	0.331	- 0.032	0.633	- 0.066	0.309	- 0.028	0.680

[1]Model 1 adjusted for current diet, socio-demographic variables, and Apoe- ε4 allele; Model 2 adjusted for other past dietary patterns; Model 3 adjusted for mechanistic health-related variables. *p < 0.05; **p < 0.01. [2]CHD: childhood; [3]EAD: early adulthood

Table 7.3 *(continued)*

Life time dietary pattern		Working memory		Retrieval fluency		Short-term memory		Reasoning	
		β weight	P value	β weight	P value	β weight	P value	β weight	P value
[4]AD 'fruit & vegetable'	Model 1	-0.093	0.102	- 0.101	0.059	- 0.096	0.074	- 0.107	0.050
	Model 2	- 0.032	0.719	- 0.148	0.082	- 0.093	0.275	- 0.115	0.188
	Model 3	- 0.039	0.660	- 0.150	0.080	- 0.096	0.257	- 0.120	0.172
AD 'non-traditional Australian'	Model 1	- 0.102	0.074	- 0.100	0.063	- 0.130	0.017*	- 0.096	0.084
	Model 2	0.031	0.735	- 0.075	0.385	- 0.064	0.460	- 0.014	0.871
	Model 3	0.010	0.912	-0.085	0.329	- 0.076	0.381	- 0.040	0.656
AD 'processed, high sugar & high fat'	Model 1	0.075	0.189	0.021	0.695	0.042	0.438	0.032	0.562
	Model 2	0.077	0.268	0.038	0.563	0.032	0.628	0.043	0.524
	Model 3	0.100	0.148	0.057	0.389	0.050	0.447	0.064	0.349
[5]MAGE 'fruit, vegetable & non-processed'	Model 1	- 0.130	0.035*	- 0.046	0.431	- 0.090	0.127	- 0.093	0.120
	Model 2	- 0.076	0.387	0.042	0.611	- 0.019	0.822	- 0.028	0.745
	Model 3	- 0.065	0.457	0.053	0.531	- 0.010	0.904	- 0.018	0.836
MAGE 'non-traditional Australian'	Model 1	- 0.061	0.349	- 0.029	0.640	- 0.064	0.302	- 0.042	0.503
	Model 2	0.107	0.224	0.090	0.283	0.070	0.401	0.099	0.248
	Model 3	0.105	0.230	0.081	0.339	0.056	0.502	0.096	0.266
MAGE 'processed, high sugar & high fat'	Model 1	0..069	0.262	0.007	0.903	0.050	0.396	0.042	0.476
	Model 2	0.071	0.338	0.012	0.862	0.058	0.410	0.069	0.341
	Model 3	0.088	0.229	0.026	0.715	0.078	0.263	0.080	0.265

[1] Model 1 unadjusted; Model 2 adjusted for current diet, socio-demographic variables, and Apoe- ε4 allele; Model 3 adjusted for other past dietary patterns; Model 4 adjusted for mechanistic health-related variables. *p < 0.05; **p < 0.01.[4] AD: adulthood; [5]MAGE: middle-age

7.5 Discussion

In models adjusted for relevant demographic covariates, the Apoe e4 allele, and current dietary intake, lifetime dietary patterns predicted cognitive performance in normally functioning older adults. In models additionally adjusted for all other dietary patterns, the associations that remained were for the period of childhood only, with all three patterns from this period demonstrating associations with cognitive performance in older-age.

Adequate nutrition is essential for childhood cognitive development (Benton, 2008; Dagnelie & van Staveren, 1994; Heys et al., 2010), and cognitive ability in childhood is strongly related to cognitive ability across the lifetime (Deary et al., 2004). The period of childhood for these participants spanned varying periods of time during the years of the Great Depression, World War Two, and the early post-war years. During this period there were food shortages and food rationing; the availability of animal products was limited, and reliance on garden-grown vegetables was promoted by the government to combat food shortages (Gaynor, 2006). The childhood 'vegetable and non-processed' pattern could be a marker for early-life nutritional deprivation that was not captured by adjusting for parental income levels, given that both rich and poor alike were subject to limited food availability during these years (Collingham, 2012). This pattern was defined by garden grown vegetables, legumes, and an absence of animal products with the exception of oily fish.[27] It was negatively associated with all cognitive constructs, and after adjustment remained a negative predictor of Simple/Choice reaction time.

[27] Given the era of recall, the oily fish consumed is likely to have been tinned sardines or salmon; fish consumption at this time was relatively low in Australia compared to other nations and the fish industry was in its infancy (ABS, 1941)

Food shortages during the war years did not necessarily impact equally across the population with those living in some farming communities having greater access to a wider range, and possibly greater quantity of food (Gregory, 1996), as would have younger participants whose childhood dietary recall period extended into the 1950s when food production and supply had recovered from war-time austerity measures (Truswell & Wahlqvist, 1988). The childhood 'traditional Australian' pattern was defined by a greater variety of foods, and a higher score on this pattern may represent more adequate nutritional intake during childhood in comparison to the more frugal 'vegetable and non-processed' pattern. In adjusted models, this pattern positively predicted Perceptual speed and Retrieval fluency although for Perceptual speed, the association did not remain significant once the mechanistic variables were controlled for.

Consumption of a processed pattern in childhood contributes to childhood obesity which has been shown to predict higher blood pressure in adulthood (Lawlor & Smith, 2005). Hypertension is a well established risk factor for cognitive decline and dementia, and has been demonstrated to predict vascular brain injury in adults as early as the forth decade (Maillard et al., 2012). Hypertension during this particular life-period therefore provides a potential pathway by which a childhood diet high in fat and sugary foods may impact on older-age cognitive performance. However, it is interesting that when systolic blood pressure and hypertensive medications were adjusted for in the final model, the associations were not attenuated. It is possible that later lifestyle modification may have reduced adulthood hypertension so it did not continue into older-age. Alternatively, higher consumption of a 'processed' (high fat and sugar content) pattern in early childhood has been associated with lower overall IQ, and in

particular verbal IQ assessed at 8.5 years (Northstone et al., 2011). Early life childhood intelligence measures strongly predict older-age cognitive functioning (Deary et al., 2004) and for participants in the current study, greater consumption of the 'coffee and high-sugar, high-fat extra' pattern in childhood may have negatively impacted on cognitive performance via its influence on the development of childhood ability.

A comparison with the findings of others is difficult because very few studies have been able to test associations between dietary patterns from the relatively distant past (> a decade previously) and late-life cognitive outcomes. Mid-life consumption of a healthy pattern in the SU.VI.MAX 2 cohort was positively associated with global cognitive functioning in addition to verbal memory 13 years later (Kesse-Guyot et al., 2012). Unexpectedly, in the current study, there were no comparable associations between the dietary pattern scores for middle-age and any of the cognitive constructs in adjusted models. It was considered possible that in these models, adjusting for current intake suppressed associations, given the previously demonstrated strong relationship between current and mid-life dietary patterns in this sample (Hosking & Danthiir, 2013). Supplementary analyses, however, demonstrated this was not the case; when current diet was excluded, no further associations emerged. It could be argued that dietary patterns extracted from recalled intake over such a long period are of questionable validity; however, the LDQ was designed around the cognitive strategies known to underpin long-term dietary recall, such as the use of generic food memories (Smith, 1993), and life-period cue questions to contextualise dietary memories (Friedenreich, 1994). In addition, plausible associations between the lifetime dietary patterns and both demographic and cardiovascular variables have been previously demonstrated in

this sample (Hosking & Danthiir, 2013), which supports the validity of both long-term dietary recall and the dietary patterns extracted.

One of the main confounders of past diet memory is the impact of current diet on the recall process (Wu et al., 1988). The adjustment for current diet in all models was one of the study strengths which ensured that associations between the past dietary factors and cognitive performance were not driven by current intake.

An inevitable limitation to the study design is the problem of controlling for unmeasured life-period specific covariates that potentially would impact upon the findings. Despite the extensive range of theoretically relevant demographic, lifestyle, and health variables included in the analyses, it is acknowledged that confounding by unmeasured life-period specific covariates cannot be discounted. The determinants of dietary choice and behaviour are embedded within complex personal and social systems (Shepherd, 1999) Given the time-period across which dietary intake was being measured, covariate control could not be comprehensive. This is particularly relevant given the associations we have reported between dietary patterns consumed in childhood and cognition in later life. It would be of interest to explore these associations further by including additional appropriate early-life autobiographical information from participants in analyses.

Cross-sectional designs investigating the impact of current dietary exposures on measures of cognition are limited by the possibility of reverse causation. Preference for sweet foods may be influenced by changes in brain glucose metabolism that occur in those that develop dementia (Talbot et al., 2012) and such changes may determine dietary choices, rather than dietary intake impacting on cognitive outcomes. Although technically cross-sectional, the current

study assessed dietary intake from earlier decades preceding the periods when such changes are likely. This adds weight to the causal direction of dietary pattern predictions of the cognitive measures. Reverse causation is also possible because early-life intellectual ability impacts on later food choice (Gale, Deary, Schoon, & Batty, 2007). However, this was unlikely in the current study because the associations between dietary patterns and later life cognitive performance were all from the childhood period, when individuals' dietary choices would have been largely determined by their families; although the influence of parental intellectual ability on family diet cannot be discounted.

The extensive test battery available to assess multiple cognitive domains in this sample was one of the study's strengths. Constructs were measured by two or more tests which increased reliability, and the battery overall was designed specifically to be sensitive to the effects of ageing on cognitive abilities (Danthiir, V. et al., 2011).

This is the first known study to examine associations between recalled dietary patterns from multiple life-periods and older-age cognitive performance; replication of this approach is necessary and results from a sample of convenience cannot be generalised to other populations. Moreover, it is acknowledged that the LDQ from which the lifetime dietary patterns were derived is a new measure and further validity testing of the questionnaire is desirable.Investigation of associations between recalled dietary patterns and longitudinal cognitive change is also warranted. Additionally, assessing long-term dietary intake and late life cognition in culturally varied cohorts would be of interest.

The finding that dietary patterns from across the life-time significantly predicted cognitive performance over and above its associations with current diet

supports the relevance of earlier-life dietary exposures to later-life cognitive outcomes. After adjustment for the variance shared between the life time patterns, childhood was the only life-period for which dietary patterns remained significant predictors of later life cognitive performance. These preliminary findings are relevant in terms of identifying childhood as a 'critical period' for intervention to minimize the possibility of later cognitive deficits.

Chapter 8 Lifetime Diet and Cognition: Longitudinal Analyses

8.1 Introduction (Study 5)

The impact of lifetime dietary intake on cognitive functioning in older age was investigated by a cross-sectional design in the previous study. Level of cognitive performance was associated with recalled dietary patterns from childhood in a cognitively healthy sample of older participants. This was a novel finding and relevant in the context of identifying possible early-life modifiable dietary contributions to intellectual functioning in older age. As discussed in Chapter 1, however, a higher level of functioning is not necessarily associated with a more favourable trajectory of cognitive change in older age. A longitudinal design is necessary to evaluate the potential contribution of lifetime diet to cognitive ageing outcomes. Longitudinal studies can directly identify within-person change, between-person differences in within-person change, and the predictors of these differences (Sliwinski & Buschke, 2004). The objective of the following study, therefore, was to further investigate the impact of lifetime diet on older-age cognitive health by examining the 18-month longitudinal associations between the lifetime dietary patterns extracted from the LDQ (Hosking & Danthiir, 2013) and the cognitive factor scores derived from the test battery of the EPOCH trial (Danthiir, V. et al., 2011).

8.2 Method

8.2.1 Participants

The longitudinal analyses for this study was carried out in the same EPOCH sub-sample (n=352) as participated in the cross-sectional study reported in Chapter

7. Over the study duration of 18-months, 18 participants withdrew; 7 males and11 females (5.11%). The sample size at each testing point was: Baseline n=352; Session 2 (6 months) n=343; Session 3 (12 months) n=335; Session 4 (18-months) n=334.

Mann Whitney non-parametric tests were carried on the variables of age, MMSE score, years of education, medication use and depression score, the baseline cognitive factor scores, and the LDQ dietary pattern scores to determine if there were significant differences between participants who completed the study compared to those lost to attrition. Those who dropped out were significantly older and less educated with significantly different distributions for the scores on Reasoning speed and the LDQ patterns of early-adulthood 'vegetable' and middle age 'non-traditional Australian'.

The age range of the cohort was 65 to90 years, but the distribution for age was positively skewed so that 67% of participants fell within the 'younger' age range of 65-75 with 33% being older than 75.

8.2.2 Cognitive testing

The cognitive testing procedure for the EPOCH trial has been described in Chapter 7. Particular attention was given to minimising sources of irrelevant test score variability across the repeated assessment sessions. Where possible, the

participants were tested together in the same small group by the same personnel over the course of the study. A strict protocol and script were utilised during test administration, with participants being closely monitored to ensure response requirements were consistently adhered to across all testing occasions. Alternate, but equivalent, versions of tests sensitive to recall effects were used for all sessions; in particular, for those tasks assessing short-term memory, working memory, and retrieval fluency.

8.2.3 Cognitive variables

The cognitive test battery and its analysis have been described previously (Danthiir, V. et al., 2011) (See also Appendix C). Both the speed and accuracy confirmatory models were metrically invariant with factor loadings, intercepts, and variances being equal over time (Ferrer & Ghisletta, 2011).

The Method section of Chapter 7 (7.3.4) has outlined the use of the cognitive constructs as outcome variables in the analyses of LDQ dietary patterns as predictors of performance. For ease of reference, they are again repeated as follows:

Speed constructs: Perceptual speed, Simple/Choice reaction time, Memory-scanning speed, Reasoning speed, Inhibition, and Psychomotor speed.

Accuracy constructs: Working memory, Short-term memory, Retrieval fluency, and Reasoning.

8.2.4 Predictor variables

The lifetime dietary patterns previously extracted from the LDQ (Hosking & Danthiir, 2013) and implemented as predictors of baseline cognitive performance (Hosking et al., 2013) were the predictor variables in these longitudinal analyses.

The dietary patterns and the loadings from their defining foods can be viewed in Chapter 6, Tables 6.2 to 6.5.

Possible covariates were the same as previously reported in Chapter 7 and included the demographic and health variables measured in the EPOCH cohort that were theoretically relevant to older-age cognition and dietary intake. In addition, current dietary pattern scores and the principal component scores for past dietary covariates were included as potential confounders of associations between LDQ dietary patterns and cognitive change.

8.2.5 Individual growth curve (IGC) models

This method models average within-person change on an outcome variable over time and can examine the effects of predictors on between-person differences in the individual growth parameters; i.e. intercepts (the initial status) and the slopes (the pattern of change over time). Unlike the design requirements of ANOVA and MANOVA, IGC analysis is flexible enough to allow the number and spacing of time points to vary across persons, and to include those with missing data in analyses (Francis, Fletcher, Stuebing, Davidson, & Thompson, 1991).

There are two levels in IGC models. The Level 1 model refers to the model of within-person initial status and within-person rate of change over time. Each individual trajectory is summarised by regressing the observed record onto the average of the trajectories using ordinary least squares regression. No predictors are included in this model. If the effect of linear growth is not statistically significant, there is no need to perform further growth curve modelling analysis. The basic linear growth model is

$$Y_{ij} = \beta_{0i} + \beta_{li\,(}Time) + \epsilon_{ij}$$

Y_{ij} represents the repeatedly measured cognitive construct for individual *i* at time *j.*

β_{0i} represents individual's i's true initial status, i.e. the value of the outcome when Time = 0.

β_{1i} represents individual i's true rate of change over the study's duration.

Єij represents the portion of i's outcome that is unpredicted on occasion j.

The trajectory of change over time of an outcome variable is not necessarily linear; it may be quadratic or cubic. A quadratic trajectory has no constant increasing or decreasing slope but rather has a single stationary point so the shape of the average change trajectory may be U-shaped or parabolic. Cubic growth has two stationary points, with one peak and one trough which makes the trajectory S-shaped. To test whether a quadratic or cubic term for 'Time' improves model fit, the terms for 'Time', 'Time^2', and 'Time^3' are progressively included and the X^2 test is used to determine if there is a significant difference between the -2 Log Likelihoods of the successive models.

The level 2 model describes whether the rate of change varies across individuals in a systematic way. The growth parameters (i.e. the within-person intercepts and slope) of Level 1 are the outcome variables to be predicted by the between-person variables at Level 2. At this level, a predictor variable may be included to determine its impact upon between-person variation on the outcome variable. The errors are assumed to be independent and normally distributed, and the variance is assumed as equal across individuals. The Level 2 model with a cubic trajectory for 'Time' is:

$$Y_{ij} = \gamma_{0i} + \gamma_{1i}(Time) + \gamma_{2i}(Time^2) + \gamma_{3i}(Time^3) + \gamma_{4i}W_j + Є_{ij}$$

Y_{ij} represents the grand mean for the factor score of the relevant cognitive construct at Time t.

γ_{0i} represents the initial status of the cognitive construct for the whole sample at Time t.

γ_{1i} represents the linear slope of change for the cognitive construct for the whole sample at Time t.

γ_{2i} represents the quadratic slope of change for the cognitive construct for the whole sample at Time t.

γ_{3i} represents the cubic slope of change for the cognitive construct for the whole sample at Time t.

γ_{4i} is used to test whether a predictor (W_j) is associated with the growth parameters (i.e. initial status, linear growth, quadratic growth, and cubic growth).

ϵ_{ij} represents the variance unexplained by the predictor (Shek & Ma, 2011; Singer & Willet, 2003).

The values for (Time), ($Time^2$), ($Time^3$) are determined by the numerical values representing each point of assessment.

In the current study:

- Assessment at baseline was coded as 0,
- Assessment at 6 months was coded as 0.5,
- Assessment at 12 months was coded as 1 and
- Assessment at 18-months assessment was coded as 1.5.

Therefore;

$Time^2$ at baseline = 0, at 6 months = 0.25, at 12 months = 1 and at 18-months = 2.25

$Time^3$ at baseline = 0, at 6 months = 0.12, at 12 months = 1 and at 18-months = 3.37.

Potential predictors may also interact with Time to influence between-person variation in the outcome, in which case interaction terms between Time and the relevant predictor can be included in the model.

8.2.6 Statistical Analyses

Cognitive change, together with the potential impact of the LDQ dietary patterns upon that change was investigated by IGC analysis implemented in SPSS using the 'MIXED' procedure with ML estimation following the guidelines of Shek and Ma (2011).

8.2.6.1 Unconditional models

One-way ANOVA models with a random effect for the intercept of Time were

run for each of the cognitive constructs. These models assessed both the overall mean of the outcome variable and the amount of variation that existed at both the within- and between-person levels in the outcome variable (Singer & Willet, 2003). The intra-class correlation coefficient (ICC) was calculated for each construct to determine if there was adequate between-person variability evident in these outcomes to proceed with IGC; the higher the value, the more of the variance in the outcome is attributable to between-person rather than within-person differences. For each cognitive construct, unconditional linear, quadratic, and cubic growth models were then tested to determine the statistical significance of Time in the models and what shape of change best described the average person's trajectory.

8.2.6.2 n-3 Intervention group status

Participants in this sample were taking part in an intervention trial of n-3 fish oil on cognitive functioning so intervention group status was tested as a

predictor of cognitive change over time. If necessary, this groupXtime term could then be controlled for in subsequent analyses. Group status did not improve model fit for any of the cognitive constructs as determined by the X^2 difference test of the -2 log likelihood ratios between the two models. Group status was therefore discounted in subsequent analyses to keep models as parsimonious as possible.

8.2.7 Covariates

All baseline covariate measures could potentially interact with time to modify the association between LDQ dietary patterns and between-person differences in cognitive change trajectories. Therefore, each covariate to be included in the model also needed an interaction term with all Time parameters. Such a large

number of parameters reduces power to detect effects and leads to unreliable estimates (Tabachnick & Fidell, 2007). As a preliminary step, only those variables that were related to both the cognitive construct and the dietary pattern of interest at an alpha level of $p \leq 0.1$ were considered as potential confounders (the specific covariates for each model are included in the tables presented in Appendix E). The variables for systolic blood pressure and BMI, together with the blood-based markers of plasma homocysteine, LDL, and HDL were excluded. These variables had been defined previously as potential mechanisms whereby lifetime diet impacted on cognition (Hosking et al., 2013) and controlling for them would potentially partition out associations between the LDQ dietary patterns and cognitive change.

8.2.8 Preliminary models

Fixed effects in all models were Intercept, Time, relevant covariates, and their interaction terms with time. Random effects were Intercept and Time which varied by person. In preliminary models, the variables for age, Apoe-ε4 status, current diet, and the interaction terms of these variables with time were common to all models. Chronological age is an obligatory predictor variable in studies of cognitive ageing (Wahlin, MacDonald, deFrias, Nilsson, & Dixon, 2006) and Apoe-ε4, has been demonstrated to specifically predict decline (Schiepers et al., 2012; Wilson, Schneider et al., 2002). The pattern variables representing current diet were also common to all preliminary models due to due to the established confounding of past diet recall by current recall (as addressed in Chapter 3). When the LDQ interaction terms approached significance as predictors of cognitive change (an an alpha of $p < 0.1$), the models were then re-run; theoutcomes of these preliminary models can be seen in Appendix E. In the interests of parsimony, the covariate interaction terms with Time that were not significantly contributing to the model were then excluded.

In OLS (Ordinary Least Squares) regression carried out in cross-sectional data, residuals are assumed to be homoscedatic. With repeated measurements on the same individuals, the pattern of residuals is likely to be heteroscedastic and correlated over time (Singer & Willet, 2003). In IGC analysis it is possible to test residual covariance structures to identify which one is the best fit for the data and so improve statistical inferences. In these preliminary analyses an unstructured residual covariance structure (UN) was specified which makes no assumptions regarding the error structure and often offers the best fit (Shek & Ma, 2011).

8.2.9 Final models

When a LDQ dietary pattern significantly predicted cognitive change, the past dietary components and their interaction terms were then included. These variables controlled for the variance shared between a given LDQ dietary pattern and the other LDQ patterns. The unique effect of one LDQ pattern could not be identified without controlling for the variance shared with other patterns from across the life-period (Hosking & Danthiir, 2013).

In these models a first-order autoregressive covariance structure (AR1) was tested to see if it improved model fit compared to the UN residual covariance structure. An AR1 covariance structure assumes that the correlations between the residuals between two adjacent time points decrease over measurement occasions (Singer & Willet, 2003). Model fit was compared between the two specifications by comparing fit indices between the models where smaller values equated to better fit. For all final models, the UN covariance structure provided the better fit.

8.3 Results

8.3.1 Unconditional models

Table 8.1 presents both the ICC values and the shape of the change trajectories for the cognitive factor scores over the 4 time points of the study. For all constructs the ICCs are high and well above 0.25, the minimum value suggested by Shek & Mar (2011) indicating that the amount of between-person variance in the outcome cognitive factor scores makes IGC analysis an appropriate analytical approach.

Table 8.1: The ICCs and growth curve term for Time for the cognitive constructs

Cognitive construct	ICC	Time
Perceptual speed	0.90	Cubic
Psychomotor speed	0.89	Cubic
Inhibition	0.49	Quadratic
Simple/Choice reaction time	0.84	Quadratic
Reasoning speed	0.79	Linear
Memory scanning	0.85	Linear
Working memory	0.87	Linear
Retrieval fluency	0.80	Cubic
Short-term memory	0.80	Cubic
Reasoning	0.89	Linear

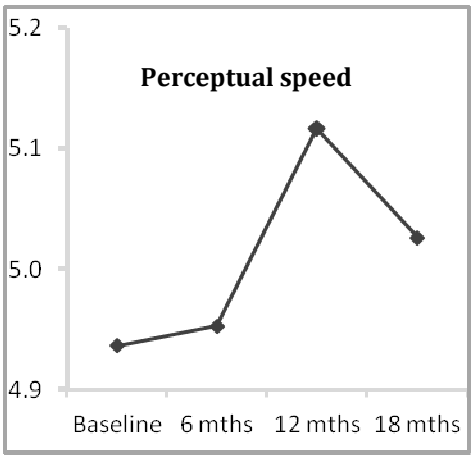
The parameter estimates from the unconditional Level 1 models were transposed into the model equation $Y_{ij} = \beta_{0i} + \beta_{li\,(}Time) + \epsilon_{ij}$. Prototypical plots enabled the average change over time to be visually represented for each of the cognitive constructs. These growth trajectories are presented in Figure 8.2 (speed-based constructs) and Figure 8.3 (accuracy-based constructs). For all constructs, a higher score equates to better performance.

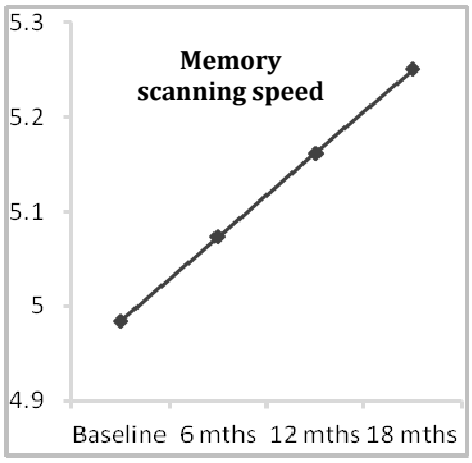
Average cognitive change over the study duration was heterogeneous across constructs in terms of both its direction and its trajectory. Inhibition[28], Retrieval and Short-term memory were the only three constructs that showed overall performance decrements. Inhibition displayed an inverted U shape trajectory, while Retrieval declined from baseline to 6 months and then from 12 months to 18-months. Short-term memory performance declined steeply from

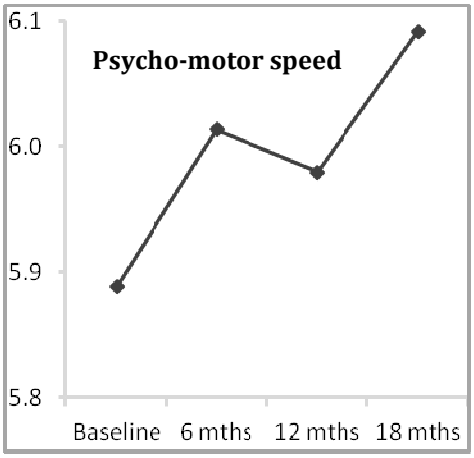
[28] For Inhibition, the direction of the parameter estimates was reversed so in line with other constructs, a higher value equated to better performance.

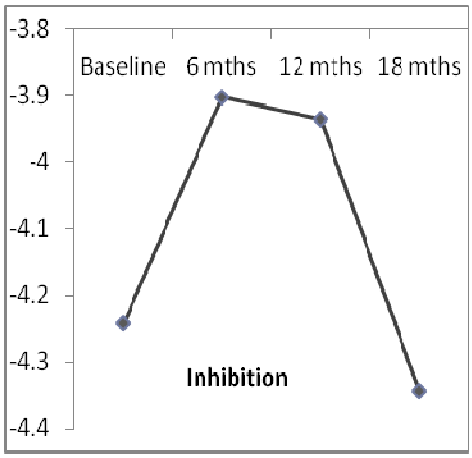
baseline to 6 months and then remained relatively stable across the remainder of testing points. Performance on all other constructs improved from baseline levels, although, as is apparent from the plots, the trajectories of change were not always linear.

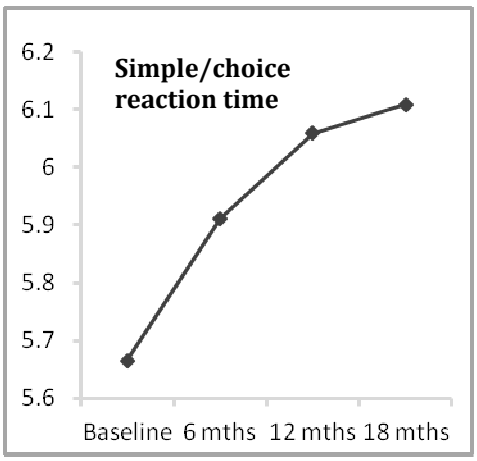
FIGURE 8.1: Average 18-month change: speed-based constructs











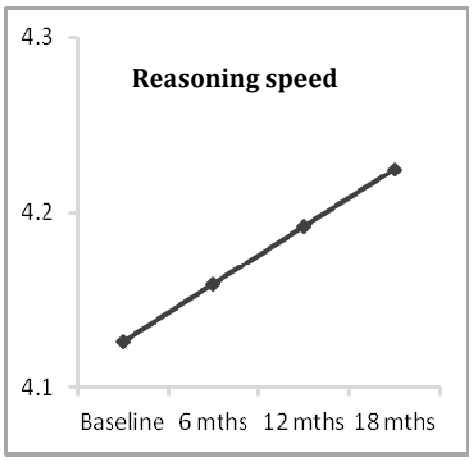
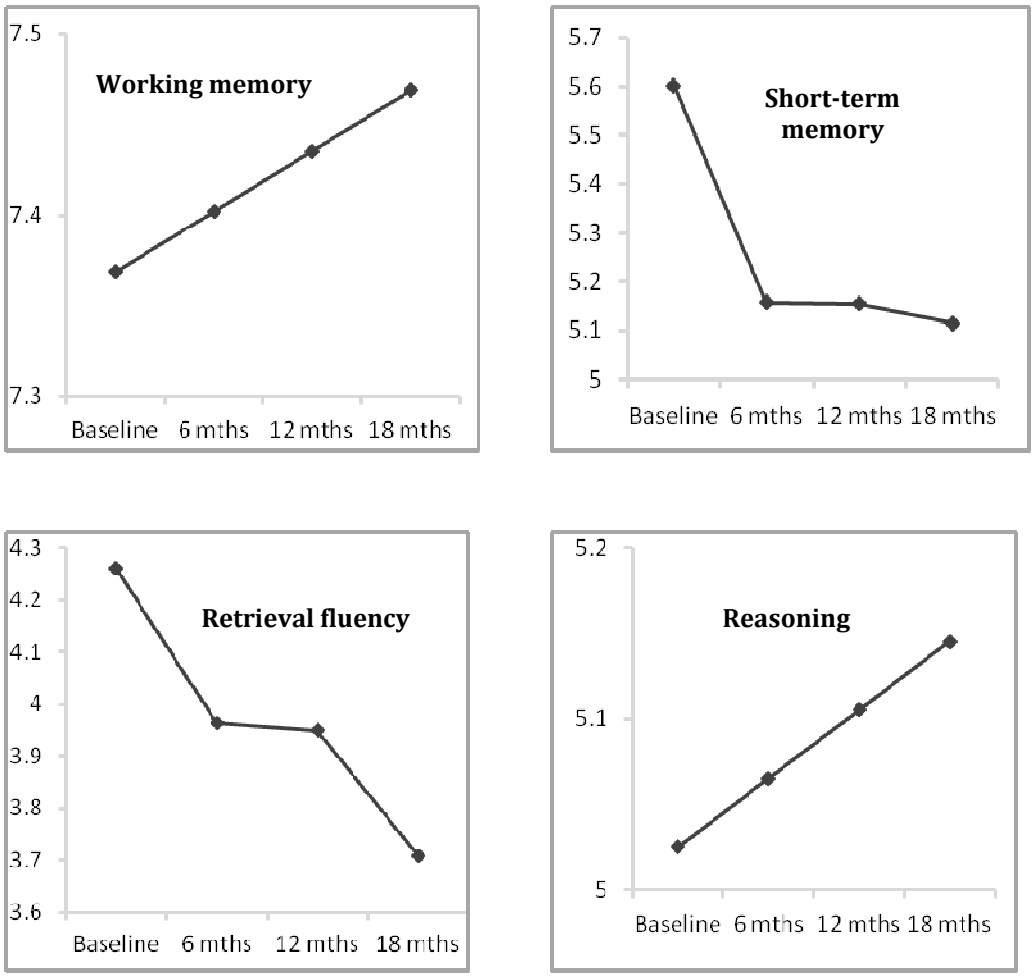


FIGURE 8.2: Average 18-months change: accuracy-based constructs



8.3.2 Level 2 models

In Level 2 models, the 'non-traditional Australian' pattern from middle-age predicted between-person differences in the rate and shape of change for Retrieval fluency and Short-term memory after adjustment for relevant covariates, including current and other past dietary patterns. Table 8.2 presents the parameter

estimates and their 95% confidence intervals for this LDQ dietary pattern variable, together

with the covariates tailored for each model. The plots showing the trajectories for a Retrieval and Short-term memory by the consumption level of a the 'non-traditional Australian' dietary pattern in middle age are presented as Figures 8.3 and enable visual interpretation of the parameter estimates given in Table 8.2.

Table 8.2: The 'non-traditional Australian' from mid-life and 18-month cognitive change

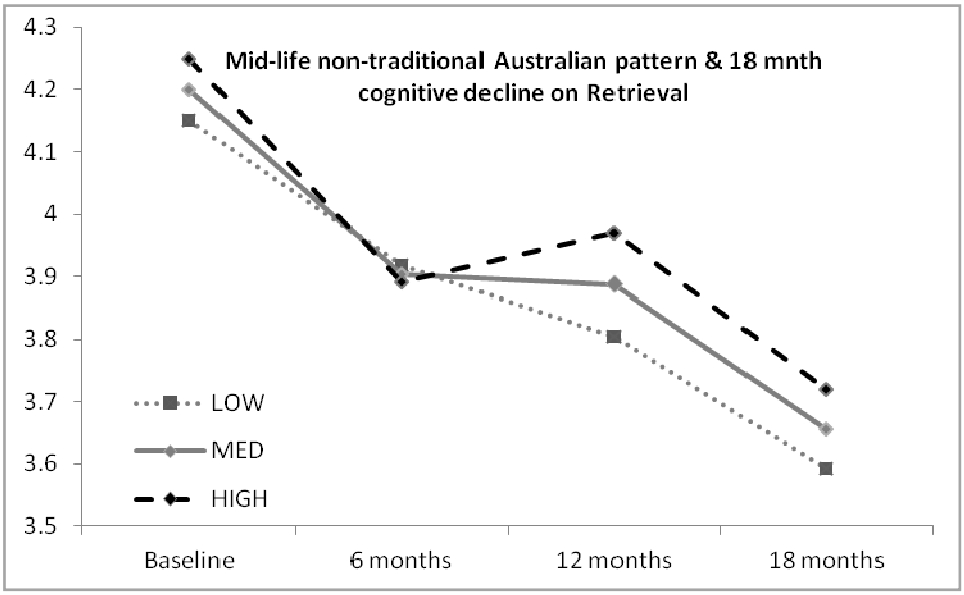
	Cognitive construct	Parameter estimate	P value	95% CI	Additional covariates*
MAGE_F2 Non-traditional Australian	Retrieval	- 0.103(Time) 0.191(Time^2) - 0.080(Time^3)	0.017 0.013 0.017	- 0.187, - 0.018 0.041, 0.341 - 0.146, - 0.014	Sex, income, pack years; Time interactions with sex, income, & past diet.
	Short-term memory	- 0.137(Time) 0.242(Time^2) - 0.103(Time^3)	0.002 0.002 0.002	- 0.223, - 0.520 0.091, 0.394 - 0.170, - 0.036	Sex, income, pack years; Time interactions with past diet.

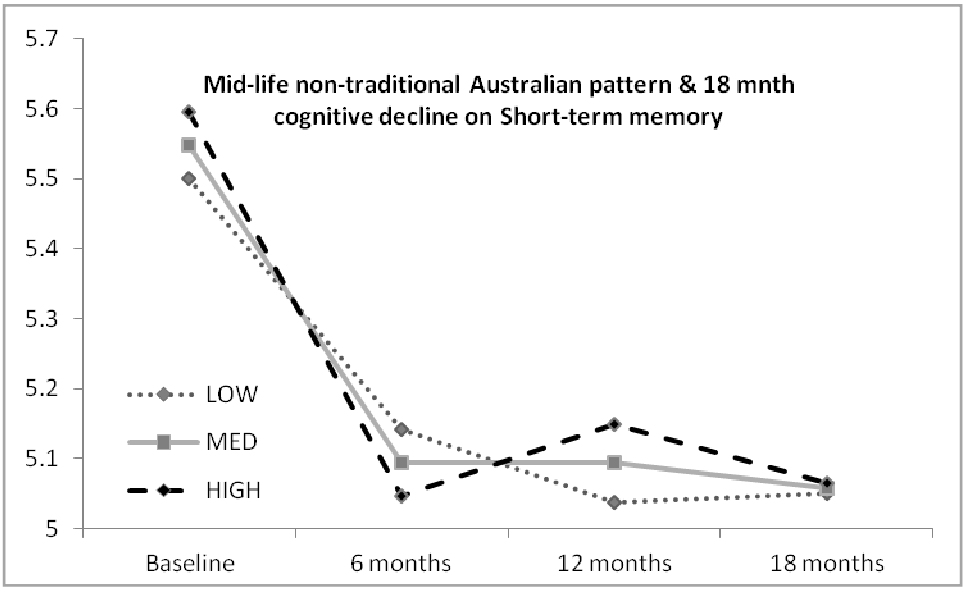
*Common covariates were age, apoe-ε4 status, current diet; interaction terms with Time were only included if these interactions had been significant predictors in preliminary models

These plots were created by using prototypical values for low, medium, and high dietary pattern consumption. Low consumption equated to the mean - 1SD of the pattern score; medium consumption equated to the mean pattern score; and high consumption equated to the mean + 1SD of the pattern score. All covariates assumed their mean value and so remained constant for the differing levels of LDQ dietary pattern consumption. The values for parameter estimates were substituted for the terms in the model equation for each different value of the LDQ dietary

pattern level. This process was automated through the SPSS MIXED procedure via the 'SAVE=FIXPRED command.

FIGURE 8.3: Cognitive decline predicted by the mid-life 'non-traditional Australian' pattern





These plots demonstrate the differential trajectories of cognitive change associated with the different consumption levels of this mid-life dietary pattern. High consumption compared to low consumption of the 'non-traditional Australian pattern' led to superior performance on Retrieval fluency, except at the 6 month time-point, with evidence of greater improvement from 6 to 12 months. For Short-term memory, differential consumption levels predicted slightly different change trajectories for this construct over time; in particular, with evidence of improvement rather than stability or decline from 6 to 12 months, although there was no difference in level of performance between the three consumption groups at 18-months.

One other dietary pattern, the 'vegetable and non-processed' pattern from childhood predicted Memory scanning where the term for Time was linear; Y=0.011(Time), p = 0.031, 95% CI (0.001, 0.021) but this association did not remain significant once the LDQ dietary patterns from the other life-periods were included in the model.

8.4 Discussion

Previous cross-sectional analyses demonstrated that recalled early-life dietary patterns from approximately five to seven decades in the past were associated with older peoples' cognitive status. The objective of this study was to further investigate whether lifetime dietary patterns predicted longitudinal cognitive change in the same sample.

The cognitive test battery designed for the EPOCH trial provided the opportunity to evaluate associations between LDQ patterns and cognitive change over 18-months in the context of a psychometric approach to cognitive ageing.

Multiple cognitive constructs were assessed and defined by the shared variance of two or more tests for each construct. Despite the general consensus that cognitive outcomes in nutritional studies need to move away from the use of global cognitive measures and small batteries of single neuropsychological tests (Macready et al., 2010; Schmitt, Benton, & Kallus, 2005; Wesnes, 2010), very few studies have been able to implement such an approach. In the current study the comprehensive and reliable measurement of multiple cognitive domains increased the potential for detection of subtle nutritional determinants of cognitive change (Danthiir, V. et al., 2011)

Average cognitive change over the 18-months of study duration was demonstrated as being heterogeneous across constructs and with all constructs except Inhibition, Retrieval fluency, and Short-term memory showing improvement between two or more testing occasions. Three possible sources of change across 18-months are due to development, re-test effects, and varying the tests or procedures during different measurement occasions (Zimprich & Rast, 2009). Typically, it would be expected that initial performance declines in older-age. However, performance stability or increase can occur depending on the length of follow-up and both sample and test-specific characteristics (Zimprich & Rast, 2009). Re-test or practice effects were not explicitly modelled for this sample, but others have found similar patterns of change due to retest effects at both the test and construct level (Trompet et al., 2010; Wilson, Beckett et al., 2002). Indeed, one study demonstrated that the improvement due to repeated testing was of the same order of magnitude as the entire, average age-related decline observed between ages 49 and 70, and to the average decline observed between 70 and 80 years (Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001). These authors found a strong

effect for socio-economic opportunity, with the more advantaged performing better than the less advantaged. Also, on difficult or complex tasks younger and more able people showed greater improvement (Rabbitt et al.). The current sample was well educated and relatively affluent. The majority of participants were under 75 years at baseline and, over the course of the study those who dropped out were significantly older. Therefore, practice effects could be expected, particularly for the complex tasks of Working memory and Reasoning.

Initial improvement did not persist over time for Perceptual speed and Inhibition and, in the case of Inhibition, 18-month status overall was lower than initial performance level, despite the improvement from baseline. Also, for Simple/Choice reaction time the performance increase from baseline to 12 months levelled off by 18-months. These findings are consistent with those of Wilson, Beckett et al. (2002) who suggested the benefit of practice gradually diminishes over time and varies greatly between constructs.

Practice effects in longitudinal studies have been cited as biasing longitudinal ageing trends due to their obvious potential to mask true decline (Salthouse, 2010a). Theoretically, therefore, in the current study the association between the middle-age 'non-traditional Australian' pattern and *positive* cognitive change should be interpreted within the context of practice/learning effects, and not necessarily as being protective against decline. Implicit in the phenomenon of practice effects, however, is the ability to learn, which may impact favourably upon developmental change (Hofer & Sliwinski, 2006). Further follow-up of this sample would clarify whether this was in fact the case; that is, whether higher consumers of the middle-age 'non-traditional Australian' retained their 18-month advantage

on Retrieval fluency that was seemingly bestowed by improvement from 6 to 12 months.

The 'non-traditional Australian' pattern in middle-age was the only LDQ dietary pattern to predict cognitive change in this sample after controlling for a comprehensive range of covariates and both current and other past dietary patterns. This pattern was defined by foods that in part characterise the Mediterranean diet such as olives and olive oil, herbs, peppers, seafood, fish, and red wine (Chapter 6: Table 6.5).

Protective effects of the Mediterranean diet against risk of AD have been demonstrated in four prospective studies from the Chicago Health and Aging Project (CHAP) (Gu, Y. et al., 2010; Scarmeas, Luchsinger et al., 2009; Scarmeas, Stern et al., 2009; Scarmeas et al., 2006). In this same cohort one study examined associations between MeDi adherence and cognitive decline (Tangney, Kwasny, Li, Evans, & Morris, 2010) and found higher MeDi scores (but not Healthy Eating Index Scores) were associated with significantly slower rates of decline over approximately seven years on a global measure of functioning (derived from four averaged *z*-scores for Immediate and Delayed Recall, the MMSE, and the Symbol Digit Modalities test). CHAP participants were all aged 65 at study entry however (Bienias, Beckett, Bennett, Wilson, & Evans, 2003). Associations between the dietary patterns assessed at mid-life and later cognitive change have been examined in one cohort only (Samieri et al., 2013). In the Nurses' Health Study, four repeated measures of diet over 13 years were used to assess adherence to the MeDi in women who ranged in age from 34-55 years in 1980, and cognitive assessments were carried out between 1995 and 2001. MeDi adherence was based

on averaging all four repeated measures of diet and no association was found with decline in either global cognition or verbal memory.

Given the dearth of comparative findings regarding the role of dietary patterns consumed in earlier life-periods on later life cognitive change, it is difficult to interpret our results in the context of others' findings. Nonetheless, there are some interesting points to be made.

No dietary patterns were associated with the average improvement that occurred over the study's duration for a number of the cognitive constructs. It is noteworthy, however, that for the two of the three constructs that showed decline, Retrieval and Short-term memory, that the between-person differences in within-person change were predicted by differing levels of the MeDi-like 'non-traditional Australian' pattern recalled from mid-life, and that this finding remained robust when both past and present diet were controlled for. The MeDi diet is the only dietary pattern that has been shown consistently to reduce the risk of AD and MCI in older populations and, as discussed previously (Chapter 2: 2.3.4), there is a strong rationale for its positive effects on cognition via antioxidant, anti-inflammatory, and vascular pathways.

As was discussed in Chapter 1, mid-life is a sensitive period in defining later-life cognitive trajectories due to the increased risk of vascular disease and metabolic syndrome, which impact unfavourably on brain structure and functioning leading to greater risk of decline. It is not unexpected, therefore, that relatively greater consumption of the 'non-traditional Australian' dietary pattern at this time would be advantageous. What is puzzling, however, is the lack of association between the other mid-life dietary patterns and any of the cognitive constructs. The 'fruit, vegetable and non-processed pattern is a particularly healthy

pattern and could equally be expected to impact positively, and higher intake of the 'processed, high-sugar and high-fat' pattern would be potentially deleterious.

The exploratory approach to define dietary patterns has been criticised within nutritional epidemiology because the patterns are determined solely by statistical relationships within the data; they do not provide mechanistic information regarding the specific quantities or qualities of the diet that drive the association (or lack thereof) with a given outcome (Michels & Schulze, 2005). An explanation for the specific association between the 'non-traditional Australian' pattern recalled from middle-age and reduced decline is that the olives and olive oil, which have relatively high loadings on this dietary pattern, are the main source of its protective effects. High olive oil consumption is one of the defining characteristics of the MeDi and contributes to the established cardiovascular benefits of this diet (Huang & Sumpio, 2007).

Although only one dietary pattern predicted cognitive change in this sample, the relevance of alternate dietary patterns to cognitive decline cannot be discounted. Average performance on the majority of constructs either improved or stayed relatively stable over the study duration. Studies of cognitive ageing with similar comprehensive cognitive measures (Sliwinski 2004, Dixon 2004, Wilson 2004, Rabbitt 2004) have shown decline on such constructs over longer follow-up periods. Other lifetime dietary patterns may therefore be relevant in predicting differential trajectories of this decline.

Confounding from some other lifestyle or socio-demographic variable specifically associated with recalled consumption of the 'non-traditional Australian' pattern is also a possible explanation for this pattern's singular association with cognitive change. The determinants of dietary choice and

behaviour are embedded within complex personal and social systems (Shepherd, 1999). Consequently, despite comprehensive covariate control in analyses, unmeasured variables may explain the relationship.

Previous cross-sectional analyses in this sample found that recalled dietary patterns from childhood alone were associated with better cognitive status after controlling for relevant covariates. The subsequent finding in these longitudinal analyses was that a quite different dietary pattern at mid-life predicted cognitive change. These preliminary findings support the theoretical proposal that differential dietary intake should inform the life-course approach to cognitive ageing. That is, that there may be critical and/or sensitive periods in development when specific dietary patterns are relevant to initial cognitive ability and to later rate of decline (Benton, 2010b).

Chapter 9 Concluding Discussion

9.1 Summary of Findings

The chapters from Section A provided a rationale for the influence of lifetime dietary intake on individual differences in cognitive ageing outcomes later in life. However, the empirical investigation of this potentially modifiable determinant of later-life cognitive health has been impeded by the lack of very long-term dietary records, together with the general consensus that retrospective dietary data from the distant past lacks reliability (Willett, 1998; Wu et al., 1988).

Studies 1 to3 investigated the reliability and validity of long-term dietary recall using the LDQ. This new measure of past diet assessment utilised the principle demonstrated by Smith (1991) that dietary memory draws on generic scripts of eating behaviour rather than precise or detailed recall of individual instances of eating. Thus, in the LDQ, participants were asked to recall their perceived average consumption frequencies of food items for any given life period on a *limited* frequency scale of four options only: Rarely/Never, 2-3 times a month, 2-3 times a week, or daily. Using these consumption frequencies, Study 1 demonstrated good recall consistency between an individual's recall of their diet from 5 years earlier, and a co-habiting family member's recall of the same person's diet from the same period. Study 2 utilised a sample of older people and extended the duration of recall to encompass multiple life periods. Reproducibility of the measure was equal to, or exceeded that found in reliability studies of relatively short-term dietary assessment instruments, and there was preliminary evidence that the measure captured dietary change also (Hosking et al., 2011).

The questions remained, however, as to whether lifetime dietary memories were valid, and whether such general dietary information was useful. Study 3 used dietary pattern methodology to instantiate lifetime dietary recall, which provided the means to investigate its relationship with outcome variables. Lifetime dietary patterns extracted from the LDQ were found to be associated with plausible demographic and cardiovascular health variables in an older sample of participants, even when the influence of current dietary intake was accounted for.

The associations between dietary patters and cross-sectional and longitudinal cognitive functioning were investigated in Studies 4 and 5 respectively. Study 4 found that dietary patterns from the period of childhood alone predicted cross-sectional associations with six of the 10 cognitive constructs assessed. There was less evidence of longitudinal relationships between lifetime dietary patterns and cognitive change, but higher consumption of the 'non-traditional Australian' pattern from middle age predicted a more favourable trajectory on Retrieval fluency and Short-term memory.

Establishing nutritional contributions to individual differences in older-age cognition using associational studies is challenging due to the potential mediating and/or moderating effects of numerous lifestyle and environmental factors. One of the strengths of these two studies was that they measured a comprehensive range of covariates including those from earlier-life periods such as levels of physical activity, parental ethnic background, and parental occupation level. Also, when determining the association between any given dietary pattern and cognitive construct, the influence of both current diet and the other past dietary patterns was accounted for in analyses, thus enabling the specific contribution of a particular dietary pattern to be identified.

9.2 Implications of Findings

The possibility that long-term dietary recall by older people may provide valid and useful dietary information from the distant past has important methodological implications for life-course epidemiology in general and the life-course approach to cognitive ageing in particular.

9.2.1 Implications for life-course epidemiology

Using retrospective data to inform life-course studies of older-age health outcomes is not a novel approach; a group of researchers in the United Kingdom devised and tested a 'life-grid' method to collect retrospective socio-demographic and health data. They argued that retrospective data, if deemed reliable, may provide very useful additional and complimentary information to longitudinal cohort studies of chronic disease. Birth cohorts either take a long time to yield results, or are confined to the period of expected disease manifestation, so earlier-life influences are necessarily neglected. Even if participants from earlier 'dormant' cohorts such as the1936 Lothian Birth cohort are re-contacted decades later, the scope of investigations may be limited by the information missing from the years between follow-ups (Blane, 1996).

Berney and Blane (1997) demonstrated that early-life socio-demographic and health information was well-recalled in a small sample of older adults who were followed up after 50 years. Dietary information, however, appeared to be recalled with disappointingly low accuracy, with only 15% agreement between recall of diet in childhood and the dietary records collected. Although, unlike the other variables assessed, no information was provided as to the metric used for

recall, or how this compared with the original assessment metric of the Boyd-Orr food records [29].

The fact that diet has a crucial role in the long-term aetiology of most chronic diseases is well recognised (Darnton-Hill et al., 2004). Until relatively recently, however, the main method of investigating diet-disease associations was by examining the relationship between the disease outcome and single, or groups of nutrients (Hu, 2002). Nutrient values could be obtained from FFQs, but only if detailed frequency and portion size information was included to allow consumption to be quantified. For example, as grams per day of a particular item (Willett, 1998). Given the imprecision of long-term memory for such detail (addressed in Chapter 3), estimating nutrient intake from long-term retrospective quantitative FFQs was not likely to be valid.

The growing use of dietary pattern methodology has provided an alternative and complimentary approach to uncovering associations between diet and health or disease outcomes (Hoffmann, Schulze, Boeing, & Altenburg, 2002). Dietary patterns are derived from statistical associations between the foods consumed and can be determined whatever the metric of consumption frequency[30]. The dietary patterns derived from the LDQ drew on generic food memories and used a limited frequency scale. Potentially, such dietary patterns could contribute to investigations that aim to identify the interactions between

[29] A couple of pertinent observations can be made here. Firstly, in this study there were only a small number of people with original dietary information (n=22). Also, these records did not consist of individual dietary intake but rather recorded the weight of household food consumed over 1 week. Quantities were divided by the number of people in the household, and then analysed to produce per capita estimates of some individual foods and overall nutrient intakes (Maynard, Gunnell, Emmett, Frankel, & Davey Smith, 2003; Ness et al., 2005). Equivalence between measures is therefore difficult to evaluate.

[30] If frequency of consumption is defined by an ordinal or dichotomous scale, the appropriate correlation matrix for analyses should be specified. Dietary pattern analysis based on a Pearson's correlation matrix is not appropriate for this type of data. Chapter 6 (6.4.2) addressed this issue.

diet and other biological or environmental factors throughout the life-course that determine the onset and progression of chronic disease.

9.2.2 Implications for the life-course approach to cognitive ageing

There is growing recognition that cognitive health, like other health outcomes, is a product of interactions between numerous biological, environmental, lifestyle, and psycho-social factors (Deary et al., 2009), and that confining measures of risk factors to late life does not capture their potential impact from earlier life-periods (Singh-Manoux & Kivimäki, 2010). The findings from Studies 4 and 5 represent the first time an attempt has been made to test associations between recalled dietary intake from across the whole lifetime and older-age cognitive functioning. It should be emphasised that these results are preliminary and the approach needs to be refined and explored further. Notwithstanding this caveat, the findings have implications for elucidating the role of diet in determining cognitive health in older age.

The recognition of the long-term aetiology of cognitive decline has led to a focus on lifestyle approaches to prevent, or at least delay its onset. In Australia, dementia has been specifically targeted by the Government for such prevention-oriented research as evidenced by its inclusion as a 'National Health Priority Area' (AIHW, 2013). Like other chronic diseases such as heart disease, diabetes, and cancer, the impact of environmental factors likely occurs long before symptoms appear.

Results of Study 4 suggest that even diet in childhood may be relevant to cognitive status in old age. Within a life-course framework of healthy ageing this is not entirely unexpected because childhood and pre-natal environmental exposures

have been linked to later health outcomes such as blood pressure (Lawlor & Smith, 2005), respiratory disease, and obesity (Power & Hertzman, 1997). Chapter 2 outlined the critical role of adequate nutrition to childhood intellectual development; if the effect of childhood diet reverberates across multiple decades to also impact upon older-age cognitive status, then this is additional evidence for the critical relevance of appropriate dietary intake in childhood.

Recently, analyses in the Lothian Birth cohort have been presented to support the hypothesis that it is in fact intelligence in childhood that accounts for associations between diet and cognition later in life. The stable trait of intelligence accounts for both better dietary choices and better older-age cognition (Corley, Starr, McNeill, & Deary, 2013). With these findings in mind, assessing the recalled childhood diets of the Lothian Cohort would also be an interesting avenue for exploration with the aim of further untangling the complex associations between dietary intake, socio-economic factors, and intelligence outcomes in this sample of older adults who have extant childhood measures of intelligence.

The protective effect of the middle-age 'non-traditional Australian' dietary pattern on two of the three measures that showed decline in Study 5 is in accord with other research that has demonstrated that consumption of a MeDi-type diet is associated with reduced odds of later decline (Scarmeas, Stern et al., 2009; Scarmeas et al., 2006). However, in the Nurses' Health Cohort, no associations were found between MeDi consumption in midlife and later life cognitive decline over two time points (Samieri et al., 2013).

Theoretically, middle-age is a particularly viable period for dietary intervention, given the relevance of diet to vascular health and the importance of vascular integrity to later cognitive functioning (Warsch & Wright, 2010). The

findings from Study 5 provide encouraging, albeit very preliminary, support for the possibility that modification of diet during this period may contribute to cognitive health in later life.

Overall, the findings from Studies 4 and 5 indicate that dietary influences on older-age cognition may stem from periods prior to older age, yet the majority of observational studies, and certainly clinical trials, assess dietary intake in late life. As reported in Chapter 2, the few positive trials of nutrient supplementation in older adults included 'younger' older adults. Interestingly, one of the only trials that has found a positive effect of an Omega-3 fish oil intervention on cognitive functioning was conducted in a cognitively healthy population of adults aged 18-45 years (Stonehouse et al., 2013).

These findings confirm that the nutritional determinants of cognitive change can operate prior to older-age. Although some studies have examined midlife nutritional determinants of dementia risk (Devore, Grodstein, & van Rooij, 2010; Laurin et al., 2004) or cognitive decline (Cadar et al., 2012), no studies were identified within the psychometric tradition of cognitive ability measurement that included dietary intake as a potential modifier of cognitive ageing trajectories in a midlife or early older-age cohort. Although some included other lifestyle, demographic, or health variables (Dixon & de Frias, 2004; Rabbitt et al., 2004; Schaie, 2005). Including dietary measures in such future studies may further elucidate the plausible association between midlife consumption of a MeDi-type diet and individual differences in the direction and rate of cognitive change.

9.2.3 Implications for the interpretation of older-age diet and cognition associations

Studies that have assessed the association between diet and cognitive functioning in older-age have provided some evidence for the contribution of nutritional factors to more favourable outcomes (Morris, 2012; Smith & Blumenthal, 2010); however, without accounting for dietary intake from earlier life-periods there is no certainty that it is older-age diet driving such associations. Study 3 demonstrated that although diet changed across the lifetime, 'current diet' (diet assessed post 65 years) was incrementally related to diet from each of the other life-periods with the weakest association being with childhood diet, and the strongest association was with diet in middle age. It is possible, therefore, that any apparent dietary effects on older-age cognition could be, at least in part, due to the relationship between older-age diet and dietary intake from earlier life-periods. No studies were identified that controlled for intake from previous life-periods when investigating the associations between dietary intake and older-age cognitive functioning. Clearly, such information would be informative when trying to identify the antecedent role of dietary factors in defining older-age cognitive health. The preliminary findings of reliability and validity for long-term dietary recall, demonstrated in Studies 2 and 3 respectively, suggest that the use of appropriately assessed retrospective dietary information may provide an option to address this problem when long-term dietary records are lacking.

9.3 Challenges and Future Directions

The development of a dietary assessment instrument to capture lifetime diet presented a number of methodological challenges, including missing data and the lack of dietary records to test further the validity of the LDQ. The following

sections address these issues in the context of future research directions, together with an additional approach to elucidate the potential cumulative effect of either a detrimental or healthful diet on cognitive health in older-age.

9.3.1 Missing data

When the single life-period of the LDQ was administered to a group of predominantly young adults and their family members (including parents), missing responses were minimal (1.6 %). The older samples of participants, however, were required to complete the 74 – 79 questionnaire items four to five times (representing the four to five life-periods assessed), which required commitment and concentration, and would have been quite a burdensome undertaking.

With hindsight, missing responses were to be expected, and certainly the tactic of skipping foods not eaten (Fraser et al., 2009) was likely employed to minimise the responses required. Although in analyses every effort was made to estimate missing data appropriately and in a manner that would minimise bias, it is of course preferable if data are not missing in the first place. In FFQs that assess current diet, participants can be re-contacted to provide the response information to the individual items they have missed (Hansson & Galanti, 2000). However, this approach was not appropriate when dealing with missing data in the LDQ because dietary recall needed to be undertaken in the context of life-period specific recall sessions. Life-period cue questions preceded the food item frequency questions and each life-period questionnaire was requested to be completed on separate days to minimise carry-over effects of dietary memory from one period seeping into another.

9.3.1.1 Computerising the LDQ

A possible option to minimise the problem of missing dietary data in future studies would be to develop a computerised version of the LDQ. Computerising the questionnaire would confer a number of important advantages. Missing data and invalid responses could be eliminated entirely by requiring completion of one item before the participant moved onto the next, and multiple responses could be negated by ensuring only one response per item could be entered. Additional benefits of a computerised instrument include minimising the effort and error inherent in entering paper-based data, and the potential for web-based delivery; thus enabling cost effective sampling of many more participants than is feasible when questionnaires need to be collated and posted out (van Gelder, Bretveld, & Roeleveld, 2010).

The reliability of paper and pencil (P & P) self-report measures in general appears robust to computer administration. A recent meta-analysis by Gwaltney et al. (2008) addressed the equivalence of electronic and P&P responses. Results of this analysis demonstrated that, of the 207 correlation coefficients calculated between P & P and computer assessments, 94% were at least 0.75. Even in older samples, the differences between the two media, although present, were non-consequential and, importantly, computer familiarity was unrelated to whether computer-based and P & P measures were found to be equivalent (Gwaltney et al., 2008). Nonetheless, testing the equivalence of the two administration mediums would still be necessary because any modification to the content and format of the original LDQ would potentially impact on the equivalence of the two measures (Coons et al., 2009).

9.3.2 Further validity testing

The associations demonstrated between dietary patterns extracted from the LDQ and relevant demographic and health variables in Study 3 provided a good foundation for pursuing further the relationships between these dietary patterns and the cognitive outcomes from the sample. Undoubtedly, however, comparison of dietary recall using the LDQ with dietary records is desirable and would provide additional verification of the utility of past diet memory as instantiated by the LDQ approach. Although there were no records available to carry out such an investigation for the purposes of this thesis, there are a number of cohort studies of 15 to 20 years duration in which participants are now entering older age, which may have dietary information available from at least late adulthood or middle-age (Anstey et al., 2011; Lee et al., 2005; Wadsworth et al., 2006).

As outlined in Chapter 3, the standard way of testing the validity of past diet recall is to determine either the level of agreement (the Kappa statistic), the correlation co-efficient, or both between recalled diet and dietary records, while controlling for the influence of current diet. This approach could be complimented by testing recall validity by utilising EFA and CFA methodology. Firstly, exploratory patterns would be extracted from the LDQ measure. These patterns, which are defined by their highest loading foods, could then be specified as the structural model underlying the associations between food items in the *original* dietary records. If this pre-specified structure fitted well to the dietary record data (after taking the variance from current diet into account) then this would further indicate validity for the recalled LDQ measure.

9.3.3 Stability of dietary patterns: Testing a cumulative model of dietary impact

The studies reported herein examined the *independent* effect of each specific lifetime dietary pattern from childhood, early-adulthood, adulthood, and middle-age on older-age cognitive health. It is possible, however, according to the life-course model, that environmental or lifestyle factors may bestow cumulative effects over the lifetime also. (Kuh et al., 2003).

Overall, in the very few studies that have measured the stability of diet across life-periods, diet appears to reflect the changes that occur in individuals' socio-demographic circumstances as they move through life (Lake, Mathers, Rugg-Gunn, & Adamson, 2006; Mishra et al., 2006). Nonetheless, as with all human behaviour, there are likely individual differences in diet stability and some people may follow a particular eating pattern over multiple life-periods. For example, in a follow-up study of Boyd-Orr Cohort survivors, a higher household intake of vegetables in childhood was associated with a healthier diet in early old age (Maynard et al., 2006). For cumulative effects to be tested, the diet of interest needs to be identified as being stable across life-periods.

An optimal method of measuring internal pattern stability over time is by using confirmatory models. Firstly, EFA is used to determine the appropriate dietary patterns to specify for the confirmatory models of dietary intake at each time point (specifically the individual life-periods). The internal stability of dietary patterns is then determined by testing the significance of changes in the covariance matrices across life-periods (Weismayer et al., 2006).

This method depends, however, on the dietary patterns extracted by EFA being consistent (as opposed to stable) across time points. In studies that span

only a few years, or a single life-period, such consistency is to be expected and has been demonstrated (Mishra et al., 2006; Weismayer et al., 2006), but, as discussed in Chapter 5, the dietary patterns extracted from the LDQ that spanned up to 60 years were not consistent across life-periods. Even those that were similar in terms of their defining foods (such as the 'processed, high-sugar & high-fat' diets) differed in their combination of food items and the strength of loadings by individual foods on the dietary pattern factor (Hosking & Danthiir, 2013).

To test the cumulative model of lifetime intake, individuals would need to be ascribed a score on a *pre-defined* consumption pattern for each life-period, based on the total consumption frequency of the foods deemed theoretically relevant to that pattern. For example, adding together all consumption frequencies of processed, sweet, and high fat foods for a life-period would provide a score on a 'detrimental' dietary pattern. Once the relevant pattern score was obtained for each life-period, the ICC could be calculated as a measure of the stability of the pattern across life-periods. The ICC is a measure of the ratio of within-person variance to between-person variance in the total variance of, specifically, all life-period measures of the relevant diet. If the dietary pattern demonstrated some stability over time (so a moderate to high ICC), then a higher total pattern scores would represent higher consumption of relevant foods across the life-time. This 'lifetime pattern exposure' variable could then be tested as a predictor of cognitive change.

Future investigations of both chronic disease and cognitive ageing aetiologies could focus on constructing a lifetime dietary measure that is specifically designed to assess the potential cumulative effects of a particular diet.

For example, the detrimental effect of processed, sweet, and high fat foods mentioned above or protective effects of a pre-defined MeDi.

9.4 Concluding Comment

This thesis has investigated the theoretical and methodological utility of retrospective lifetime diet as a contribution to investigating individual differences in people's cognitive functioning in older-age. Although, on average, some decline in cognitive abilities is inevitable as we move through older-age, cognitive impairment and dementia are not. There is a pressing need to identify the modifiable environmental determinants of older-age cognitive health to minimise the probability of developing these debilitating diseases.

Evidence is accruing that the antecedents of older-age outcomes stretch far back into the earlier periods of life. If dietary intake impacts upon the cognitive ageing trajectory, then intake from periods prior to older-age is likely to be relevant. Such was the rationale underpinning this dissertation. Assessing and utilising retrospective dietary intake is challenging. Nonetheless, these exploratory studies have demonstrated that lifetime dietary recall provides a useful, relevant, and hitherto untapped resource that may contribute to constructing the "*multivariate recipe for successful cognitive ageing*" (Deary et al., 2009, p. 15).

References

ABS. (1941). *Official Year Book of the Commonwealth of Australia*. Commonwealth of Australia.

AIHW. (2007). *Older Australia at a glance*. Canberra: Australian Institute of Health and Welfare.

AIHW. (2010). *Australia's health 2010*. Australian Government Retrieved from http://www.aihw.gov.au/publicationdetail/?id=6442468376&libID=644246837.

AIHW. (2013). *National Health Priority Areas*. Australian Government Retrieved from http://www.aihw.gov.au/national-health-priority-areas/.

Akbaraly, T., Sabia, S., Hagger-Johnson, G., Tabak, A., Shipley, M., Jokela, M. (2013). Does overall diet in midlife predict future aging phenotypes? A cohort study. *The American Journal of Medicine, 126*(5), 411-419. doi: 10.1016/j.amjmed.2012.10.028

Akbaraly, T.N., Singh-Manoux, A., Marmot, M.G., & Brunner, E.J. (2009). Education attenuates the association between dietary patterns and cognition. *Dementia and Geriatric Cognitive Disorders, 27*(2), 147-154.

Aleman, A., Muller, M., de Haan, E.H.F., & van der Schouw, Y.T. (2005). Vascular risk factors and cognitive function in a sample of independently living men. *Neurobiology of Aging, 26*(4), 485-490.

Alfonso, V.C., Flanagan, D.P., & Radwan, S. (2005). The impact of the Cattell-Horn-Carroll theory on test development and interpretation of cognitive and academic abilities. In D. P. Flanagan & P. L.Harrison (Eds.), *Contempory intellectual assessment* (pp. 185-202). New York: The Guillford Press.

Alley, D., Suthers, K., & Crimmins, E. (2007). Education and cognitive decline in older Americans: Results from the AHEAD sample (Vol. 29, pp. 73-94).

Altman, D.G. (1991). *Practical statistics for medical research*. London: Chapman and Hall.

Alwin, D.F. (2009). History, cohorts, and patterns of cognitive aging. In H. B. Bosworth & C. Hertzog (Eds.), *Aging and cognition: Research methodologies and empirical advances* (pp. 9-37). Washington: American Psychological Association.

Alwin, D.F., McCammon, R.J., Wray, L.A., & Rodgers, W.L. (2008). Population processes and cognitive aging. In S. M. Hoffer & D. F. Alwin (Eds.), *Handbook of cognitive aging: Interdisciplinary perspectives* (pp. 69-89). California: Sage Publications.

Ambrose, J.A., & Barua, R.S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American College of Cardiology, 43*(10), 1731-1737.

Ambrosini, G., Mackerras, D., de Klerk, N., & Musk, A. (2003). Comparison of an Australian food-frequency questionnaire with diet records: implications for nutrition surveillance. *Public Health Nutrition, 6*(4), 415-422.

Ambrosini, G., van Roosbroeck, S.A.H., Mackerras, D., Fritschi, L., de Klerk, N.H., & Musk, A.W. (2003). The reliability of ten-year dietary recall: Implications for cancer research. *J. Nutr., 133*(8), 2663-2668.

Anderson, J.W., Johnstone, B.M., & Remley, D.T. (1999). Breast-feeding and cognitive development: a meta-analysis (Vol. 70, pp. 525-535).

Anstey, K.J., Christensen, H., Butterworth, P., Easteal, S., Mackinnon, A., Jacomb, T. (2011). Cohort Profile: The PATH through life project.

Anstey, K.J., von Sanden, C., Salim, A., & O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *American Journal of Epidemiology, 166*(4), 367-378.
Arbuckle, J.L. (2006). Amos (Version 7.0). Chicago: SPSS.
Bäckman, L., Jones, S., Berger, A.-K., Laukka, E.J., & Small, B.J. (2005). Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology, 19*(4), 520-531.
Balasubramanian, A.B., Kawas, C.H., Peltz, C.B., Brookmeyer, R., & Corrada, M.M. (2012). Alzheimer disease pathology and longitudinal cognitive performance in the oldest-old with no dementia. *Neurology, 79*(9), 915-921.
Baltes, P.B., & Schaie, K.W. (1976). On the plasticity of intelligence in adulthood and old age: Where Horn and Donaldson fail. *American Psychologist, 31*(10), 720-725.
Barberger-Gateau, P., Raffaitin, C., Letenneur, L., Berr, C., Tzourio, C., Dartigues, J.F. (2007). Dietary patterns and risk of dementia: the three city cohort study. *Neurology, 69*(20), 1921-1930.
Bartrés-Faz, D., & Arenaza-Urquijo, E.M. (2011). Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. *Brain Topography, 24*, 340-357.
Basile, J.N. (2004). The Importance of systolic blood bressure elevation in elderly persons. *The Journal of Clinical Hypertension, 6*(8), 461-465.
Bégin, M.E., Plourde, M., Pifferi, F., & Cunnane, S.C. (2010). Are fish and docosahexaenoic acid linked to lower risk of cognitive decline and Alzheimer's disease? *Recent Advances on Nutrition and the Prevention of Alzheimer's DIsease*, 71-95.
Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology, 31*(2), 285-293.
Bennett, D., Schneider, J., Arvanitakis, Z., & Wilson, R. (2012). Overview and findings from the Religious Orders study. *Current Alzheimer Research, 9*(6), 628-645.
Benton, D. (2001). Micro-nutrient supplementation and the intelligence of children. *Neuroscience and Behavioral Reviews, 26*(4), 297-309.
Benton, D. (2008). The influence of children's diet on their cognition and behaviour. *European Journal of Nutrition, 47*(Supplement 3), 25-37.
Benton, D. (2010a). The influence of dietary status on the cognitive performance of children. *Molecular Nutrition & Food Research, 54*(4), 457-470.
Benton, D. (2010b). Neurodevelopment and neurodegeneration: are there critical stages for nutritional intervention? *Nutrition Reviews, 68*, S6-S10.
Benton, D. (2012). Vitamins and neural and cognitive developmental outcomes in children. *Proceedings of the Nutrition Society, 71*(01), 14-26. doi: doi:10.1017/S0029665111003247
Benton, D., & Roberts, G. (1988). Effect of vitamin and mineral supplementation on intelligence of a sample of scholochildren. *The Lancet, 331*(8578), 140-143.
Berlau, D.J., Corrada, M.M., Head, E., & Kawas, C.H. (2009). APOE ε2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. *Neurology, 72*(9), 829-834. doi: 10.1212/01.wnl.0000343853.00346.a4
Bertsias, G., Linardakis, M., Mammas, I., & Kafatos, A. (2005). Fruit and vegetables consumption in relation to health and diet of medical students in Crete, Greece. *International Journal for Vitamin and Nutrition Research., 75*(2), 107.

Bienias, J.L., Beckett, L., Bennett, D.A., Wilson, R.S., & Evans, D.A. (2003). Design of the Chicago Health and Aging Project (CHAP). *Journal of Alzheimer's Disease, 5*(5), 349-355.

Birch, E., Garfield, S., Castañeda, Y., Hughbanks-Wheaton, D., Uauy, R., & Hoffman, D. (2007). Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Human Development, 83*(5), 279-284.

Bjelakovic, G., Nikolova, D., Gluud, L.L., Simonetti, R.G., & Gluud, C. (2012). Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev. , 14*(3). doi: 10.1002/14651858.CD007176.pub2.

Blair, C.K., Folsom, A.R., Knopman, D.S., Bray, M.S., Mosley, T.H., & Boerwinkle, E. (2005). APOE genotype and cognitive decline in a middle-aged cohort. *Neurology, 64*(2), 268-276.

Blane, D., Netuveli, G., & Sone, J. (2007). The development of life course epidemiology. *Revue d'Épidémiologie et de Santé Publique 55*, 31-38.

Blane, D.B. (1996). Collecting retrospective data: Development of a reliable method and a pilot study of its use. *Social Science & Medicine, 42*(5), 751-757.

Boake, C. (2002). From the Binet-Simon to the Wechsler-Bellevue:Tracing the history of intelligence testing. *Journal of Clinical and Experimental Neuropsychology 24*(3), 383-405.

Boden-Albala, B., Sacco, R.L., Lee, H.-S., Grahame-Clarke, C., Rundek, T., Elkind, M.V. (2008). Metabolic Syndrome and Ischemic Stroke Risk: Northern Manhattan Study. *Stroke, 39*(1), 30-35. doi: 10.1161/strokeaha.107.496588

Bourne, V.J., Fox, H.C., Deary, I.J., & Whalley, L.J. (2007). Does childhood intelligence predict variation in cognitive change in later life? *Personality and Individual Differences, 42*(8), 1551-1559.

Breteler, M.M.B., Claus, J.J., Grobbee, D.E., & Hofman, A. (1994). Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. *British Medical Journal 308*(6944), 1604-1608.

Bretsky, P., Guralnik, J.M., Launer, L., Albert, M., & Seeman, T.E. (2003). The role of APOE-ε4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Neurology, 60*(7), 1077-1081.

Brickman, A.M., Siedlecki, K.L., Muraskin, J., Manly, J.J., Luchsinger, J., Yeung, L.-K. (2011). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology of Aging, 32*(9), 1588-1598.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H.M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia, 3*(3), 186-191.

Brunner, E.J., Mosdol, A., Witte, D.R., Martikainen, P., Stafford, M., Shipley, M.J. (2008). Dietary patterns and 15-y risks of major coronary events, diabetes, and mortality. *American Journal of Clinical Nutrition, 87*(5), 1414-1421.

Bryan, J., Osendarp, S., Hughes, D., Calvaresi, E., Baghurst, K., & Van Klinken, J.-W. (2004). Nutrients for cognitive development in school-aged children. *Nutrition Reviews, 62*(8), 295-306.

Bunce, D., Fratiglioni, L.M., Small, B.J., Winblad, B.M.D.P., & Backman, L. (2004). APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. *Neurology, 63*(5), 816-821.

Byers, T., Marshall, J., Anthony, E., Fielder, R., & Zielezny, M. (1987). The reliability of dietary history from the distant past. *American Journal of Epidemiology, 125*(6), 999-1011.

Caamaño-Isorna, F., Corral, M., Montes-Martínez, A., & Takkouche, B. (2006). Education and dementia: A meta-analytic study. *Neuroepidemiology, 26*(4), 226-232.

Cadar, D., Pikhart, H., Mishra, G., Stephen, A., Kuh, D., & Richards, M. (2012). The role of lifestyle behaviors on 20-Year cognitive decline. *Journal of Aging Research*, 1-13.

Calon, F., & Cole, G. (2007). Neuro-protective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: Evidence from animal studies. *Prostaglandins Leukotrienes and Essential Fatty Acids, 77*(5-6), 287-293.

Carroll, J.B. (1993). *Human Cognitive Abilities: A survey of factor-analytic studies*. Cambridge: Cambridge University Press.

Caslake, M.J., Miles, E.A., Kofler, B.M., Lietz, G., Curtis, P., Armah, C.K. (2008). Effect of sex and genotype on cardiovascular biomarker response to fish oils: the FINGEN Study. *American Journal of Clinical Nutrition, 88*(3), 618-629.

Cattell, R.B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. *Journal of Educational Psychology, 54*, 1-22.

Chavarro, J.E., Rosner, B.A., Sampson, L., Willey, C., Tocco, P., Willett, W.C. (2009). Validity of adolescent diet recall 48 years later *American Journal of Epidemiology* (Vol. 170, pp. 1563-1570).

Cherbuin, N., & Anstey, K.J. (2012). The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH Through Life study. *American Journal of Geriatric Psychiatry, 20*, 635-639.

Chrysohoou, C., Panagiotakos, D.B., Pitsavos, C., Das, U.N., & Stefanadis, C. (2004). Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adultsThe Attica study. *Journal of the American College of Cardiology, 44*(1), 152-158.

Clarke, R., Grimley Evans, J., Schneede, J., Nexo, E., Bates, C., Fletcher, A. (2004). Vitamin B12 and folate deficiency in later life. *Age and Ageing, 33*(1), 34-41. doi: 10.1093/ageing/afg109

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences* (2nd ed.). New Jersey: Lawrence Erbaum Associates, Inc.

Cole, G.M., Qiu-Lan, M., & Frautschy, S.A. (2010). Dietary fatty acids and the aging brain. *Nutrition Reviews, 68*, S102-S111.

Collingham, L. (2012). *World War Two and the battle for food*. New York: Penguin Press.

Conway, M.A. (1992). A structural model of theoretical autobiographical memory. . In M.A. Conway, D.C Rubin, H. Spinnler & W. A. Wagenaar (Eds.), *Theoretical perspectives on autobiographical memory.* (pp. 167-194). Dordrecht: Kluwer Academic Publishers.

Conway, M.A. (1996). Autobiographical knowledge and autobiographical memories. In D. C. Rubin (Ed.), *Remembering our past* (pp. 67-93). Cambridge: Cambridge University Press.

Coons, S.J., Gwaltney, C.J., Hays, R.D., Lundy, J.J., Sloan, J.A., Revicki, D.A. (2009). Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome measures:Good research practices task force report. *Value in Health 12*(4), 419-429.

Corley, J., Starr, J.M., McNeill, G., & Deary, I.J. (2013). Do dietary patterns influence cognitive function in old age? (Vol. 25, pp. 1393-1407): Cambridge Journals Online.

Costello, A.B., & Osborne, J.W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research & Evaluation, 10*(7), 1-9.

Crum, R.M., Anthony, J.C., Bassett, S.S., & Folstein, M.F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *Journal of the American Medical Association, 269*(12), 2386-2391.

Cumming, R.G., & Klineberg, R.J. (1994). A study of the reproducibility of long-term recall in the elderly. *Epidemiology, 5*(1), 116-119.

Cunnane, S.C., Francescutti, V., Brenna, J.T., & Crawford, M.A. (2000). Breast-fed infants achieve a higher rate of brain and whole-body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahexaenoate. *Lipids, 35*(1), 105-111.

Cunnane, S.C., Plourde, M., Pifferi, F., Bégin, M., Féart, C., & Barberger-Gateau, P. (2009). Fish, docosahexaenoic acid and Alzheimer's disease. *Progress in Lipid Research, 48*(5), 239-256.

Daffner, K.R. (2010). Promoting successful cognitive aging: A comprehensive review. *Journal of Alzheimer's Disease, 19*(4), 1101-1122.

Dagnelie, P.C., & van Staveren, W.A. (1994). Macrobiotic nutrition and child health: results of a population-based, mixed-longitudinal cohort study in The Netherlands *American Journal of Clinical Nutrition* (Vol. 59, pp. 1187S-1196S).

Dai, J., Jones, D., Goldberg, J., Ziegler, T., Bostick, R., Wilson, P. (2008). Association between adherence to the Mediterranean diet and oxidative stress. *American Journal of Clinical Nutrition, 88*(5), 1364-1370.

Dai, Q., Borenstein, A.R., Wu, Y., Jackson, J.C., & Larson, E.B. (2006). Fruit and vegetable juices and Alzheimer's disease: The Kame Project. *American Journal of Medicine, 119*(9), 751-759.

Damoiseaux, J.S., Seeley, W.W., Zhou, J., Shirer, W.R., Coppola, G., Karydas, A. (2012). Gender modulates the APOE ε-4 effect in healthy older adults: Convergent evidence from functional brain connectivity and spinal fluid tau levels (Vol. 32, pp. 8254-8262).

Dangour, A.D., Allen, E., Elbourne, D., Fasey, N., Fletcher, A.E., Hardy, P. (2010). Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *American Journal of Clinical Nutrition, 91*, 1725-1732. doi: 10.3945/ajcn.2009.29121

Danthiir, V., Burns, N.R., Nettelbeck, T., Wilson, C., & Wittert, G. (2011). The older people, omega-3, and cognitive health (EPOCH) trial design and methodology: A randomised, double-blind, controlled trial investigating the effect of long-chain omega-3 fatty acids on cognitive ageing and wellbeing in cognitively healthy older adults. *Nutrition Journal, 10*(117), 1-36.

Danthiir, V., Hosking, D., Burns, N.R., Wilson, C., Nettelbeck, T., Calvaresi, E. (2013). Cognitive performance is negatively associated with fish consumption but not erythrocyte membrane n-3 fatty acids in older adults. *The Journal of Nutrition, submitted*.

Danthiir, V., Roberts, R.D., Schultz, R., & Wilhelm, O. (2005). Mental speed: On frameworks, paradigms, and a platform for the future. In O. Wilhelm & R. W.

Engle (Eds.), *Understanding and measuring intelligence* (pp. 27-46). Thousand Oaks: Sage.
Danthiir, V., Wilhelm, O., & Roberts, R.D. (2011). Further evidence for a multifaceted model of mental speed: Factor structure and validity of computerized measures. *Learning and Individual Differences*(0).
Darmon, N., & Drewnowski, A. (2008). Does social class predict diet quality? *American Journal of Clinical Nutrition, 87*(5), 1107-1117.
Darnton-Hill, I., Nishida, C., & James, W. (2004). A life course approach to diet, nutrition and the prevention of chronic diseases. *Public Health Nutrition, 7*(1A), 101-121.
Das, J.P., Kirby, J., & Jarman, R.F. (1975). Simultaneous and successive synthesis: An alternative model for cognitive abilities. *Psychological Bulletin, 82*(1), 87-103.
de Graaf-Peters, V.B., & Hadders-Algra, M. (2006). Ontogeny of the human central nervous system: What is happening when? *Early Human Development, 82*(4), 257-266.
De Irala-Estévez, J., Groth, M., Johansson, L., Oltersdorf, U., Prättälä, R., & Martínez-González, M.A. (2000). A systematic review of socio-economic differences in food habits in Europe: consumption of fruit and vegetables. *European Journal of Clinical Nutrition, 54*(9), 706-714.
de la Torre, J.C. (2002). Alzheimer disease as a vascular disorder: Nosological Evidence. *Stroke, 33*(4), 1152-1162. doi: 10.1161/01.str.0000014421.15948.67
de Lorgeril, M., Salen, P., Martin, J., Monjaud, I., Delaye, J., & Mamelle, N. (1999). Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation, 99*(6), 779-785.
Deary, I.J. (2000). *Looking Down on Human Intelligence: From Psychometrics to the Brain* (Vol. 34). Oxford: Oxford University Press.
Deary, I.J., Corley, J., Gow, A.J., Harris, S.E., Houlihan, L.M., Marioni, R.E. (2009). Age-associated cognitive decline. *British Medical Bulletin, 92*(1), 135-152. doi: 10.1093/bmb/ldp033
Deary, I.J., Gow, A.J., Pattie, A., & Starr, J.M. (2011). Cohort Profile: The Lothian Birth Cohorts of 1921 and 1936.
Deary, I.J., Johnson, W., & Starr, J.M. (2010). Are processing speed tasks biomarkers of cognitive aging? *Psychology and Aging, 25*(1), 219-228.
Deary, I.J., Leaper, S.A., Murray, A.D., Staff, R.T., & Whalley, L.J. (2003). Cerebral white matter abnormalities and lifetime cognitive change: A 67-Year follow-up of the Scottish Mental Survey of 1932. *Psychology & Aging, 18*(1), 140-148.
Deary, I.J., MacLennan, W.J., & Starr, J.M. (1998). Is age kinder to the initially more able?: Differential ageing of a verbal ability in the Healthy Old People in Edinburgh Study. *Intelligence, 26*(4), 357.
Deary, I.J., Whalley, L.J., Lemmon, H., Crawford, J.R., & Starr, J.M. (2000). The stability of individual differences in mental ability from childhood to old age: Follow-up of the 1932 Scottish Mental Survey. *Intelligence, 28*, 49 - 55.
Deary, I.J., Whiteman, M.C., Pattie, A., Starr, J.M., Hayward, C., Wright, A.F. (2002). Ageing: Cognitive change and the APOEe4 allele. *Nature Biotechnology, 418*, 932.
Deary, I.J., Whiteman, M.C., Starr, J.M., Fox, H.C., & Whalley, L.J. (2004). The impact of childhood intelligence in later life: Following up the scottish mental surveys of 1932 and 1947 *Journal of Personality and Social Psychology* (Vol. 86, pp. 130 - 147).

Debette, S.M., Seshadri, S., Beiser, A., Au, R., Himali, J.J., Palumbo, C. (2011). Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology, 77*(5), 461-468.

Dempster, A.P., Laird, N.M., & Rubin, D.B. (1977). Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society. Series B (Methodological), 39*(1), 1-38.

Denis, I., Potier, B., Vancassel, S., Heberden, C., & Lavialle, M. (2013). Omega-3 fatty acids and brain resistance to ageing and stress: Body of evidence and possible mechanisms. *Ageing Research Reviews, 12*(2), 579-594.

Devore, E., Grodstein, F., & van Rooij, F.A. (2010). Dietary antioxidants and long-term risk of dementia. *Archives of Neurology, 67*(7), 819-825.

Devore, E.E., Kang, J.H., Breteler, M.M.B., & Grodstein, F. (2012). Dietary intakes of berries and flavonoids in relation to cognitive decline. *Annals of Neurology, 72*(1), 135-143.

Dipietro, L., Caspersen, C.J., Ostfeld, A.M., & Nadel, E.R. (1993). A Survey for Assessing Physical-Activity among Older Adults. *Medicine and Science in Sports and Exercise, 25*(5), 628-642.

DiStefano, C., Zhu, M., & Mîndrilă, D. (2009). Understanding and using factor scores:Considerations for the applied researcher. *Practical Assessment, Research & Evaluation, 14*(20), 1-7.

Dixon, R.A., & de Frias, C.M. (2004). The Victoria Longitudinal Study: From characterizing cognitive aging to ilustrating changes in memory compensation. *Aging, Neuropsychology & Cognition, 11*(2/3), 346-376.

Dobbing, J., & Sands, J. (1973). Quantitative growth and development of human brain. *Archives of Disease in Childhood, 48*, 757-767

Doets, E.L., van Wijngaarden, J.P., Szczecińska, A., Dullemeijer, C., Souverein, O.W., Dhonukshe-Rutten, R. (2013). Vitamin B12 intake and status and cognitive function in elderly people. *Epidemiologic Reviews, 35*(1), 2-21. doi: 10.1093/epirev/mxs003

Dregan, A., Stewart, R., & Gulliford, M.C. (2013). Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. *Age and Ageing, 42*(3), 338-345. doi: 10.1093/ageing/afs166

Driscoll, I., Resnick, S.M., Troncoso, J.C., An, Y., O'Brien, R., & Zonderman, A.B. (2006). Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. *Annals of Neurology, 60*(6), 688-695.

Durga, J., van Boxtel, M.P.J., Schouten, E.G., Kok, F.J., Jolles, J., Katan, M.B. (2007). Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *The Lancet, 369*(9557), 208-216.

Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. *Vascular Health and Risk Management, 4*(2), 363-381.

Dwyer, J.T., & Coleman, K. (1997). Insights into dietary recall from a longitudinal study: accuracy over four decades. *American Journal of Clinical Nutrition 65(suppl)*, 1153S-1158S.

Dwyer, J.T., Gardner, J., Halvorsen, K., Krall, E.A., Cohen, A., & Valadian, I. (1989). Memory of food intake in the distant past. *American Journal of Epidemiology, 130*(5), 1033-1046.

Elias, M.F., Beiser, A., Wolf, P.A., Au, R., White, R.F., & D'Agostino, R.B. (2000). The preclinical phase of Alzheimer disease: A 22-year prospective study of the Framingham cohort. *Archives of Neurology, 57*(6), 808-813.

Engelhart, M.J., Geerlings, M.I., Ruitenberg, A., van Swieten, J.C., Hofman, A., Witteman, J.C.M. (2002). Diet and risk of dementia: Does fat matter? *Neurology, 59*(12), 1915-1921. doi: 10.1212/01.WNL.0000038345.77753.46

Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B. (2010). Physical activity predicts gray matter volume in late adulthood *Neurology*.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L. (2011). Exercise training increases size of hippocampus and improves memory *Proceedings of the National Academy of Sciences of the United States of America*.

Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.-I., Corella, D., Arós, F. (2013). Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (Vol. 368, pp. 1279-1290).

Eussen, S.J., de Groot, L.C., Joosten, L.W., Bloo, R.J., Clarke, R., Ueland, P.M. (2006). Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. *American Journal of Clinical Nutrition, 84*(2), 361-370.

Eysteinsdottir, T., Gunnarsdottir, I., Thorsdottir, I., Harris, T., Launer, L., Gudnason, V. (2010). Validity of retrospective diet history: Assessing recall of midlife diet using food frequency questionnaire in later life. *The Journal of Nutrition, Health & Aging, 15*(10), 809-814.

Fabrigar, L.R., Wegener, D.T., MacCallum, R.C., & Strahan, E.J. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods, 4*(3), 272-299.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods, 39*(2), 175-191.

Feinstein, L., Sabates, R., Sorhaindo, A., Rogers, I., Herrick, D., Northstone, K. (2008). Dietary patterns related to attainment in school: the importance of early eating patterns. *Journal of Epidemiology and Community Health, 62*, 734-740.

Fernandes, J.S., Mori, M.A., Ekuni, R., Oliveira, R.M.W., & Milani, H. (2008). Long-term treatment with fish oil prevents memory impairments but not hippocampal damage in rats subjected to transient, global cerebral ischemia. *Nutrition Research, 28*(11), 798-808.

Ferrer, E., & Ghisletta, P. (2011). Methodological and analytical issues in the psychology of aging. In K. W. Schaie & S. L. Willis (Eds.), *Handbook of the psychology of aging* (pp. 25-39). Amsterdam: Elsevier.

Ferrer, E., Salthouse, T.A., Stewart, W.F., & Schwartz, B.S. (2004). Modelling age and retest processes in longitudinal studies of cognitive abilities. *Psychology & Aging, 19*(2), 243-259.

Fields, R.D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences, 31*(7), 361-370.

Fjell, A.M., & Walhovd, K.B. (2011). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences, 21*(3), 187-122. doi: 10.1515/REVNEURO.2010.21.3.187

Fjellström, F. (2004). Mealtime and meal patterns from a cultural perspective. *Food and Nutrition Research, 48*(4), 161-168.

Floyd, R.A., & Hensley, K. (2002). Oxidative stress in brain aging: Implications for therapeutics of neurodegenerative diseases. *Neurobiology of Aging, 23*(5), 795-807.

Floyd, R.F. (2005). Information-processing approaches to interpretaion of contemporary intellectual assessment instruments. In D. P. Flanningan & P. L. Harrison (Eds.), *Contemporary Intellectual Assessment: Theories, Tests, and Issues* (pp. 203-233). New York: The Guilford Press.

Flynn, J.R. (1987). Massive IQ gains in 14 Nations: What IQ tests really measure. *Psychological Bulletin, 101*(2), 171-191.

Flynn, J.R. (1998). IQ gains Over Time: Toward finding the causes. In U. Neisser (Ed.), *The rising curve: Long term gains in IQ and related measures* (pp. 25-66). Washington D.C: American Psychological Association.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). Mini-Mental State. *Journal Of Psychiatric Research, 12*, 189-198.

Ford, A., Flicker, L., Alfonso, H., Thomas, J., Clarnette, R., Martins, R. (2010). Vitamins B(12), B(6), and folic acid for cognition in older men. *Neurology, 75*(17), 1540-1547. doi: 10.1212/WNL.0b013e3181f962c4

Francis, D.J., Fletcher, J.M., Stuebing, K.K., Davidson, K.C., & Thompson, N.M. (1991). Analysis of change: Modelling individual growth. *Journal of Consulting and Clinical Psychology, 59*(1), 27-37. doi: 10.1037/0022-006X.59.1.27

Fraser, G.E., Lindsted, K.D., Knutsen, S.F., Beeson, W.L., Bennett, H., & Shavlik, D.J. (1998). Validity of dietary recall over 20 years among California Seventh-day Adventists. *American Journal of Epidemiology, 148*(8), 810-818.

Fraser, G.E., Yan, R., Butler, T.L., Jaceldo-Siegl, K., Beeson, W.L., & Chan, J. (2009). Missing data in a long food frequency questionnaire: Are imputed zeroes correct? . *Epidemiology, 20*(2), 289-294.

Frazier, A.L., Wilett, W.C., & Colditz, G.A. (1995). Reproducibility of recall of adolescent diet: Nurses' Health Study (United States). *Cancer Causes and Control, 6*(6), 499-506.

Freeman, L.R., & Granholm, A.E. (2012). Vascular changes in rat hippocampus followig a high saturated fat and cholesterol diet. *Journal of Cerebral Blood Flow and Metabolism, 32*, 643-653.

Frensham, L.J., Bryan, J., & Parletta, N. (2012). Influences of micronutrient and omega-3 fatty acid supplementation on cognition, learning, and behavior: methodological considerations and implications for children and adolescents in developed societies. *Nutrition Reviews, 70*(10), 594-610.

Friedenreich, C.M. (1994). Improving long-term recall in epidemiologic studies. *Epidemiology, 5*(1), 1-4.

Friedenreich, C.M., Howe, G.R., & Miller, A.B. (1991). An investigation of recall bias in the reporting of past food intake among breast cancer cases and controls. *Annals of Epidemiology, 1*(5), 439-453.

Friedenreich, C.M., Slimani, N., & Riboli, E. (1992). Measurement of past diet: Review of previous and proposed methods. *Epidemiologic Reviews, 14*(1), 177-196.

Fuglestad, A.J., Raghavendra, R., & Georgieff, M.K. (2008). The role of nutrition in cognitive development. In C. A. Nelson & M. Luciana (Eds.), *Handbook of Developmental Cognitive Neuroscience* (pp. 623-643). London: MIT Press.

Gale, C.R., Deary, I.J., Schoon, I., & Batty, G.D. (2007). IQ in childhood and vegetarianism in adulthood: 1970 British cohort study. *British Medical Journal (Clinical Research Ed.), 334*.

Gale, C.R., Martyn, C.N., Marriott, L.D., Limond, J., Crozier, S., Inskip, H.M. (2009). Dietary patterns in infancy and cognitive and neuropsychological function in childhood. *Journal of Child Psychology and Psychiatry, 50*(7), 816-823.

Galli, R.L., Bielinski, D.F., Szprengiel, A., Shukitt-Hale, B., & Joseph, J.A. (2006). Blueberry supplemented diet reverses age-related decline in hippocampal HSP70 neuroprotection. *Neurobiology of Aging, 27*(2), 344-350.
Gallinat, J., Meisenzahl, E., Jacobsen, L.K., Kalus, P., Bierbrauer, J., Kienast, T. (2006). Smoking and structural brain deficits: a volumetric MR investigation. *European Journal of Neuroscience, 24*(6), 1744-1750.
Galton, F. (1879). Psychometric experiments. *Brain: A Journal of Neurology, 2*(2), 149-162. doi: 10.1093/brain/2.2.149
Garcia, A., & Zanibbi, K. (2004). Homocysteine and cognitive function in elderly people. *CMAJ, 171*(8), 897-904. doi: 10.1503/cmaj.1031586
Garson, G.D. (2008). 'Correlation', from Statnotes: Topics in multivariate analysis. from http://faculty.chass.ncsu.edu/garson/pa765/statnote.htm.
Gaynor, A. (2006). *Harvest of the suburbs: An environmental history of growing food in Australian cities*. Crawley, W.A: University of Western Australia Press.
Geleijnse, J.M., Giltay, E.J., & Kromhout, D. (2012). Effects of n-3 fatty acids on cognitive decline: A randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's & Dementia, 8*(4), 278-287.
Georgieff, M.K. (2007). Nutrition and the developing brain: nutrient priorities and measurement. *American Journal of Clinical Nutrition, 85*(2), 614S-620S.
Giles, G.G., & Ireland, P.D. (1996). *Dietary Questionnaire for Epidemiological Studies (Version 2)*. Melbourne: Cancer Council Victoria.
Gillette-Guyonnet, S., Abellan van Kan, G., Andrieu, G., Barberger-Gateau, P., Berr, C., Bonnefoy, M. (2007). IANA task force on nutrition and cognitive decline with ageing. *Journal of Nutrition Health and Aging, 11*(2), 132-152.
Gillette-Guyonnet, S., & Vellas, B. (2008). Caloric restriction and brain function. *Current Opinion in Clinical Nutrition and Metabolic Care, 11*(6), 686-692.
Glisky, E.L. (2007). Changes in cognitive function in human aging. In D. R. Riddle (Ed.), *Brain Aging: Models, Methods, and Mechanisms* CRC press.
Golding, J., Pembrey, M., & Jones, R. (2001). ALSPAC - the Avon Longitudinal Study of Parents and Children: Study methodology. *Paediatric and Perinatal Epidemiology, 15*(1), 74-87.
Gómez-Pinilla, F. (2008). Brain foods: the effects of nutrients on brain function. *Nature reviews neuroscience, 9*(7), 568-578.
Good, P. (2005). *Permutation, parametric and bootstrap tests of hypotheses* (3rd ed.). New York: Springer.
Gow, A.J., Johnson, W., Mishra, G., Richards, M., Kuh, D., & Deary, I.J. (2012). Is age kinder to the initially more able?: Yes, and no. *Intelligence, 40*(1), 49-59.
Grantham-McGregor, S., & Baker-Henningham, H. (2005). Review of the evidence linking protein and energy to mental development. *Public Health Nutrition, 8*(7a), 1191-1201. doi: doi:10.1079/PHN2005805
Greaud, V.A., & Green, B.F. (1986). Equivalence of conventional and computer presentation of speed tests. *Applied Psychological Measurement, 10*, 23-34.
Green, S.B. (1991). How many subjects does it take to do a regression analysis. *Multivariate Behavioral Research, 26*(3), 499.
Gregory, J. (Ed.). (1996). *On the Home Front: Western Australia and World War 11*. Nedlands: University of Western Australia Press.
Gregory, S.M., Parker, B., & Thompson, P.D. (2012). Physical activity, cognitive function, and brain health: What is the role of exercise training in the prevention of dementia? *Brain Sciences, 2*, 684-708. doi: 10.3390/brainsci2040684

Gregory, T., Nettelbeck, T., Howard, S., & Wilson, C. (2008). Inspection time: A biomarker for cognitive decline. . *Intelligence, 36*, 664-671.
Gregory, T., Nettelbeck, T., & Wilson, C. (2009). Within person changes in inspection time predict memory. *Personality and Individual Differences, 46*(7), 741-743.
Grodstein, F. (2007). Cardiovascular risk factors and cognitive function. *Alzheimer's & Dementia, 3*(2, Supplement), S16-S22.
Grodstein, F., Kang, J.H., Glynn, R.J., Cook, N.R., & Gaziano, J.M. (2007). A randomized trial of beta carotene supplementation and cognitive function in men: The Physicians' Health Study II. *Arch Intern Med, 167*(20), 2184-2190. doi: 10.1001/archinte.167.20.2184
Grudnik, J.L., & Kranzler, J.H. (2001). Meta-analysis of the relationship between intelligence and inspection time. *Intelligence, 29*(6), 523-535.
Gu, Y., Luchsinger, J.A., Stern, Y., & Scarmeas, N. (2010). Mediterranean diet, Inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *Journal of Alzheimer's Disease, 22*(25). doi: 10.3233/JAD-2010-100897
Gu, Y., Nieves, J.W., Stern, Y., Luchsinger, J.A., & Scarmeas, N. (2010). Food combination and Alzheimer disease risk: A protective diet. *Archives of Neurology, 67*(6), E2-E8. doi: 10.1001/archneurol.2010.84
Gu, Y., & Scarmeas, N. (2011). Dietary patterns in Alzheimers disease and cognitive aging. *Current Alzheimer Research, 8*(5), 510-519.
Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med, 163*(13), 1524-1528. doi: 10.1001/archinte.163.13.1524
Gwaltney, C.J., Shields, A.L., & Shiffman, S. (2008). Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: A meta-analytic review. *Value in Health (Wiley-Blackwell), 11*(2), 322-333.
Hachinski, V.M.D. (2007). The 2005 Thomas Willis Lecture: Stroke and vascular cognitive impairment: A transdisciplinary, translational and transactional approach. *Stroke, 38*(4), 1396-1403.
Hansson, G.K., Robertson, A.-K.L., & Söderberg-Nauclér, C. (2006). Inflammation and atherosclerosis. *Annual Review of Pathology: Mechanisms of Disease, 1*(1), 297-329. doi: doi:10.1146/annurev.pathol.1.110304.100100
Hansson, L.M., & Galanti, M.R. (2000). Diet-associated risks of disease and self-reported food consumption: How shall we treat partial nonresponse in a food frequency questionnaire? *Nutrition & Cancer, 36*(1), 1-6.
Harris, S.E., & Deary, I. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Sciences, 15*(9), 388-394.
He, J., & Whelton, P.K. (1997). Potassium, blood pressure, and cardiovascular disease: An epidemiologic perspective. *Cardiology in Review, 5*(5), 255-260.
Heird, W.C. (2001). The Role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. *Pediatric clinics of North America, 48*(1), 173-188.
Hercberg, S., Galan, P., Preziosi, P., Roussel, A., Arnaud, J., Richard, M. (1998). Background and rationale behind the SU.VI.MAX Study, a prevention trial using nutritional doses of a combination of antioxidant vitamins and minerals to reduce cardiovascular diseases and cancers. Supplementation en vItamines et minéraux antioxydants study. *Internal Journal for Vitamin and MIneral Research, 68*(1), 3-20.
Heroux, M., Janssen, I., Lam, M., Lee, D.-c., Hebert, J.R., Sui, X. (2010). Dietary patterns and the risk of mortality: impact of cardiorespiratory fitness. *International Journal of Epidemiology, 39*(1), 197-209. doi: 10.1093/ije/dyp191

Herrmann, W., & Obeid, R. (2011). Homocysteine: a biomarker in neurodegenerative diseases. *Clinical Chemistry and Laboratory Medicine, 49*(3), 435-444. doi: 10.1515/CCLM.2011.084

Herrnstein, R.J., & Murray, C. (1994). *The bell curve: Intelligence and class structure in American life*. New York: Simon and Schuster.

Hertzman, C. (1999). The biological embedding of early experience and Its effects on health in adulthood. *Annals of the New York Academy of Sciences, 896*(1), 85-95.

Hertzog, C., & Nesselroade, J.R. (2003). Assessing psychological change in adulthood: An overview of methodological issues. *Psychology & Aging, 18*(4), 639-657.

Heys, M., Jiang, C., Schooling, C.M., Zhang, W., Cheng, K.K., Lam, T.H. (2010). Is childhood meat eating associated with better later adulthood cognition in a developing population? *European Journal of Epidemiology, 25*(7), 507-516.

Hislop, T.G., Lamb, C.W., & Ng, V.T.Y. (1990). Differential misclassification bias and dietary recall for the distant past using a food frequency questionnaire (Vol. 13, pp. 223 - 233): Routledge.

Hofer, S.M., & Alwin, D.F. (2008). Opportunities and challenges for interdisciplinary research *Handbook of Cognitive Aging: Interdisciplinary Perspectives.* (pp. 2-33). California: SAGE Publications, Inc.

Hofer, S.M., & Piccinin, A.M. (2010). Toward an integrative science of life-span development and aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65*(3), 269-278.

Hofer, S.M., & Sliwinski, M. (2006). Design and analysis of longitudinal studies on aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of The Psycology of Aging* (Vol. 2, pp. 15-37). Masachuttes: Elsevier.

Hoffmann, K., Schulze, M.B., Boeing, H., & Altenburg, H.P. (2002). Dietary patterns: report of an international workshop. *Public Health Nutrition, 5*(01), 89-90. doi: doi:10.1079/PHN2001252

Homocysteine reduction. (2013). from http://www.lef.org/protocols/heart_circulatory/homocysteine_reduction_01.htm

Horn, J.L., & Cattell, R.B. (1966). Refinement and test of the theory of fluid and crystallised general intelligence. *Journal of Educational Psychology, 57*, 253-270.

Horn, J.L., & Cattell, R.B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychologica, 26*, 107-129.

Horn, J.L., & Donaldson, G. (1976). On the myth of intellectual decline in adulthood. *American Psychologist, 31*(10), 701-719.

Horn, J.L., & Donaldson, G. (1977). Faith is not enough: A response to the Baltes-Schaie claim that intelligence does not wane. *American Psychologist, 32*(5), 369-373.

Hosking, D., & Danthiir, V. (2013). Retrospective lifetime dietary patterns are associated with demographic and cardiovascular health variables in an older community-dwelling Australian population. *British Journal of Nutrition*. doi: 10.1017/S000711451300144X

Hosking, D., Danthiir, V., Nettelbeck, T., & Wilson, C. (2011). Assessing lifetime diet: reproducibility of a self-administered, non-quantitative FFQ. *Public Heath Nutrition, 14*(5), 801-808. doi: 10.1017/S1368980010003174

Hosking, D., Nettelbeck, T., Wilson, C., & Danthiir, V. (2013). Retrospective lifetime dietary patterns predict cognitive performance in community-dwelling older Australians. *British Journal of Nutrition, (submitted)*.

Hu, F.B. (2002). Dietary pattern analysis: a new direction in nutritional epidemiology. *Current Opinion in Lipidology, 13*(1), 3-9.
Hu, P., Bretsky, P., Crimmins, E.M., Guralnik, J.M., Reuben, D.B., & Seeman, T.E. (2006). Association between serum beta-carotene levels and decline of cognitive function in high-functioning older persons with or without Apolipoprotein E 4 alleles. *Journals of Gerontology, Series A, Biological Sciences and Medical Sciences, 61*(6), 616-620.
Huang, C.L., & Sumpio, B.E. (2007). Olive oil, the Mediterranean diet, and cardiovascular health. *Journal of the American College of Surgeons, 207*(3), 407-416. doi: 10.1016/j.jamcollsurg.2008.02.018
Huang, T.L. (2010). Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: A critical review and evaluation of the literature. *Journal of Alzheimer's Disease, 21*(3), 673-690.
Huijbregts, P., Feskens, E., Rasanen, L., Fidanza, F., Nissinen, A., Menotti, A. (1997). Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and the Netherlands: longitudinal cohort study. *BMJ, 315*(7099), 13-17.
Hvas, A.-M., Juul, S., Lauritzen, L., Nexø¸, E., & Ellegaardâœ , J. (2004). No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. *Journal of Affective Disorders, 81*(3), 269-273.
Isaacs, E., Fischl, B., Quinn, B., Chong, W., Gadian, D., & Lucas, A. (2010). Impact of breast milk on intelligence quotient, brain size, and white matter development. *Pediatric Research, 67*(4), 357-362.
Isaacs, E.B., Morley, R., & Lucas, A. (2009). Early diet and general cognitive outcome at adolescence in children born at or below 30 weeks gestation. *The Journal of Pediatrics, 155*(2), 229-234.
Jack, C.R., Lowe, V.J., Weigand, S.D., Wiste, H.J., Senjem, M.L., Knopman, D.S. (2009). Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease (Vol. 132, pp. 1355-1365).
Jacqmin-Gadda, H., Fabrigoule, C., Commenges, D., & Dartigues, J.-F. (1997). A 5-Year longitudinal study of the Mini-Mental State Examination in normal aging. *American Journal of Epidemiology, 145*(6), 498-506.
Jensen, O.M., Wahrendorf, J., Rosenqvist, A., & Geser, A. (1984). The reliability of questionnaire-derived historical dietary information and temporal stability of food habits in individuals. *American Journal of Epidemiology, 120*(2), 281-290.
Jobe, J.B., & Mingay, D.J. (1991). Cognition and survey measurement: History and overview. *Applied Cognitive Psychology, 5*(3), 175-192.
Jones, R.N., Manly, J., Glymour, M.M., Rentz, D.M., Jefferson, A.L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society, 17*, 993-601.
Joseph, J., A., Shukitt-Hale, B., Denisova, N., Bielinski, D., Martin, A., McEwen, J. (1999). Reversal of age-related declines in neuronal signal transduction, cognitive, and motor behavioural deficits with blueberry, spinach, or strawberry dietary supplementation
Journal of Neuroscience, 15(19), 8114-8121.
Joseph, J., Cole, G., Head, E., & Ingram, D. (2009). Nutrition, brain aging, and neurodegeneration. *The Journal of Neuroscience, 29*(41), 12795-12801. doi: 10.1523/jneurosci.3520-09.2009
Joseph, J.A., Shukitt-Hale, B., & Casadesus, G. (2005). Reversing the deleterious effects of aging on neuronal communication and behavior: beneficial properties

of fruit polyphenolic compounds. *American Journal of Clinical Nutrition., 81*(1), 313S-316.
Kalmijn, S. (2002). Dietary fatty acids and cognitve function. In M.P.Matteson (Ed.), *Diet-brain connections*
New York: Springer Science and Buiness Media
Kalmijn, S., Feskins, E.J.M., Launer, L.J., & Kromhourt, D. (1997). Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *American Journal of Epidemiology, 145*(1), 33-41.
Kang, J., Cook, N., Manson, J., Buring, J., Albert, C., & Grodstein, F. (2008). A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. *American Journal of Clinical Nutrition, 86*(6), 1602-1610. doi: doi: 10.3945/ajcn.2008.26404
Kang, J., Cook, N., Manson, J., Buring, J., Albert, C., & Grodstein, F. (2009). Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: The Women's Antioxidant and Cardiovascular Study. *Circulation, 119*(21), 2772-2780. doi: 10.1161/CIRCULATIONAHA.108.816900
Kant, A.K. (2004). Dietary patterns and health outcomes. *Journal of the American Dietetic Association, 104*(4), 615-635.
Kastorini, C.-M., Milionis, H.J., Esposito, K., Giugliano, D., Goudevenos, J.A., & Panagiotakos, D.B. (2011). The effect of mediterranean diet on metabolic syndrome and its components: A meta-analysis of 50 Studies and 534,906 Individuals. *Journal of the American College of Cardiology, 57*(11), 1299-1313. doi: 10.1016/j.jacc.2010.09.073
Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology, 23*(2), 138-144.
Kennedy, E.T., Ohls, J., Carlson, S., & Fleming, K. (1995). The Healthy Eating Index: Design and applications. *Journal of the American Dietetic Association, 95*(10), 1103-1108.
Kerola, T., Kettunen, R., & Nieminen, T. (2011). The complex interplay of cardiovascular system and cognition: How to predict dementia in the elderly? *International Journal of Cardiology, 150*(2), 123-129.
Kesse-Guyot, E., Amieva, H., Castetbon, K., Henegar, A., Ferry, M., Jeandel, C. (2011). Adherence to nutritional recommendations and subsequent cognitive performance: findings from the prospective Supplementation with Antioxidant Vitamins and Minerals 2 (SU.VI.MAX 2) study *American Journal of Clinical Nutrition* (Vol. 93, pp. 200-210).
Kesse-Guyot, E., Andreeva, V., Lassale, C., Ferry, M., Jeandel, C., Hercberg, S. (2013). Mediterranean diet and cognitive function: a French study. *American Journal of Clinical Nutrition, 97*(2), 369-376. doi: 10.3945/ajcn.112.047993.
Kesse-Guyot, E., Andreeva, V.A., Jeandel, C., Ferry, M., Hercberg, S., & Galan, P. (2012). A healthy dietary pattern at midlife is associated with subsequent cognitive performance. *The Journal of Nutrition*. doi: 10.3945/jn.111.156257
Kesse-Guyot E, A.V., Lassale C, Ferry M, Jeandel C, Hercberg S, Galan P; SU.VI.MAX 2 Research Group. (2013). Mediterranean diet and cognitive function: a French study. *American Journal of Clinical Nutrition, 97*(2), 369-376. doi: 10.3945/ajcn.112.047993.

Kesse-Guyot, E., Fezeu, L., Jeandel, C., Ferry, M., Andreeva, V., Amieva, H. (2011). French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial *American Journal of Clinical Nutrition*.

Kesse-Guyot, E., Péneau, S., Ferry, M., Jeandel, C., Hercberg, S., & Galan, P. (2010). Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function. *The Journal of Nutrition, Health and Aging*, 1-6.

Key, T.J., Schatzkin, A., Willett, W.C., Allen, N.E., Spencer, E.A., & Travis, R.C. (2004). Diet, nutrition, and the prevention of cancer. *Public Health Nutrition, 7(*(1A)), 187-200.

Kim, H.S., Park, S.Y., Grandinetti, A., Holck, P.S., & Waslien, C. (2008). Major dietary patterns, ethnicity, and prevalence of type 2 diabetes in rural Hawaii. *Nutrition, 24*(11-12), 1065-1072.

Kivipelto, M., Helkala, E.-L., Hänninen, T., Laakso, M.P., Hallikainen, M., Alhainen, K. (2001). Midlife vascular risk factors and late-life mild cognitive impairment. *Neurology, 56*(12).

Kline, P. (1994). *An easy guide to factor analysis*. London: Routledge.

Knopman, D., Boland, L.L., Mosley, T., Howard, G., Liao, D., Szklo, M. (2001). Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology, 56*(1), 42-48.

Knopman, D.S., Mosley, T.H., Catellier, D.J., & Coker, L.H. (2009). Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI Study. *Alzheimer's and Dementia, 5*(3), 207-214.

Knopman, D.S., Parisi, J.E., Salviati, A., Floriach-Robert, M., Boeve, B.F., Ivnik, R.J. (2003). Neuropathology of cognitively normal elderly. *Journal of Neuropathology & Experimental Neurology, 62*(11), 1087-1095.

Kramer, M.S., Aboud, F., Mironova, E., Vanilovich, I., Platt, R.W., Matush, L. (2008). Breastfeeding and child cognitive development: New evidence from a large randomized trial. *Archives of General Psychiatry, 65*(5), 578-584.

Kuh, D. (2007). A life course approach to healthy aging, frailty, and capability (Vol. 62, pp. 717-721).

Kuh, D., Ben-Shlomo, Y., Lynch, J., Hallqvist, J., & Power, C. (2003). Life course epidemiology. *Journal of Epidemiology and Community Health, 57*(10), 778-783. doi: 10.1136/jech.57.10.778

Kuzma, J.W., & Lindsted, K.D. (1988). Determinants of long-term (24-year) diet recall ability using a 21-item food frequency questionnair. *Nutrition and Cancer, 12*(2), 151-160.

Kuzma, J.W., & Lindsted, K.D. (1990). Determinants of eight-year diet recall ability. *Epidemiology, 1*(5), 386-391.

Kyllonen, P.C., & Christal, R.E. (1990). Reasoning ability is (little more than) working-memory capacity?! *Intelligence, 14*(4), 389-433.

La Vecchia, C., Negri, E., Franceschi, S., Parazzini, F., & Decarli, A. (1992). Differences in dietary intake with smoking, alcohol, and education. *Nutrition and Cancer, 17*(3), 297-304.

Lake, A.A., Mathers, J.C., Rugg-Gunn, A.J., & Adamson, A.J. (2006). Longitudinal change in food habits between adolescence (11 - 12 years) and adulthood (32 - 33 years): the ASH30 Study. *Journal of Public Health, 28*(1), 10-16. doi: 10.1093/pubmed/fdi082

Lake, A.A., Rugg-Gunn, A.J., Hyland, R.M., Wood, C.E., Mathers, J.C., & Adamson, A.J. (2004). Longitudinal dietary change from adolescence to adulthood: perceptions, attributions and evidence. *Appetite, 42*(3), 255-263.

Lambrinoudaki, I., Ceasu, I., Depypere, H., Erel, T., Rees, M., Schenck-Gustafsson, K. (2013). EMAS position statement: Diet and health in midlife and beyond. *Maturitas, 74*(1), 99-104.

Lau, F.C., Shukitt-Hale, B., & Joseph, J.A. (2005). The beneficial effects of fruit polyphenols on brain aging. *Neurobiology of Aging, 26*(1, Supplement), 128-132.

Launer, L.J. (2002). Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Research Reviews, 1*(1), 61-77.

Laurin, D., Masaki, K.H., Foley, D.J., White, L.R., & Launer, L.J. (2004). Midlife dietary intake of antioxidants and risk of late-life incident dementia: The Honolulu-Asia Aging Study. *American Journal of Epidemiology, 159*(10), 959-967. doi: 10.1093/aje/kwh124

Lawlor, D.A., & Smith, G.D. (2005). Early life determinants of adult blood pressure. *Current Opinion in Nephrology and Hypertension, 14*(3), 259-264.

Lazarus, R., Wilson, A., Gliksman, M., & Aiken, J. (1995). Repeatability of nutrient intakes estimated by a semi-quantitative food frequency questionnaire in elderly subjects. *Annals of Epidemiology, 5*(1), 65-68.

Lee, C., Dobson, A.J., Brown, W.J., Bryson, L., Byles, J., Warner-Smith, P. (2005). Cohort Profile: The Australian Longitudinal Study on Women's Health (Vol. 34, pp. 987-991).

Lee, H., Carolyn, D.S., Julian, P.T.H., Rachel, L.T., Nigel, E.C., George Davey, S. (2001). Dietary fat intake and prevention of cardiovascular disease: systematic review. *British Medical Journal, 322*(7289), 757-763. doi: 10.1136/bmj.322.7289.757

Lee, T., Henry, J.D., Trollor, J.N., & Sachdev, P.S. (2010). Genetic influences on cognitive functions in the elderly: A selective review of twin studies. *Brain Research Reviews, 64*(1), 1-13.

Levin, E.D., McClernon, F.J., & Rezvani, A.H. (2006). Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology, 184*(3/4), 523-539.

Lewerin, C., Matousek, M., Steen, G., Johansson, B., Steen, B., & Nilsson-Ehle, H. (2005). Significant correlations of plasma homocysteine and serum methylmalonic acid with movement and cognitive performance in elderly subjects but no improvement from short-term vitamin therapy: a placebo-controlled randomized study (Vol. 81, pp. 1155-1162).

Lezak, M., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological assessment* (4th ed.). Oxford: Oxford University Press.

Liu-Ambrose, T., Nagamatsu, L.S., Graf, P., Beattie, B.L., Ashe, M.C., & Handy, T.C. (2010). Resistance training and executive functions: A 12-month randomized controlled trial. *Archives of Internal Medicine, 170*(170-178).

Liu, S., Jones, R., N. , & Glymour, M.M. (2010). Implications of lifecourse epidemiology for research on determinants of adult disease. *Public Health Reviews, 32*(2), 489-511.

Loef, M., & Walach, H. (2012). Fruit, vegetables, and prevention of cognitive decline or dementia: A systematic review of cohort studies. *The Journal of Nutrition Health and Aging, 16*.

Loef, M., & Walach, H. (2013). The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence. *Journal of nutrition in gerontology and geriatrics, 1*, 1-23. doi: 10.1080/21551197.2012.752335.

Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I.A., Ukoumunne, O.C. (2013). Mediterranean diet, cognitive function, and dementia: A systematic review (Vol. 24, pp. 479-489 410.1097/EDE.1090b1013e3182944410).

Luchsinger, J.A., Tang, M.-X., Shea, S., & Mayeux, R. (2002). Caloric intake and the risk of Alzheimer disease. *Archives of Neurology, 59*(8), 1258-1263. doi: 10.1001/archneur.59.8.1258

Lukiw, W.J., & Bazan, N.G. (2008). Docosahexaenoic acid and the aging brain. *The Journal of Nutrition, 138*(12), 2510-2514. doi: 10.3945/jn.108.096016

Luria, A.R. (1966). *Human brain and psychological process*. New York: Harper and Row.

MacDonald, S.W.S., Dixon, R.A., Cohen, A.L., & Hazlitt, J.E. (2004). Biological age and 12-year cognitive change in older adults: Findings from the Victoria Longitudinal Study. *Gerontology, 50*(2), 64-81.

Macready, A.L., Butler, L.T., Kennedy, O.B., Ellis, J.A., Williams, C.M., & Spencer, J.P.E. (2010). Cognitive tests used in chronic adult human randomised controlled trial micronutrient and phytochemical intervention studies (Vol. 23, pp. 200-229): Cambridge Journals Online.

Maillard, P., Seshadri, S., Beiser, A., Himali, J.J., Au, R., Fletcher, E. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *The Lancet Neurology, 11*(12), 1039-1047.

Mariani, E., Polidori, M.C., Cherubini, A., & Mecocci, P. (2005). Oxidative stress in brain aging, neurodegenerative and vascular diseases: An overview. *Journal of Chromatography B, 827*(1), 65-75.

Marmot, M., & Brunner, E. (2005). Cohort profile: The Whitehall II study. *The International Journal of Epidemiology, 34*(2), 251-256. doi: 10.1093/ije/dyh372

Martin, R.M., Gunnell, D., Pemberton, J., Frankel, S., & Davey Smith, G. (2005). Cohort Profile: The Boyd Orr cohort - an historical cohort study based on the 65 year follow-up of the Carnegie Survey of Diet and Health (1937-1939). *International Journal of Epidemiology, 34*(4), 742-749. doi: 10.1093/ije/dyi124

Martinez, M. (1992). Tissue levels of polyunsaturated fatty acids during early human development. *The Journal of Pediatrics, 120*(4 (part 2)), S129-S138.

Martínez, M.E., Marshall, J.R., & Sechrest, L. (1998). Invited commentary: Factor analysis and the search for objectivity. *American Journal of Epidemiology, 148*(1), 17-19.

Maruti, S.S., Feskanich, D., Colditz, G.A., Frazier, A.L., Sampson, L.A., Michels, K.B. (2005). Adult recall of adolescent diet: Reproducibility and comparison with maternal reporting. *American Journal of Epidemiology, 161*(1), 89-97. doi: 10.1093/aje/kwi019

Mattson, M.P., Chan, S.L., & Duan, W. (2002). Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. *Physiol. Rev., 82*(3), 637-672.

Mattson, M.P., Duan, W., Chan, S.L., Cheng, A., Haughey, N., Gary, D.S. (2002). Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior. *Neurobiology of aging, 23*, 695-705.

Maynard, M., Gunnell, D., Emmett, P., Frankel, S., & Davey Smith, G. (2003). Fruit, vegetables, and antioxidants in childhood and risk of adult cancer: the Boyd Orr cohort. *J Epidemiol Community Health, 57*(3), 218-225. doi: 10.1136/jech.57.3.218

Maynard, M., Gunnell, D., Ness, A.R., Abraham, L., Bates, C.J., & Blane, D. (2006). What influences diet in early old age? Prospective and cross-sectional analyses of the Boyd Orr cohort (Vol. 16, pp. 315-323).

McArdle, J.J., Hamagami, F., Meredith, W., & Bradway, K.P. (2000). Modeling the dynamic hypotheses of Gf-Gc theory using longitudinal life-span data. *Learning & Individual Differences, 12*(1), 53.

McDonald, M., Hertz, R.P., Unger, A.N., & Lustik, M.B. (2009). Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among US adults aged 65 and older. *Journal of Gerontology: Medical Sciences, 64*(259-263).

McGrew, K.S. (2005). The Cattel-Horrn-Carroll theory of cognitive abilities. In D. P. Flannigan & P. L. Harrison (Eds.), *Contempory intellectual assessment:Theories, tests, and issues* (2nd ed., pp. 136-202). New York: The Guilford Press.

McGue, M., & Christensen, K. (2001). The heritability of cognitive functioning in very old adults: evidence from danish twins aged 75 years and older. *Psychology & Aging, 16*(2), 272-280.

McGue, M., & Christensen, K. (2007). Social activity and healthy aging: A study of aging danish twins. *Twin Research and Human Genetics, 10*(02), 255-265. doi: doi:10.1375/twin.10.2.255

McKeown-Eyssen, G.E., Yeung, K.S., & Bright-See, E. (1986). Assessment of past diet in epidimiologic studies. *American Journal of Epidemiology, 124*(1), 94-103.

McMahon, J.A., Green, T.J., Skeaff, C.M., Knight, R.G., Mann, J.I., & Williams, S.M. (2006). A controlled trial of homocysteine lowering and cognitive performance. *The New England Journal of Medicine, 354*(26), 2764-2772. doi: doi:10.1056/NEJMoa054025

Mendez, M.A., & Adair, L.S. (1999). Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. *The Journal of Nutrition, 129*(8), 1555-1562.

Mente, A., de Koning, L., Shannon, H.S., & Anand, S.S. (2009). A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Archives of Internal Medicine, 169*(7), 659-669. doi: 10.1001/archinternmed.2009.38

Meredith, W., & Horn, J.L. (2001). The role of factorial invariance in modeling growth and change. In L. M. Collins & A. G. Sayer (Eds.), *New methods for the analysis of change* (pp. 201-240). Washington: American Psychological Association.

Michelakos, T., Kousoulis, A.A., Katsiardanis, K., Dessypris, N., Anastasiou, A., Katsiardani, K.-P. (2013). Serum folate and B12 levels in association with cognitive impairment among seniors: Results from the VELESTINO study in Greece and meta-analysis. *Journal of Aging and Health, 25*(4), 589-616. doi: 10.1177/0898264313482488

Michels, K.B., & Schulze, M.B. (2005). Can dietary patterns help us detect diet/disease associations? (Vol. 18, pp. 241-248): Cambridge Journals Online.

Michels, K.B., & Willett, W.C. (2009). Self-administered semiquantitative food frequency questionnaires: Patterns, predictors, and interpretation of omitted tems. *Epidemiology, 20*(2), 295-301.

Miller, D.I., Taler, V., Davidson, P., & Messier, C. (2012). Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiology of Aging, 33*(3), 29-43.

Miller, L.T. (1999). Psychometric and information processing approaches to measuring cognitive abilities: Paradigms in military testing. *Canadian Psychology, 40*(3), 241-254.

Minihane, A.M., Khan, S., Leigh-Firbank, E.C., Talmud, P., Wright, J.W., Murphy, M.C. (2000). ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. *Arteriosclerosis,Thrombosis and Vascular Biology, 20*(8), 1990-1997.

Mishra, G., Ball, K., Arbuckle, J., & Crawford, D. (2002). Dietary patterns of Australian adults and their association with socioeconomic status: results from the 1995 National Nutrition Survey. *European Journal of Clinical Nutrition, 56*(7), 687.

Mishra, G.D., Malik, N.S., Paul, A.A., Wadsworth, M.E.J., & Bolton-Smith, C. (2003). Childhood and adult dietary vitamin E intake and cardiovascular risk factors in mid-life in the 1946 British Birth Cohort. *European Journal of Clinical Nutrition, 57*(11), 1418-1425.

Mishra, G.D., McNaughton, S.A., Ball, K., Brown, W.J., Giles, G.G., & Dobson, A.J. (2010). Major dietary patterns of young and middle aged women: results from a prospective Australian cohort study. *European Journal of Clinical Nutrition, 64*(10), 1125-1133.

Mishra, G.D., McNaughton, S.A., Bramwell, G.D., & Wadsworth, M.E.J. (2006). Longitudinal changes in dietary patterns during adult life. *British Journal of Nutrition, 96*(04), 735-744. doi: doi:10.1079/BJN20061871

Mishra, G.D., Prynne, C.J., Paul, A.A., Greenberg, D.C., & Bolton-Smith, C. (2004). The impact of inter-generational social and regional circumstances on dietary intake patterns of British adults: results from the 1946 British Birth Cohort. *Public Health Nutrition, 7*(06), 737-744. doi: doi:10.1079/PHN2004610

Moeller, S.M., Reedy, J., Millen, A.E., Dixon, L.B., Newby, P.K., Tucker, K.L. (2007). Dietary patterns: Challenges and opportunities in dietary patterns research: An experimental biology workshop. *Journal of the American Dietetic Association, 107*(7), 1233-1239.

Molloy, D.W., & Standish, T.I.M. (1997). Mental status and neuropsychological assessment: A guide to the standatized Mini-Mental State Examination. *International Psycholgeriatrics, 9: Supplement 1*, 87-94.

Moore, J.V., Prestridge, L.L., & Newell, G.R. (1981). Research technique for epidemiologic investigation of nutrition and cancer. *Nutrition and Cancer, 3*(4), 249-256.

Morris, M.C. (2012). Nutritional determinants of cognitive aging and dementia. *Proceedings of the Nutrition Society, 71*, 1-13. doi: 10117/S0029665111003296

Morris, M.C., Evans, D.A., Bienias, J.L., Tangney, C.C., Bennett, D.A., Aggarwal, N. (2002). Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA, 287*(24), 3230-3237. doi: 10.1001/jama.287.24.3230

Morris, M.C., Evans, D.A., Tangney, C.C., Bienias, J.L., & Wilson, R.S. (2006). Associations of vegetable and fruit consumption with age-related cognitive change. *Neurology, 67*(8).

Mullie, P., Clarys, P., Hulens, M., & Vansant, G. (2010). Dietary patterns and socioeconomic position. *Eur J Clin Nutr, 64*(3), 231-238.

Mungas, D., Beckett, L., Harvey, D., Tomaszewski Farias, S., Reed, B., Carmichael, O. (2010). Heterogeneity of cognitive trajectories in diverse older persons. *Psychology and Aging*.

Murtaugh, M.A., Sweeney, C., Giuliano, A.R., Herrick, J.S., Hines, L., Byers, T. (2008). Diet patterns and breast cancer risk in Hispanic and non-Hispanic white women: the Four-Corners Breast Cancer Study. *American Journal of Clinical Nutrition, 87*(4), 978-984.

Muthén, L.K., & Muthén, B.O. (2007). *Mplus User's Guide* (5th ed.). Los Angeles, CA: Muthén & Muthén.

Myers, R.H. (1990). *Classical and modern regression with applications*. Boston: Duxbury.

Nash, D.T., & Howard., F. (2006). Cardiovascular disease risk factors and cognitive impairment. *American Journal of Cardiology, 97*, 1262-1265.

Nelson, K. (1993). The psychological and social origins of autobiographical memory. *Psychological science, 4*(1), 7-14.

Nelson, M., & Bingham, S.A. (1997). Assessment of food consumption and nutrient intake. In B. M. Margetts & M. Nelson (Eds.), *Design concepts in nutritional epidemiology* (pp. 123-169). Oxford: Oxford University Press.

Ness, A.R., Maynard, M., Frankel, S., Davey Smith, G., Frobisher, C., Leary, S.D. (2005). Diet in childhood and adult cardiovascular and all cause mortality: the Boyd Orr cohort. *Heart, 91*(7), 894-898. doi: 10.1136/hrt.2004.043489

Nesselroade, J.R., & Estabrook, R. (2009). Factor invariance, measurement, and studying development over the life span. In H. B. Bosworth & C. Hertzog (Eds.), *Aging and Cognition: Research Methodologies and Empirical Advances* (pp. 39-52). Washington: American Psychological Association.

Nettelbeck, T. (2001). Correlation between inspection time and psychometric abilities: A personal interpretation. *Intelligence, 29*(6), 459-474.

Nettelbeck, T. (2011). Basic processes of intelligence. In R. J. Sternberg & S. B. Kaufman (Eds.), *The Cambridge handbook of intelligence*. New York: Cambridge University Press.

Nettiksimmons, J., Beckett, L., Schwarz, C., Carmichael, O., Fletcher, E., & DeCarli, C. (2013). Subgroup of ADNI normal controls characterized by atrophy and cognitive decline associated with vascular damage. *Psychology & Aging, 28*(1), 191-201.

Newby, P.K., & Tucker, K.L. (2004). Empirically derived eating patterns using factor or cluster analysis: A review. *Nutrition Reviews, 62*(5), 177-203.

Newby, P.K., Weismayer, C., Akesson, A., Tucker, K.L., & Wolk, A. (2006). Long-term stability of food patterns identified by use of factor analysis among Swedish women (Vol. 136, pp. 626-633).

Newkirk, L.A., Kim, J.M., Thompson, J.M., Tinklenberg, J.R., Yesavage, J.A., & Taylor, J.L. (2004). Validation of a 26-point telephone version of the Mini-Mental State Examination. *Journal of Geriatric Psychiatry and Neurology, 17*(2), 81-87.

NHMRC. (2003). *Dietary Guidelines for Australian Adults*. Commonwealth of Australia.

NHMRC. (2009). Nutrient reference values for Australia and New Zealand., from http://www.nrv.gov.au/disease/introduction.htm

Northstone, K., & Emmett, P.M. (2008). Are dietary patterns stable throughout early and mid-childhood? A birth cohort study (Vol. 100, pp. 1069-1076): Cambridge Journals Online.

Northstone, K., Joinson, C., Emmett, P., Ness, A., & Paus, T. (2011). Are dietary patterns in childhood associated with IQ at 8 years of age? A population-based cohort study. *Journal of Epidemiology and Community Health*. doi: 10.1136/jech.2010.111955

Nunnally, J.C., & Bernstein, I.H. (Eds.). (1994). *Psychometric theory* (3rd ed.). New York: McGraw Hill, Inc.

Nurk, E., Refsuma, H., Drevona, C., Tella, G., Nygaarda, H., Engedala, K. (2010). Cognitive performance among the elderly in relation to the intake of plant foods. The Hordaland Health Study. *British Journal of Nutrition*(104), 1190-1201.

Nyaradi, A., Jianghong, L., Hickling, S., Foster, J., & Oddy, W. (2013). The role of nutrition in children's neurocognitive development, from pregnancy thorough childhood. *Frontiers in Human Neuroscience, 7*, 1-16.

O'Bryant, S.E., Humphreys, J.D., Smith, G.E., Ivnik, R.J., Gragg-Radford, M.D., Petersen, M.D. (2008). Detecting dementia with the mini-mental state examination in highly educated individuals. *Archives of Neurology, 65*(7), 963-967.

O'Doherty, Skidmore, Young, McKinley, Cardwell, Yarnell. (2011). Dietary patterns and smoking in Northern Irish men: A population at high risk of coronary heart disease. *International Journal for Vitamin and Nutrition Research, 81*(1), 21-33. doi: 10.1024/0300-9831/a000047

Ockene, I.S., & Miller, N.H. (1997). Cigarette smoking, cardiovascular disease, and stroke: A statement for healthcare professionals from the american heart association (Vol. 96, pp. 3243-3247).

Oh, K., Hu, F.B., Manson, J.E., Stampfer, M.J., & Willett, W.C. (2005). Dietary fat iIntake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *American Journal of Epidemiology, 161*(7), 672-679. doi: 10.1093/aje/kwi085

Okayama, A., Kadowaki, T., Okamura, T., Hayakawa, T., & Ueshima, H. (2006). Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men *Journal of Hypertension, 24*(3), 459-462.

Okereke, O.I., Rosner, B.A., Kim, D.H., Kang, J.H., Cook, N.R., Manson, J.E. (2012). Dietary fat types and 4-year cognitive change in community-dwelling older women. *Annals of Neurology, 72*(1), 124-134.

Osendarp, S.J., Baghurst, K.I., Bryan, J., Calvaresi, E., Hughes, D., Hussaini, M. (2007). Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia (Vol. 86, pp. 1082-1093).

Packard, C.J., Westendorp, R.G.J., Stott, D.J., Caslake, M.J., Murray, H.M., Shepherd, J. (2007). Association between apolipoprotein e4 and cognitive decline in elderly adults. *Journal of the American Geriatrics Society, 55*(11), 1777-1785.

Park, S.-Y., Murphy, S.P., Wilkens, L.R., Yamamoto, J.F., Sharma, S., Hankin, J.H. (2005). Dietary patterns using the food guide pyramid groups are associated

with sociodemographic and lifestyle factors: The multiethnic cohort study. *The Journal of Nutrition, 135*(4), 843-849.
Pedersen, N.L. (2000). Genetics of human aging: Swedish twin studies. *Generations, 24*(1), 31.
Peduzzi, P., Concato, J., Kemper, E., Holford, T.R., & Feinstein, A.R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology, 49*(12), 1373-1379.
Pellegrini, N., Serafini, M., Colombi, B., Del Rio, D., Salvatore, S., Bianchi, M. (2003). Total antioxidant capacity of plant foods, beverages and oils consumed in italy assessed by three different In vitro assays. *Journal of Nutrition 133*(9), 2812-2819.
Pereira, A.C., Huddleston, D.E., Brickman, A.M., Sosunov, A.A., Hen, R., McKhann, G.M. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America, 104*(13), 5638-5643. doi: 10.1073/pnas.0611721104
Persson, P.-G., Ahlbom, A., & Norell, S.E. (1990). Retrospective versus original information on diet: Implications for epidemiological studies *The Internaitional Journal of Epidemiology* (Vol. 19, pp. 343-348).
Peters, R., Poulter, R., Warner, J., Beckett, N., Burch, L., & Bulpitt, C. (2008). Smoking, dementia and cognitive decline in the elderly, a systematic review (Vol. 8, pp. 36).
Pillemer, D.B. (1998). What is remembered about early childhood events? *Clinical Psychology Review, 18*(8), 895-913.
Plassman, B.L., Williams, J.W., Burke, J.R., Holsinger, T., & Benjamin, S. (2010). Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine, 153*(3), 182-W.169.
Plourde, M. (2011). Fatty acid intake and cognitive decline. In D. Benton (Ed.), *Lifetime nutrtional influences on cognition, behaviour and psychiatric illness*. Cambridige: Woodhead publishing.
Plourde, M., Vohla, M., Vandal, M., Couture, P., Lemieuxa, S., & Cunnanea, S. (2009). Plasma n-3 fatty acid response to an n-3 fatty acid supplement is modulated by apoE 4 but not by the common PPAR-α L162V polymorphism in men. *British Journal of Nutrition, 102,* 1121-1124.
Pocernich, C., Butterfield, D.A., & Head, E. (2013). Diet and brain aging: effects on cell and mitochondrial function and structure. In R. R. Watson & V. R. Preedy (Eds.), *Bioactive Food as Dietary Interventions for the Aging Population* (Vol. 20, pp. 249-262). San Diego: Academic Press.
Pollitt, E., Gorman, K.S., Engle, P., Martorell, R., & Rivera, J. (1993). Early supplementary feeding and cognition: effects over two decades. *Monographs of the Society for Research in Child Development, 58*(7), 1-99.
Power, C., & Hertzman, C. (1997). Social and biological pathways linking early life and adult disease. *British Meidcal Bulletin, 53*(1), 210-221.
Price, J.L., & Morris, J.C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of Neurology, 45*(3), 358-368.
Pryer, J.A., Nichols, R., Elliott, P., Thakrar, B., Brunner, E., & Marmot, M. (2001). Dietary patterns among a national random sample of British adults. *Journal of Epidemiology and Community Health, 55*(1), 29-37. doi: 10.1136/jech.55.1.29
Prynne, C.J., Paul, A.A., Mishra, G.D., Greenberg, D.C., & Wadsworth, M.E. (2005). Changes in intake of key nutrients over 17 years during adult life of a British

birth cohort. *British Journal of Nutrition, 94*(03), 368-376. doi: doi:10.1079/BJN20041404

Rabbitt, P., Diggle, P., Smith, D., Holland, F., & Mc Innes, L. (2001). Identifying and separating the effects of practice and of cognitive ageing during a large longitudinal study of elderly community residents. *Neuropsychologia, 39*(5), 532-543.

Rabbitt, P., Scott, M., Lunn, M., Thacker, N., Lowe, C., Pendleton, N. (2007). White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology, 21*(3), 363-370.

Rabbitt, P.M.A., McInnes, L., Diggle, P., Holland, F., Bent, N., Abson, V. (2004). The University of Manchester longitudinal study of cognition in normal healthy old age, 1983 through 2003. *Aging, Neuropsychology & Cognition, 11*(2/3), 245-279.

Rabinovici, G.D., & Jagust, W.J. (2009). Amyloid imaging in aging and dementia: Testing the amyloid hypothesis in vivo. *Behavioural Neurology, 21*(1), 117-128.

Radloff, L.S. (1977). The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401.

Raman, G., Tatsioni, A., Chung, M., Rosenberg, I.H., Lau, J., Lichtenstein, A.H. (2007). Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function. *The Journal of Nutrition, 137*(7), 1789-1794.

Raz, N., & Rodrigue, K.M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews, 30*, 730-748.

Raz, N., Rodrigue, K.M., Kennedy, K.M., & Acker, J.D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology, 21*(2), 149-157.

Reddy, K.S., & Katan, M.B. (2004). Diet, nutrition and the prevention of hypertension and cardiovascular diseases. *Public Health Nutrition, 7*(1a), 167-186. doi: 10.1079/PHN2003587

Reed, B.R., Mungas, D., Farias, S.T., Harvey, D., Beckett, L., Widaman, K. (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. *Brain, 133*(8), 2196-2209. doi: 10.1093/brain/awq154

Reynolds, C.A., Finkel, D., McArdle, J.J., Gatz, M., Berg, S., & Pedersen, N.L. (2005). Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Developmental Psychology, 41*(1), 3-16.

Riboli, E. (1989). Methodological issues in the investigation of diet and cancer in humans. In A. B. Miller (Ed.), *Diet and the aetiology of cancer* (pp. 55-63). Berlin: Springer-Verlag

Richards, M., & Deary, I. (2005). A life course approach to cognitive reserve: A model for cognitive aging and development? *Annals of Neurology, 58*(4), 617-622.

Richards, M., Jarvis, M.J., Thompson, N., & Wadsworth, M.E.J. (2003). Cigarette smoking and cognitive decline in midlife: Evidence from a prospective birth cohort study *American Journal of Puublic Health* (Vol. 93, pp. 994-998).

Riley, K.P., Snowdon, D.A., Desrosiers, M.F., & Markesbery, W.R. (2005). Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. *Neurobiology of Aging, 26*(3), 341-347.

Roberts, R.O., Geda, Y.E., Cerhan, J.R., Knopman, D.S., Cha, R.H., Christianson, T.J. (2010). Vegetables, unsaturated fats, moderate alcohol intake, and mild

cognitive impairment. *Dementia and Geriatric Cognitive Disorders Extra, 29*(5), 413-423. doi: 10.1159/000305099
Rohan, T.E., & Potter, J.D. (1984). Retrospective assessment of dietary intake. *American Journal of Epidemiology., 120*(6), 876-887.
Rowe, C.C., Ellis, K.A., Rimajova, M., Bourgeat, P., Pike, K.E., Jones, G. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of Aging, 31*(8), 1275-1283.
Sabia, S., Elbaz, A., Dugravot, A., & et al. (2012). Impact of smoking on cognitive decline in early old age: The Whitehall-II cohort study. *Archives of General Psychiatry, 69*(6), 627-635.
Salthouse, T. (1988). *Adult cognition: An experimental psychology of human aging*. New York: Spriinger-Verlag.
Salthouse, T. (2010a). *Major issues in cognitive aging*. New York: Oxford University Press.
Salthouse, T. (2010b). Selective review of cognitive aging. *Journal of the International Neuropsychological Society, 16*(05), 754-760. doi: 10.1017/S1355617710000706
Salthouse, T., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Psychology and Aging, 18*(1), 91-110.
Salthouse, T., Schroeder, D.H., & Ferrer, E. (2004). Estimating retest effects in longitudinal assessments of cognitve functioning in adults between 18 and 60 years of age. *Developmental Psychology, 40*(5), 813-822.
Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428.
Salthouse, T.A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507-514.
Samieri, C., Jutand, M.A., Feart, C., Capuron, L., Letenneur, L., & Barberger-Gateau, P. (2008). Dietary patterns derived by hybrid clustering method in older people: Association with cognition, mood, and self-rated health. *Journal of the American Dietetic Association, 108*(9), 1461-1471. doi: 10.1016/j.jada.2008.06.437
Samieri, C., Okereke, O.I., Devore, E.E., & Grodstein, F. (2013). Long-term adherence to the Mediterranean diet Is associated with overall cognitive status, but not cognitive decline, in women.
Sattler, C., Erickson, K.I., Toro, P., & Schröder, J. (2011). Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in germany. *Journal of Alzheimer's Disease, Epub ahead of print*.
Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273-295.
Savva, G.M., Wharton, S.B., Ince, P.G., Forster, G., Matthews, F.E., & Brayne, C. (2009). Age, neuropathology, and dementia. *New England Journal of Medicine, 360*(22), 2302-2309. doi: doi:10.1056/NEJMoa0806142
Scarmeas, N., Luchsinger, J.A., Schupf, N., Brickman, A.M., Cosentino, S., Tang, M.X. (2009). Physical activity, diet, and risk of Alzheimer disease. *The Journal of the American Medical Association, 302*(6), 627-637. doi: 10.1001/jama.2009.1144
Scarmeas, N., Luchsinger, J.A., Stern, Y., Gu, Y., He, J., DeCarli, C. (2011). Mediterranean diet and magnetic resonance imaging–assessed cerebrovascular disease. *Annals of Neurology, 69*(2), 257-268.

Scarmeas, N., Stern, Y., Mayeux, R., Manly, J.J., Schupf, N., & Luchsinger, J.A. (2009). Mediterranean diet and mild cognitive impairment. *Archives of Neurology, 66*(2), 216-225. doi: 10.1001/archneurol.2008.536

Scarmeas, N., Stern, Y., Tang, M., Mayeux, R., & Luchsinger, J. (2006). Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology, 59*(6), 912-921.

Schafer, J.L., & Graham, J.W. (2002). Missing data: Our view of the state of the art. *Psychological Methods, 7*(2), 147-177.

Schaie, K.W. (1988). Internal validity threats in studies of adult cognitive development. In M. L. Lowe & C. J. Brainard (Eds.), *Cognitive development in adulthood: Progress in cognitive development research* (pp. 241-272). New York: Springer-Verlag.

Schaie, K.W. (1994). The course of adult intellectual development. *American Psychologist, 49*(4), 304-313. doi: 10.1037/0003-066X.49.4.304

Schaie, K.W. (2005). *Developmental influences on adult intelligence:The Seattle Longitudinal Study*. New York: Oxford University Press Inc.

Schaie, K.W., & Baltes, P.B. (1977). Some faith helps to see the forest: A final comment on the Horn and Donaldson myth of the Baltes-Schaie position on adult intelligence. *American Psychologist, 32*(12), 1118-1120.

Schiepers, O.J.G., Harris, S.E., Gow, A.J., Pattie, A., Brett, C.E., Starr, J.M. (2012). Apoe ε-4 status predicts age-related cognitive decline in the ninth decade: Longitudinal follow-up of the Lothian Bitith Cohort 1921. *Molecular Psychiatry, 17*, 315-324.

Schipper, H.M. (2011). Apolipoprotein E: Implications for AD neurobiology, epidemiology and risk assessment. *Neurobiology of Aging, 32*, 778-790.

Schmitt, J.A.J., Benton, D., & Kallus, W.K. (2005). General methodological considerations of the assessment of nutritional influences on human cognitive functions. *European Joournal of Nutrition.*, 459-464.

Schulze, M.B., & Hoffmann, K. (2006). Methodological approaches to study dietary patterns in relation to risk of coronary heart disease and stroke. *British Journal of Nutrition, 95*(05), 860-869. doi: doi:10.1079/BJN20061731

Schulze, M.B., Hoffmann, K., Manson, J.E., Willett, W.C., Meigs, J.B., Weikert, C. (2005). Dietary pattern, inflammation, and incidence of type 2 diabetes in women. *American Journal of Clinical Nutrition, 82*(3), 675-684.

Schwenke, D.C. (2010). Dietary patterns: designs for progress and approaches for health impact. *21*(3), 276-279 210.1097/MOL.1090b1013e328339b328358c.

Selhub, J., Troen, A., & Rosenberg, I.H. (2010). B vitamins and the aging brain. *Nutrition Reviews, 68*, S112-S118.

Serra-Majem, L., Roman, B., & Estruch, R.n. (2006). Scientific evidence of interventions using the Mediterranean diet: A systematic review. *Nutrition Reviews, 64*(2), S27-S47.

Shatenstein, B., Payette, H., Nadon, S., & Gray-Donald, K. (2003). An approach for evaluating lifelong intakes of functional foods in elderly people. *Journal of Nutrition*, 2384-2391.

Shek, D.T.L., & Ma, C.M.S. (2011). Longitudinal data analyses using linear mixed models in SPSS: Concepts, procedures and illustrations. *The Scientific World Journal, 11*, 42-76. doi: 10.1100/tsw.2011.2

Shepherd, R. (1999). Social determinants of food choice. *Proceedings of the Nutrition Society, 58*(04), 807-812. doi: 10.1017/S0029665199001093

Shukitt-Hale, B., Carey, A., Simon, L., Mark, D.A., & Joseph, J.A. (2006). Effects of Concord grape juice on cognitive and motor deficits in aging. *Nutrition, 22*(3), 295-302.
Sim, J., & Wright, C.C. (2005). The kappa statistic in reliability studies: Use, interpretation, and sample size requirements. *Physical Therapy, 85*(3), 257-268.
Simopoulos, A. (1991). Omega-3 fatty acids in health and disease and in growth and development. *American Journal of Clinical Nutrition, 54*(3), 438-463.
Singer, J.D., & Willet, J.B. (2003). *Applied longitudinal data analysis*. New York: Oxford University Press.
Singh-Manoux, A., & Kivimäki, M. (2010). The importance of cognitive ageing for understanding dementia. *AGE, 32*(4), 509-512.
Singh-Manoux, A., Marmot, M.G., Glymour, M., Sabia, S., Kivimäki, M., & Dugravot, A. (2011). Does cognitive reserve shape cognitive decline? *Annals of Neurology, 70*(2), 296-304.
Singh-Manoux, A., Sabia, S., Lajnef, M., Ferrie, J.E., Nabi, H., Britton, A.R. (2008). History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. *Eur Heart J, 29*(17), 2100-2107. doi: 10.1093/eurheartj/ehn298
Slattery, M.L., & Boucher, K.M. (1998). The senior authors' response: Factor analysis as a tool for evaluating eating patterns. *American Journal of Epidemiology, 148*(1), 20-21.
Sliwinski, M., & Buschke, H. (2004). Modeling intra-individual cognitive change in aging adults: Results from the Einstein Aging Studies. *Aging, Neuropsychology & Cognition, 11*(2/3), 196-211.
Small, B.J., Rosnick, C.B., Fratiglioni, L., & Backman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology & Aging, 19*(4), 592-600.
Smith, A. (1991). *Cognitive procesess in long-term dietary recall* (Vol. 4). Hyattsville: U.S. Department of Health and Human Services.
Smith, A. (1993). Cognitive psychological issues of relevance to the validity of dietary reports. *European Journal of Clinical Nutrition, 47, Suppl.2*, S6-S18.
Smith, A., Jobe, J., & Mingay, D. (1991). Retrieval from memory of dietary information. *Applied Cognitive Psychology, 5*, 269-296.
Smith, A.D., Smith, S.M., de Jager, C.A., Whitbread, P., Johnston, C., Agacinski, G. (2010). Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. *PLoS ONE, 5*(9), e12244.
Smith, P.J., & Blumenthal, J.A. (2010). Diet and neurocognition: review of evidence and methodological considerations. *Current Aging Science, 3*(1), 57-66.
Smithers, L., Golley, R., Mittinty, M., Brazionis, L., Northstone, K., Emmett, P. (2012). Dietary patterns at 6, 15 and 24 months of age are associated with IQ at 8 years of age. *European Journal of Epidemiology, 27*(7), 525-532.
Snowdon, D.A., Kemper, S.J., Mortimer, J.A., Greiner, L.H., Wekstein, D.R., & Markesbery, W.R. (1996). Linguistic ability in early life and cognitive function and alzheimer's disease in late life: Findings from the nun study. *JAMA, 275*(7), 528-532.
Sobell, J., Block, G., Koslowe, P., Tobin, J., & Andres, R. (1989). Validatiion of a retrospective questionnaire assessing diet 10 - 15 years ago. *Am. J. Epidemiol., 130*(1), 173-187.
Solfrizzi, V., Colacicco, A.M., D'Introno, A., Capurso, C., Torres, F., Rizzo, C. (2006). Dietary intake of unsaturated fatty acids and age-related cognitive decline: A

8.5-year follow-up of the Italian Longitudinal Study on Aging. *Neurobiology of Aging, 27*(11), 1694-1704.
Solfrizzi, V., Panza, F., Torres, F., Mastroianni, F., Del Parigi, A., Venezia, A. (1999). High monounsaturated fatty acids intake protects against age-related cognitive decline. *Neurology, 12*(52), 1563-1569.
Song, W., Derito, C., Liu, M., He, X., Dong, M., & Liu, R. (2010). Cellular antioxidant activity of common vegetables. *Journal of Agricultural and Food Chemistry, 58*(11), 6621-6629. doi: 10.1021/jf9035832
Spearman, C. (1904). "General Intelligence," Objectively determined and measured. *The American Journal of Psychology, 15*(2), 201-292.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280-292.
Spiro, A., & Brady, C.B. (2011). Integrating health into cognitive aging: Toward a preventive cognitive neuroscience of aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 66B*(suppl 1), i17-i25. doi: 10.1093/geronb/gbr018
Staff, R.T., Murray, A.D., Deary, I.J., & Whalley, L.J. (2004). What provides cerebral reserve? *Brain, 127*(5), 1191-1199. doi: 10.1093/brain/awh144
Stellefson, M.L., Hanik, B.W., Chaney, B.H., & Chaney, J.D. (2009). Factor retention in EFA: Strategies for health behavior researchers. *American Journal of Health Behavior, 33*(5), 587-599.
Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8*(03), 448-460. doi: doi:10.1017.S1355617702813248
Stern, Y. (2006). Cognitive reserve and Alzheimer disease (Vol. 20, pp. 112 - 117).
Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*, 2015-2018.
Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006-1012.
Sternberg, R.J. (1977). *Intelligence, information processing, and analogical reasoning: the componential analysis of human abilities*. Hillsdale, New Jersey: Erlbaum.
Sternberg, R.J. (1981). Testing and cognitive psychology. *American Psychologist, 36*(10), 1181-1189.
Sternberg, S. (1969). Memory-scanning: Mental processes revealed by reaction-time experiments. *American Scientist, 4*, 421-457.
Stonehouse, W., Conlon, C.A., Podd, J., Hill, S.R., Minihane, A.M., Haskell, C. (2013). DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial (Vol. 97, pp. 1134-1143).
Sudheendran, S., Chang, C., & Deckelbaum, R. (2010). N-3 vs. saturated fatty acids: effects on the arterial wall. *Prostaglandins and Leukotrienes, and Essential Fatty Acids, 82*(4-6), 205-209. doi: 10.1016/j.plefa.2010.02.020.
Summers, W., Martin, R., Cunningham, M., DeBoynton, V., & Marsh, G. (2010). Complex antioxidant blend improves memory in community-dwelling seniors. *Journal of Alzheimer's Disease, 19*(2), 429-439. doi: 10.3233/JAD-2010-1229
Szeto, Y.T., Tomlinson, B., & Benzie, I.F.F. (2007). Total antioxidant and ascorbic acid content of fresh fruits and vegetables: implications for dietary planning and food preservation. *British Journal of Nutrition, 87*(01), 55-59. doi: 10.1079/BJN2001483

Tabachnick, B.G., & Fidell, L.S. (2007). *Using multivariate statistics* (5th ed.). Sydney: Pearson Education Incorporated.

Talbot, K., Wang, H.-Y., Kazi, H., Han, L.-Y., Bakshi, K.P., Stucky, A. (2012). Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *The Journal of Clinical Investigation, 122*(4), 1316-1338.

Tamosiunas, A., Baceviciene, M., Reklaitiene, R., Radisauskas, R., Jureniene, K., Azaraviciene, A. (2012). Cardiovascular risk factors and cognitive function in middle aged and elderly Lithuanian urban population: results from the HAPIEE study. *BMC Neurology, 12*(1), 149.

Tan, Z.S., Harris, W.S., Beiser, A.S., Au, R., Himali, J.J., Debette, S. (2012). Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology, 78*(9), 658-664.

Tangney, C.C., Kwasny, M.J., Li, H., Evans, D.A., & Morris, M.C. (2010). Adherence to a Mediterranean type dietary pattern may reduce cognitive decline. *The Journal of the Federation of American Societies for Experimental Biology, 24*(1_MeetingAbstracts), 742.748-.

Tangney, C.C., Kwasny, M.J., Li, H., Wilson, R.S., Evans, D.A., & Morris, M.C. (2011). Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. *American Journal of Clinical Nutrition, 93*(3), 601-607. doi: 10.3945/ajcn.110.007369

Thompson, F., Lamphiear, D., Metzner, H., Hawthorne, V., & Oh, M. (1987). Reproducibility of reports of frequency of food use in the Tecumseh Diet Methodology Study. *American Journal of Epidemiology, 125*(4), 658-671.

Thompson, F.E., Metzner, H.L., Lamphiear, D.E., & Hawthorn, V.M. (1990). Characteristics of individuals and long term reprocuctibility of dietary reports: the techmesh diet methodology study. *Journal of Clinical Epidemiology, 43*(11), 1169-1178.

Thompson, F.E., & Subar, A.F. (2013). Dietary assessment methodology. In A. M. Coulston, C. J. Boushey & M. G. Ferruzzi (Eds.), *Nutrition in the prevention and treatment of disease* (pp. 5-46). London: Academic Press.

Thompson, F.E., Subar, A.F., Brown, C.C., Smith, A.F., Sharbaugh, C.O., Jobe, J.B. (2002). Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *Journal of the American Dietetic Association, 102*(2), 212-225.

Thurstone, L.L. (1936). The factorial isolation of primary abilities. *Psychometrika, 1*(3), 175-182.

Tombaugh, T.N., & McIntyre, N.J. (1992). The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society, 40*(9), 922-935.

Torres, S., Lautenschlager, N., Wattanapenpaiboon, N., Greenop, K., Beer, C., Flicker, L. (2012). Dietary patterns are associated with cognition among older people with mild cognitive impairment *Nutrients* (Vol. 4, pp. 1542-1551).

Tourangeau, R., Rips, L.J., & Rasinski, K. (2000). *The psychology of survey response*. Cambridge: Cambridge University Press.

Tourlouki, E., Matalas, A.-L., & Panagiotakos, D.B. (2009). Dietary habits and cardiovascular disease risk in middle-aged and elderly populations: a review of evidence. *Clinical Interventions in Aging, 4*, 319-330.

Trichopoulos, D., & Lagiou, P. (2001). Dietary patterns and mortality. *British Journal of Nutrition, 85*(02), 133-134. doi: 10.1079/BJN2000282

Trichopoulou, A., Costacou, T., Bamia, C., & Trichopoulos, D. (2003). Adherence to a Mediterranean Diet and Survival in a Greek Population (Vol. 348, pp. 2599-2608).

Trompet, S., Vliet, P., Craen, A.M., Jolles, J., Buckley, B., Murphy, M. (2010). Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *Journal of Neurology, 257*(1), 85-90.

Truswell, A.S., & Wahlqvist, M.L. (1988). *Food Habits in Australia: the first Deakin/Syndey universities symposium on Australian nutrition* (1st ed.). North Balwyn: Renè Gordon Pty Ltd.

Twamley, E.W., Ropacki, S.A.L., & Bondi, M.W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 12*(05), 707-735. doi: doi:10.1017/S1355617706060863

Uauy, R., & Dangour, A.D. (2006). Nutrition in brain development and aging: Role of essential fatty acids. *Nutrition Reviews, 64*(5), S24-S33.

Uebersax, J.S. (2006). Introduction to the tetrachoric and polychoric correlation coefficients. from http://john-uebersax.com/stat/tetra.htm

United States Department of Agriculture National Nutrient Database for Standard Reference, Release 24. (2011, 05/03/2013). from http://www.ars.usda.gov/nutrientdata

Vafeiadou, K., Weech, M., Sharma, V., Yaqoob, P., Todd, S., Williams, C. (2012). A review of the evidence for the effects of total dietary fat, saturated, monounsaturated and n-6 polyunsaturated fatty acids on vascular function, endothelial progenitor cells and microparticles. *British Journal of Nutrition, 107*(3), 303-324. doi: 10.1017/S0007114511004764

Valls-Pedret, C., Lamuela-Raventós, R.M., Medina-Remón, A., Quintana, M., Corella, D., Pintó, X. (2012). Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *Journal of Alzheimer's Disease, 29*(4), 773-782.

Valls-Pedret, C., & Ros, E. (2013). Commentary: Mediterranean diet and cognitive outcomes: Epidemiological evidence suggestive, randomized trials needed. *Epidemiology, 24*(4), 503-506.

van Dam, R.M., Grievink, L., Ocke, M.C., & Feskens, E.J.M. (2003). Patterns of food consumption and risk factors for cardiovascular disease in the general Dutch population. *American Journal of Clinical Nutrition, 77*(5), 1156-1163.

van de Rest, O., Geleijnse, J., Kok, F., van Staveren, W., Dullemeijer, C., OldeRikkert, M. (2008). Effect of fish oil on cognitive performance in older subjects: A randomized, controlled trial. *Neurology, 71*, 430-438.

van den Berg, E., Kloppenborg, R.P., Kessels, R.P.C., Kappelle, L.J., & Biessels, G.J. (2009). Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1792*(5), 470-481.

van Gelder, M., Bretveld, R.W., & Roeleveld, N. (2010). Web-based questionnaires: The future in epidemiology? *American Journal of Epidemiology, 172*(11), 1292-1298. doi: 10.1093/aje/kwq291

van Praag, H., Shubert, T., Zhao, C., & Gage, F.H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *THe journal of Neuroscience, 25*(38), 8680-8685. doi: 10.1523/jneurosci.1731-05.2005

VandenBos, G.R. (Ed.). (2007). *APA dictionary of psychology*. Washington: American Psychological Association.

Vasilopoulos, T., Kremen, William S, Kim, K., Panizzon, M.S., Stein, P.K., Xian, H. (2012). Untreated hypertension decreases heritability of cognition in late middle age. *Behavior Genetics, 42*(1), 107-120.
Verhaeghen, P., Borchelt, M., & Smith, J. (2003). Relation between cardiovascular and metabolic disease and cognition in very old age: Cross-sectional and longitudinal findings from the Berlin Aging Study. *Health Psychology, 22*(6), 559-569.
Verhaeghen, P., & Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neuroscience & Biobehavioral Reviews, 26*(7), 849-857.
Verhaeghen, P., & Salthouse, T.A. (1997). Meta-analyses of age-cognition relations in adulthood: Estimates of linear and nonlinear age effects and structural models. *Psychological Bulletin, 122*(3), 231-249.
Villegas, R., Salim, A., Collins, M.M., Flynn, A., & Perry, I.J. (2004). Dietary patterns in middle-aged Irish men and women defined by cluster analysis. *Public Health Nutrition, 7*(08), 1017-1024. doi: 10.1079/PHN2004638
Vlismas, K., Stavrinos, V., & Panagiotakos, D.B. (2009). Socio-economic status, dietary habits and health-related outcomes in various parts the world: A review. *Central European Journal of Public Health, 17*(2), 55-63.
Voss, M., Nagamatsu, L., Liu-Ambrose, T., & Kramer, A. (2011). Exercise, brain, and cognition across the lifespan. *Journal of applied Physiology*(in press).
Voss, M.W., Prakash, R.S., Erickson, K.I., Basak, C., Chaddock, L., Kim, J.S. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults (Vol. 2).
Wachs, T.D. (2000). Nutritional deficits and behavioural development. *International Journal of Behavioral Development, 24*(4), 435-441.
Wadsworth, M., Kuh, D., Richards, M., & Hardy, R. (2006). Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development) (Vol. 35, pp. 49-54).
Wadsworth, M.E.J., Butterworth, S.L., Hardy, R.J., Kuh, D.J., Richards, M., Langenberg, C. (2003). The life course prospective design: an example of benefits and problems associated with study longevity. *Social Science and Medicine, 57*(11), 2193-2205.
Wahlin, Å., MacDonald, S.W.S., deFrias, C.M., Nilsson, L.-G., & Dixon, R.A. (2006). How do health and biological age influence chronological age and sex differences in cognitive aging: Moderating, mediating, or both? *Psychology and Aging, 21*(2), 318-332.
Walker, J., Batterham, P., Mackinnon, A., Jorm, A., Hickie, I., Fenech, M. (2012). Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms: the Beyond Ageing Project: a randomized controlled trial. *American Journal of Clinical Nutrition, 95*(1), 194-203. doi: 10.3945/ajcn.110.007799
Warsch, J.R.L., & Wright, C.B. (2010). The aging mind: Vascular health in normal cognitive aging. *Journal of the American Geriatrics Society, 58*, S319-S324.
Wasserman, J.D., & Tulsky, D.S. (2005). A history of intelligence assessment. In D. P. Flannigan & P. L. Harrison (Eds.), *Contemporary intellectual assessment: Theories, tests, and issues* (2nd ed., pp. 3-23). New York: The Guilford Press.
Wechsler, D. (1939). *The measurement of adult intelligence*. Baltimore: Wiliams and Wilkins.

Weih, M., Degirmenci, Ã.t., Kreil, S., & Kornhuber, J. (2010). Physical activity and Alzheimer's disease: A meta-analysis of cohort studies. *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry, 23*(1), 17-20.

Weikert, C., Hoffmann, K., Dierkes, J., Zyriax, B.-C., Klipstein-Grobusch, K., Schulze, M.B. (2005). A homocysteine metabolism-related dietary pattern and the risk of coronary heart disease in two independent german study populations. *The Journal of Nutrition, 135*(8), 1981-1988.

Weismayer, C., Anderson, J.G., & Wolk, A. (2006). Changes in the stability of dietary patterns in a study of middle-aged Swedish women. *The Journal of Nutrition, 136*(6), 1582-1587.

Wendt, M., & Kinsey, J. (2007). Do eating patterns follow a cohort or change over a lifetime? Answers emerging from the literature (pp. 1-34): The Food Industry Center, University of Minnesota.

Wengreen, H.J., Neilson, C., Munger, R., & Corcoran, C. (2009). Diet quality is associated with better cognitive test performance among aging men and women. *The Journal of Nutrition, 139*(10), 1944-1949. doi: 10.3945/jn.109.106427

Wesnes, K.A. (2010). Evaluation of techniques to identify beneficial effects of nutrition and natural products on cognitive function. *Nutrition Reviews, 68*, S22-S28.

Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M.B., Ware, J.H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *Journal of the American Medical Association, 292*(12), 1454-1461. doi: 10.1001/jama.292.12.1454

Whalley, L.J., Deary, I.J., Starr, J.M., Wahle, K.W., Rance, K.A., Bourne, V.J. (2008). n-3 Fatty acid erythrocyte membrane content, APOE 4, and cognitive variation: an observational follow-up study in late adulthood. *American Journal of Clinical Nutrition, 87*(2), 449-454.

Whalley, L.J., Dick, F.D., & McNeill, G. (2006). A life-course approach to the aetiology of late-onset dementias. *Lancet Neurology, 5*(1), 87-96.

Whichelow, M.J., & Prevost, A.T. (1996). Dietary patterns and their associations with demographic, lifestyle and health variables in a random sample of British adults. *British Journal of Nutrition, 76*(01), 17-30. doi: doi:10.1079/BJN19960006

White, L.R., Petrovitch, H., Ross, G.W., Masaki, K., Hardman, J., Nelson, J. (2000). Brain aging and midlife tofu consumption. *Journal of the American College of Nutrition, 19*(2), 242-255.

Whitmer, R.A., Sidney, S., Selby, J., Claiborne Johnston, S., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology, 64*, 277-281.

WHO. (2002). Active Ageing: A Policy Framework (pp. 1-59). Geneva: World Health Organisation.

WHO. (2004). Global strategy on diet, physical activity and health: The Americas' regional consultation meeting report. San Josè.

Willatts, P., Forsyth, S., Agostoni, C., Casaer, P., Riva, E., & Boehm, G. (2013). Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood. *American Journal of Clinical Nutrition*. http://ajcn.nutrition.org/content/early/2013/06/19/ajcn.112.038612.abstract doi:10.3945/ajcn.112.038612

Willett, W., Sampson, L., Browne, M., Stampfer, M., Rosner, B., Hennekens, C. (1988). The use of a self-administered questionnaire to assess diet four years in the past *American Journal of Epidemiology, 127*(1), 188-189.

Willett, W.C. (1998). *Nutritional epidemiology*. New York: Oxford University Press.

Willett, W.C. (2006). The Mediterranean diet: science and practice. *Public Health Nutrition, 9*(1A), 105-110.
Willis, S.L., & Schaie, K.W. (2005). Cognitive trajectories in midlife and cognitive functioning in old age. In S. L. Willis & M. Martin (Eds.), *Middle adulthood: A lifespan perspective* (pp. 243-275). Thousand Oaks: Sage.
Wilson, R.S., Beckett, L.A., Barnes, L.L., Schneider, J.A., Bach, J., Evans, D.A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychology and Aging, 17*(2), 179-193.
Wilson, R.S., Hebert, L.E., Scherr, P.A., Barnes, L.L., Mendes de Leon, C.F., & Evans, D.A. (2009). Educational attainment and cognitive decline in old age. *Neurology 72*, 460-465.
Wilson, R.S., Schneider, J.A., Barnes, L.L., Beckett, L.A., Aggarwal, N.T., Cochran, E.J. (2002). The Apolipoprotein E {epsilon}4 allele and decline in different cognitive systems during a 6-year period (Vol. 59, pp. 1154-1160).
Wirfält, E. (1998). Cognitive aspects of dietary assessment. *Food & Nutrition Research 42* 56-59
Wisdom, N.M., Callahan, J.L., & Hawkins, K.A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging, 32*(1), 63-74.
Wolf, P.A., D'Agostino, R.B., Belanger, A.J., & Kannel, W.B. (1991). Probability of stroke: a risk profile from the Framingham Study. *Stroke, 22*(3), 312-318. doi: 10.1161/01.str.22.3.312
Wolfe, K.L., Kang, X., He, X., Dong, M., Zhang, Q., & Liu, R.H. (2008). Cellular antioxidant activity of common fruits. *Journal of Agricultural and Food Chemistry, 56*(18), 8418-8426.
Wolk, A., Bergstrom, R., Hansson, L., & Nyren, O. (1997). Reliability of retrospective information on diet 20 years ago and consistency of independent measurements of remote adolescent diet. *Nutrition and cancer, 29*(3), 234-241.
World Wide Alzheimer's Disease Neuroimaging Initiative. (2013). from http://www.alz.org/research/funding/partnerships/ww-adni_overview.asp
Wu, M.L., Whittemore, A.S., & Jung, D.L. (1988). Errors in reported dietary intakes: Long-term recall. *American Journal of Epidemiology, 128*(5), 1137-1145.
Xiong C, R.C.M.B.V., & et al. (2011). Role of family history for alzheimer biomarker abnormalities in the adult children study. *Archives of Neurology, 68*(10), 1313-1319.
Yaffe, K., Clemons, T.E., McBee, W.L., & Lindblad, A.S. (2004). Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology, 63*(9), 1705-1707.
Yurko-Mauro, K., McCarthy, D., Rom, D., Nelson, E.B., Ryan, A.S., Blackwell, A. (2010). Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimer's and Dementia, In Press, Corrected Proof.*
Zahodne, L.B., Glymour, M.M., Sparks, C., Bontempo, D., Dixon, R.A., MacDonald, S.W.S. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. *Journal of the International Neurological Society, 17*(6), 1039-1046.
Zelinski, E.M., & Kennison, R.F. (2007). Not your parents' test scores: Cohort reduces psychometric aging effects. *Psychology and Aging, 22*(3), 546-557.
Zelinski, E.M., Kennison, R.F., Watts, A., & Lewis, K.L. (2009). Convergence between cross-sectional and longitudinal studies: Cohort matters. In H. B. Bosworth & C.

Hertzog (Eds.), *Aging and cognition: Research methodologies and empirical advances* (pp. 101-118). Washington: American Psychological Association.
Zimprich, D., & Rast, P. (2009). Verbal learning changes in older adults across 18 months. *Aging, Neuropsychology, and Cognition, 16*(4), 461-484.
Zylberstein, D.E., Lissner, L., Björkelund, C., Mehlig, K., Thelle, D.S., Gustafson, D. (2011). Midlife homocysteine and late-life dementia in women. A prospective population study. *Neurobiology of Aging, 32*(3), 380-386.

APPENDICES

Appendix A	Participant questionnaire pack for the Family-member Reliability Study.
Appendix B	Participant letter and full LDQ full LDQ and Ethics approval for Study 1 and Study 2.
Appendix C	Additional details of the cognitive test battery analyses.
Appendix D	Introductory letter and instructions for EPOCH LDQ participants.
Appendix E	Additional covariates for Study 5(LDQ dietary patterns and 18-month cognitive change).
Appendix F	Preliminary models of LDQ dietary patterns as predictors of 18-month cognitive change on all constructs.
Appendix G	Published manuscripts: Study 2 (Chapter 4) and Study 3 (Chapter 5) and Statements of Authorship.

APPENDIX A

Validation of a New Measure of Past Diet Assessment

Information for Participants

What people eat during their lifetime has been associated with the onset of a number of chronic diseases, in particular, cardiovascular disease and some types of cancer. Recently, research has focused on the effect of our diet on our cognitive functions; that is our thinking, reasoning and memory. A number of foods such as fish, vegetables and foods high in antioxidants have been suggested as having long-term benefits for cognitive functioning. However to explore the relationships between people's past intake of these foods and their present functioning, it is necessary to establish whether memory of diet is a reliable source of information.

This project uses autobiographical cue questions to 'locate' individuals in a particular time, so aiding them in their dietary recall for that period. The purpose of the project is to assess the reliability of these food memories by comparing an individual's recall of their diet for a particular time with other family members' recall of that person's diet for the same period.

To participate in this study, you will be asked to complete a questionnaire that asks you to remember how often you ate certain foods during your childhood. You then need to give a similar questionnaire to a parent and/or a sibling who lived with you during this time. They will be asked to recall ***your*** diet for the same period. It is essential that each person who completes the questionnaire does so entirely by themselves and does not collaborate with anyone else (i.e. another family member)

It is expected that the questionnaires will take approximately 10 - 15 minutes to complete.

All questionnaire responses are confidential and you are free to withdraw from the study at any time. Results will be made available via email or letter.

Please address any questions regarding this study to one of the researchers listed below.

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Validation of a New Measure of Past Diet Assessment

INSTRUCTIONS FOR PARTICIPANTS

Dear participant,

Thank you for volunteering to take part in this study to validate a Memory for Past Diet Questionnaire. Your questionnaire pack contains:

- These instructions,
- Information sheets,
- Consent forms for you and your family member,
- A childhood diet questionnaire for you to complete,
- A questionnaire for your family member to complete.

Remember, you only need **one** other family member to complete a questionnaire to take part in the study but the more family members you recruit to do the study, the greater research participation time you receive. If you would like extra family questionnaires please request them from the Psychology office. To complete the study you need to:

1. Fill out the Past Diet questionnaire for yourself and write your student number on all pages.
2. Give your parent and/or sibling their copy of the study information sheet and a consent form; ask them to sign the consent form and you witness it
3. Once they have agreed to participate, write **your** student ID on all pages of their questionnaires. **PTO**

4. Ask your family members to complete the Past Diet Questionnaires that refer to your childhood diet. Please do not collaborate with your family member(s) while they are answering the Past Diet Questionnaire and ask them not to collaborate with any other family members when filling it in.
5. Place **all** signed consent forms and **all** completed questionnaires back into the envelope you received them in, and seal.

6. Return the envelope containing the questionnaires and consent forms to the box outside the Psychology office in the Hughes Building.

Validation of a New Measure of Past Diet Assessment

PARTICIPANT QUESTIONNAIRE

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Validation of a New Measure of Past Diet Assessment

CHILDHOOD DIET QUESTIONNAIRE

AGE:

SEX : M F (Please circle)

This questionnaire asks you to remember some of the foods you ate during your childhood. For this period, you will be asked some autobiographical questions that will help 'locate' yourself in that time and so aid in the recall of your diet. The questions are not for any purpose other than to help your memory.

Please write your answers to the questions below in the spaces provided.

1. Between which years were you aged **10** – **15**?

2. Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

3. Where were you living? (eg. street/suburb, city, country) Include multiple places if you moved over this period.

4. What school(s) did you attend?

5. What hobbies, sports, or interests did you enjoy?

6. How many people lived with you in your household?

7. Who did the shopping and who did the cooking in your household?

1. Where were you living? (eg. street/suburb, city, country) Include multiple places if you moved over this period.

2. What school(s) did your child or sibling attend during this period and what work did you do?

3. What hobbies, sports, or interests did you enjoy?

4. How many people lived in your household during this time?

5. During this period who did the shopping in your household and who did the cooking?

Childhood

During the period you were aged **10 – 15** years, indicate how often you ate the following foods by placing a tick in the spaces below.

VEGETABLES (Fresh or Juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergine (Eggplant)				
Carrots				
Potatoes				
Parsnip, Turnip, Swede				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions,				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh Herbs				
Vegetable Soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheeses				
Icecream				

Childhood **10 – 15 yrs** (continued)

FRUIT (Dried or fresh or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons				
Blueberries, Blackberries, Cranberries, Strawberries				
Red Grapes				
White Grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fiber breakfast cereals (eg. Weetbix)				
Oats (porridge, Muesli)				
Brown Pasta or Brown Rice				
TAKEAWAY FOOD				
Any takeaway food				

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat				
Lentils & Dried Peas				
Beans (eg kidney beans, Haricot Beans – used in baked beans)				
Eggs				
Tofu				
Soya Milk				
Soya Sauce				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following:; Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (eg. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Desserts				
Lollies				
Chocolate				
Cakes				
Sweet Biscuits				
Soft Drinks				
SNACK FOOD				
Any snack foods (eg chips)				

Childhood 10 – 15 yrs (continued

FATS & OILS (On bread or in cooking)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Butter				
Margarine (Unspecified content)				
Margarine (Canola based)				
Vegetable Oil				
Olive oil				
TEA				
Green Tea				
Herbal Tea				
Black Tea				
White Tea				
Sweetened				
COFFEE				
Black Coffee				
White Coffee				
Sweetened				
MULTI-VITAMINS				
Any vitamin or mineral supplements				

THANKYOU FOR COMPLETING THE QUESTIONNAIRE

Validation of a New Measure of Past Diet Assessment

FAMILY MEMBER'S QUESTIONNAIRE

Researchers

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Validation of a New Measure of Past Diet Assessment

CHILDHOOD DIET OF YOUR FAMILY MEMBER

(To be completed by a parent or sibling who lived with the participant when that person was aged between 10 and 15 years)

YOUR AGE:

YOUR SEX: M F (Please circle)

Please circle whether you are a PARENT or a SIBLING of the person whose diet you are going to recall for this questionnaire.

This questionnaire asks you to remember the foods eaten by your family member when they were aged between 10 and 15 years old. For this period, you will be asked some autobiographical questions that will help 'locate' yourself in that time and so aid in the recall of your family member's diet. The questions are not for any purpose other than to help your memory.

Please write your answers to the questions below in the spaces provided.

1. Between which years was this family member aged **10 – 15?**

2. Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

3. Where were you living? (eg. street/suburb, city, country) Include multiple places if you moved over this period.

4. What school(s) did your child or sibling attend during this period and what work did you do?

5. What hobbies, sports, or interests did you enjoy?

6. How many people lived in your household during this time?

7. During this period who did the shopping in your household and who did the cooking?

Your Family Member's Childhood Diet

Please select and circle which family member's diet you will be recalling in this questionnaire.

Son's Diet; Daughter's Diet; Sibling's Diet

During the period your family member was aged **10 – 15** years, indicate how often you remember them eating the following foods by placing a tick in the spaces below.

VEGETABLES (Fresh or Juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergine (Eggplant)				
Carrots				
Potatoes				
Parsnip, Turnip, Swede				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh Herbs				
Vegetable Soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheese				
Icecream				

Family Member's Childhood Diet when aged 10 – 15 yrs (continued)

FRUIT (Dried or fresh or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons				
Blueberries, Blackberries, Cranberries, Strawberries				
Red Grapes				
White Grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fiber breakfast cereals (e.g. Weetbix)				
Oats (porridge, Muesli)				
Brown Pasta or Brown Rice				
TAKEAWAY FOOD				
Any takeaway food				

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat				
Lentils & Dried Peas				
Beans (eg kidney beans, Haricot Beans – used in baked beans)				
Eggs				
Tofu				
Soya Milk				
Soya Sauce				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following; Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Desserts				
Lollies				
Chocolate				
Cakes				
Sweet Biscuits				
Soft Drinks				
SNACK FOOD				
Any snack food (e.g. chips)				

Family Member's Childhood Diet when aged 10 – 15 yrs (continued)

FATS & OILS (On bread or in cooking)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Butter				
Margarine (Unspecified content				
Margarine (Canola based)				
Vegetable Oil				
Olive oil				
TEA				
Green Tea				
Herbal Tea				
Black Tea				
White Tea				
Sweetened				
COFFEE				
Black Coffee				
White Coffee				
Sweetened				
MULTI-VITAMINS				
Any vitamin or mineral supplements				

THANKYOU FOR COMPLETING THE QUESTIONNAIRE

CSIRO
HUMAN NUTRITION

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

THE RELIABILITY OF A LIFETIME DIET QUESTIONNAIRE

Diane Hosking.
PhD Research Candidate
T: 8303 8858
Diane.Hosking@csiro.au
August 2008.

Dear

Thank you for participating in this study. The purpose of the study is to assess whether people can remember, in a very general way, how often they have eaten some foods across their lifetime.

A brief background to the study, and some instructions for completing the questionnaire, can be found on the attached information sheet.

As Professor Nettelbeck's earlier letter mentioned, you will be asked to again complete the questionnaire in approximately a month's time. Please be assured, *this is not a test of your memory* but rather an indication of the questionnaire's reliability.

Your time and effort given to completing the Lifetime Diet Questionnaire, on both occasions, are very much appreciated and you will be kept informed of the study's outcome.

Best wishes,
Diane Hosking.

APPENDIX A/B

ETHICS APPROVAL FOR STUDIES 1 AND 2

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

School of Psychology

The University of Adelaide
Adelaide, South Australia, 5005
Telephone + 61 8 8303 5693
FAX: + 61 8 8303 3770

Human Research Ethics Subcommittee

Approval sheet

Date: 3/10/07

Dear TED

The members of the subcommittee have considered your application:

Code Number: 07/89 [VALIDATION OF A PATS DEOT QUESTIONNAIRE]

With [Student Name, if applicable]: DENNIS HOPKINS

I am writing to confirm that approval has been granted for this project to proceed.

Yours sincerely,

Dr. Paul Delfabbro
Acting Convener of the Human Research Ethics Subcomittee
School of Psychology
Ph. 8 303 5744
Paul.delfabbro@psychology.adelaide.edu.au

LIFETIME DIET QUESTIONNAIRE

Information about your Lifetime Diet Questionnaire.

Recent research has found associations between eating certain foods and cognitive functioning; that is thinking, reasoning and memory. However, possible relationships between peoples' diet over their lifetime and their cognition have not yet been explored. This is the purpose of the Lifetime Diet Questionnaire. (You might remember from the information sessions that this is a sub-aim of the EPOCH trial). You will only need to complete the Lifetime Diet Questionnaire ONCE, and that is in the next few weeks (when convenient for you).

You will be asked to remember some of the foods you ate during **a number of different periods** of your life. For each period of time, some autobiographical questions will help 'locate' you in that time and so aid in the recall of your diet; your responses to these questions will not be used in the study (and will be discarded when you return your questionnaire) but we do need to check that you have completed this aspect of the questionnaire in order for your results to be valid. Thus the questions are not for any purpose other than to help your memory and you are free to write as much or little as you need to.

In addition, you will be asked to remember how physically active you were during each life period. As with all our data, all your responses will remain anonymous and will not be linked to your name

There are 5 mini-questionnaires that make up the Life Time Diet Questionnaire. Please complete ONE of these mini-questionnaires per consecutive day over 5 days, to minimise the chance of your diet memories from one period of your life influencing diet memories from another period.

When you have completed all of the mini-questionnaires that make up the Lifetime Diet Questionnaire, please place them in the reply-paid envelope and post back to CSIRO at your earliest convenience. If you have any questions regarding the questionnaire please call Diane Hosking on 8303 8858 or email Diane.Hosking@csiro.au

PLEASE FILL OUT YOUR FIRST LIFETIME DIET QUESTIONNAIRE NOW FOR THE PERIOD OF YOUR CHILDHOOD

Questionnaire 1

For ages 5-18 (childhood)

AGE 5 - 18

Between which years were you aged 5 – 18?

Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

Where were you living (e.g. street/suburb, city, country)? Include multiple places if you moved over this period.

What schools did you attend?

What hobbies, sports, or interests did you enjoy?

How many people, including yourself, lived in your household?

Who did the shopping and who did the cooking in your household?

Childhood

During the period you were aged **5 – 18** years, please indicate how often you ate the following foods by placing a tick in the appropriate spaces below (only **one tick** per line). If your diet changed significantly during this time, answer for your most representative diet.

VEGETABLES (Fresh or Juice)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergines (Eggplant)				
Carrots				
Potatoes				
Parsnips, Turnips, Swedes				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh herbs				
Vegetable soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheese				
Icecream				

Childhood 5 – 18 yrs (continued)

FRUIT (fresh, tinned, or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons, Limes				
Blueberries, Blackberries, Cranberries, Strawberries				
Red grapes				
White grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Wholegrain bread				
High-fibre breakfast cereals (e.g. Weetbix, bran)				
Oats (porridge, muesli)				
Brown pasta or Brown rice				
White pasta or White rice				
TAKEAWAY FOOD				
Any takeaway food				

Childhood 5 – 18 yrs (continued)

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat (e.g. ham)				
Lentils & Dried peas/ beans (e.g. kidney beans, haricot beans – used in baked beans)				
Eggs				
Tofu				
Soya milk				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen, or canned)				
Any of the following: Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Sweets/Desserts (other than milk-based) including lollies, cakes, sweet biscuits etc.				
Chocolate				
Soft drinks				
SNACK FOOD				
Any snack foods (e.g. crisps, savoury biscuits)				

Childhood **5 – 18 yrs** (continued)

FATS & OILS (On bread or in cooking)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 - 3 TIMES A MONTH**	**RARELY/ NEVER**
Butter				
Lard/Dripping				
Margarine (polyunsaturated; e.g. Meadowlea)				
Oil (vegetable or seed-based; e.g. sunflower)				
Olive oil				
TEA				
Green tea				
Herbal tea				
Black tea				
White tea				
Sweetened?				
COFFEE				
Black coffee				
White coffee				
Sweetened?				
MULTI-VITAMINS				
Any multi-vitamin supplements				

Childhood **5 – 18 yrs** (continued)

Physical Activity Question

Please answer the following physical activity question for the period when you were aged **5 – 18 years**. If your level of activity varied during this time, give an approximation of your activity levels.

- During your childhood, how often did you engage in walking, or any other exercise, for **greater than 30 mins** at a time?

  Please indicate, by placing a tick in one of the boxes below, if this exercise was

  - *Vigourous* (breathlessness, heavy sweating, heart pounding)
  - *Moderate* (light sweat, some increase in heart rate) or
  - *Light* (no noticeable physical symptoms)

  You may tick **more than one box** if appropriate.

Frequency	Vigourous activity	Moderate activity	Light activity
1/2 - 1 hour a week			
2 - 3 hours a week			
4 - 7 hours a week			
7 - 14 hours a week			
14 + hours a week			

THANK YOU FOR COMPLETING THE 5 – 18 YRS QUESTIONNAIRE

PLEASE STOP & CONTINUE WITH THE EARLY ADULT QUESTIONNAIRE TOMORROW.

Questionnaire 2

For ages 19 - 30 (young adulthood).

AGE 19 - 30

Between which years were you aged 19 - 30?

Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

Where were you living (e.g. street/suburb, city, country)? Include multiple places if you moved over this period.

Did you work or study? If so where?

What hobbies, sports, or interests did you enjoy? Include any travel you did.

How many people, including yourself, lived in your household?

Who did the shopping and who did the cooking in your household?

Did you make any definite changes to your diet during this period (e.g. become a vegetarian)?

YES NO

If YES, what changes did you make? Please describe.

Young Adulthood

During the period you were aged **19 – 30** years, please indicate how often you ate the following foods by placing a tick in the spaces below. If your diet changed significantly during this period, answer for your most representative diet.

VEGETABLES (Fresh or Juice)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergines (Eggplant)				
Carrots				
Potatoes				
Parsnips, Turnips, Swedes				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh herbs				
Vegetable soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheeses				
Icecream				

Young Adulthood 19 – 30 yrs (continued)

FRUIT (Fresh, tinned or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons, Limes				
Blueberries, Blackberries, Cranberries, Strawberries				
Red grapes				
White grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fibre breakfast cereals (e.g. Weetbix, bran)				
Oats (porridge, muesli)				
Brown pasta or Brown rice				
White pasta or White rice				
TAKEAWAY FOOD				
Any takeaway food				

Young Adulthood **19 – 30 yrs** (continued)

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat (e.g. ham)				
Lentils & Dried peas/ beans (e.g. kidney beans, haricot beans – used in baked beans)				
Eggs				
Tofu				
Soya milk				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following: Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Sweets/Desserts (other than milk-based) including lollies, cakes, sweet biscuits etc.				
Chocolate				
Soft drinks				
SNACK FOOD				
Any snack foods (e.g. crisps, savoury biscuits)				

Young Adulthood 19 – 30 yrs (continued)

FATS & OILS (On bread or in cooking)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 - 3 TIMES A MONTH**	**RARELY/ NEVER**
Butter				
Lard/Dripping				
Margarine (polyunsaturated; e.g. Meadowlea)				
Oil (vegetable or seed-based; e.g. sunflower)				
Olive oil				
ALCOHOL				
Red wine				
Other wine				
Beer				
Cider				
Spirits				
TEA				
Green tea				
Herbal tea				
Black tea				
White tea				
Sweetened?				
COFFEE				
Black coffee				
White coffee				
Sweetened?				
MULTI-VITAMINS				
Any multi-vitamin supplements				

Young Adulthood **19 – 30 yrs** (continued)

Physical Activity Questions

Please answer the following physical activity questions for the period when you were aged **19 – 30 years**. If your level of activity varied during this time, give an approximation of your activity levels.

- Please circle how much physical activity you did in your **main occupation**.
  - LITTLE physical activity (e.g. office work, studying)
  - SOME physical activity (e.g. light cleaning, retail work, café work, hairdressing),
  - FREQUENT physical activity (e.g. home duties with small children, primary teaching, lifting and packing)
  - HEAVY & FREQUENT physical activity (e.g. builder's labourer, farmer, road worker, gardener)
- IN ADDITION to the physical activity demanded by your main occupation, how often did you engage in walking, or any other exercise, for **greater than 30 mins** at a time?

  Please indicate, by placing a tick in one of the boxes below, if this exercise was
  - *Vigourous* (breathlessness, heavy sweating, heart pounding)
  - *Moderate* (light sweat, some increase in heart rate) or
  - *Light* (no noticeable physical symptoms)

  You may tick **more than one box** if appropriate.

Frequency	Vigourous activity	Moderate activity	Light activity
1/2 - 1 hour a week			
2 - 3 hours a week			
4 - 7 hours a week			
7 - 14 hours a week			
14 + hours a week			

THANK YOU FOR COMPLETING THE 19 – 30 YRS QUESTIONNAIRE

PLEASE STOP & CONTINUE WITH THE ADULT QUESTIONNAIRE TOMORROW

Questionnaire 3

For ages 31 - 45 (adulthood)

AGE 31 - 45

Between which years were you aged 31 - 45?

Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

Where were you living (e.g. street/suburb, city, country)? Include multiple places if you moved over this period.

Did you work or study? If so where?

What hobbies, sports, or interests did you enjoy? Include any travel you did.

How many people, including yourself, lived in your household?

Who did the shopping and who did the cooking in your household?

Did you make any definite changes to your diet during this period (e.g. become a vegetarian)?

YES NO

If YES, what changes did you make? Please describe.

Adulthood

During the period you were aged **31 – 45** years, please indicate how often you ate the following foods by placing a tick in the spaces below. If your diet changed significantly during this period, answer for your most representative diet.

VEGETABLES (Fresh or Juice)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergines (Eggplant)				
Carrots				
Potatoes				
Parsnips, Turnips, Swedes				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions,				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh herbs				
Vegetable soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheeses				
Icecream				

Adulthood 31 – 45 yrs (continued)

FRUIT (Fresh, tinned or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons, Limes				
Blueberries, Blackberries, Cranberries, Strawberries				
Red grapes				
White grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fibre breakfast cereals (e.g. Weetbix, bran)				
Oats (porridge, muesli)				
Brown pasta or Brown rice				
White pasta or White rice				
TAKEAWAY FOOD				
Any takeaway food				

Adulthood **31 – 45 yrs** (continued)

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat (e.g. ham)				
Lentils & Dried peas/ beans (e.g. kidney beans, haricot beans – used in baked beans)				
Eggs				
Tofu				
Soya milk				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following: Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Sweets/Desserts (other than milk-based) including lollies, cakes, sweet biscuits etc.				
Chocolate				
Soft drinks				
SNACK FOOD				
Any snack foods (e.g. crisps, savoury biscuits)				

Adulthood **31 – 45 yrs** (continued)

FATS & OILS (On bread or in cooking)	**DAILY**	**2 - 3 TIMES A WEEK**	**2- 3 TIMES A MONTH**	**RARELY/ NEVER**
Butter				
Margarine (polyunsaturated; e.g. Meadowlea)				
Oil (vegetable or seed-based; e.g. sunflower)				
Olive oil				
ALCOHOL				
Red wine				
Other wine				
Beer				
Cider				
Spirits				
TEA				
Green tea				
Herbal tea				
Black tea				
White tea				
Sweetened?				
COFFEE				
Black coffee				
White coffee				
Sweetened?				
MULTI-VITAMINS				
Any multi-vitamin supplements				

Adulthood **31 – 45 yrs** (continued)

Physical Activity Questions

Please answer the following physical activity questions for the period when you were aged **31 – 45 years**. If your level of activity varied during this time, give an approximation of your activity levels.

- Please circle how much physical activity you did in your **main occupation**.
  - LITTLE physical activity (e.g. office work, studying)
  - SOME physical activity (e.g. light cleaning, retail work, café work, hairdressing)
  - FREQUENT physical activity (e.g. home duties with small children, primary school teaching, lifting and packing)
  - HEAVY & FREQUENT physical activity (e.g. builder's labourer, farmer, road worker, gardener)
- IN ADDITION to the physical activity demanded by your main occupation, how often did you engage in walking, or any other exercise, for **greater than 30** mins at a time?

  Please indicate, by placing a tick in one of the boxes below, if this exercise was
  - *Vigourous* (breathlessness, heavy sweating, heart pounding)
  - *Moderate* (light sweat, some increase in heart rate) or
  - *Light* (no noticeable physical symptoms)

  You may tick **more than one box** if appropriate.

Frequency	Vigourous activity	Moderate activity	Light activity
1/2 - 1 hour a week			
2 - 3 hours a week			
4 - 7 hours a week			
7 - 14 hours a week			
14 + hours a week			

THANK YOU FOR COMPLETING THE 31– 45 YRS QUESTIONNAIRE

PLEASE STOP & CONTINUE WITH THE MIDDLE AGE QUESTIONNAIRE TOMORROW.

Questionnaire 4

For ages 46 - 60 (middle age)

AGE 46 - 60

Between which years were you aged 46 - 60?

Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

Where were you living (e.g. street/suburb, city, country)? Include multiple places if you moved over this period.

Did you work or study? If so where?

What hobbies, sports, or interests did you enjoy? Include any travel you did

How many people, including yourself, lived in your household?

Who did the shopping and who did the cooking in your household?

Did you make any definite changes to your diet during this period (e.g. become a vegetarian)?

YES NO

If YES, what changes did you make? Please describe.

Middle Age

During the period you were aged **46 – 60** years, please indicate how often you ate the following foods by placing a tick in the spaces below. If your diet changed significantly during this period, answer for your most representative diet.

VEGETABLES (Fresh or Juice)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergines (Eggplant)				
Carrots				
Potatoes				
Parsnips, Turnips, Swedes				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions,				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh herbs				
Vegetable soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheeses				
Icecream				

Middle Age 46 – 60 yrs (continued)

FRUIT (Fresh, tinned or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons, Limes				
Blueberries, Blackberries, Cranberries, Strawberries				
Red grapes				
White grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fibre breakfast cereals (e.g. Weetbix, bran)				
Oats (porridge, muesli)				
Brown pasta or Brown rice				
White pasta or White rice				
TAKEAWAY FOOD				
Any takeaway food				

Middle Age **41 – 60 yrs** (continued)

PROTEIN FOODS	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat (e.g. ham)				
Lentils & Dried peas/ beans (e.g. Kidney beans, haricot beans – used in baked beans)				
Eggs				
Tofu				
Soya Milk				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following: Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Sweets/Desserts (other than milk-based) including lollies, cakes, sweet biscuits etc.				
Chocolate				
Soft drinks				
SNACK FOOD				
Any snack foods (e.g. crisps, savoury biscuits)				

Middle Age **46 – 60 yrs** (continued)

FATS & OILS (On bread or in cooking)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 –3 TIMES A MONTH**	**RARELY/ NEVER**
Butter				
Margarine (polyunsaturated; e.g. Meadowlea)				
Oils (vegetable or seed-based; e.g. sunflower)				
Olive oil				
ALCOHOL				
Red wine				
Other wine				
Beer				
Cider				
Spirits				
TEA				
Green tea				
Herbal tea				
Black tea				
White tea				
Sweetened?				
COFFEE				
Black coffee				
White coffee				
Sweetened?				
MULTI-VITAMINS				
Any multi-vitamin supplements				

Middle Age **46 – 60 yrs** (continued)

Physical Activity Questions

Please answer the following physical activity questions for the period when you were aged **46 – 60 years**. If your level of activity varied during this time, give an approximation of your activity levels.

- Please circle how much physical activity you did in your **main occupation**.
  - LITTLE physical activity (e.g. office work, studying,)
  - SOME physical activity (e.g. light cleaning, retail work, café work, hairdressing)
  - FREQUENT physical activity (e.g. primary school teaching, caring for grandchildren, lifting and packing)
  - HEAVY & FREQUENT physical activity (e.g. builder's labourer, farmer, road worker)
- IN ADDITION to the physical activity demanded by your main occupation, how often did you engage in walking, or any other exercise, for **greater than 30 mins** at a time?

  Please indicate, by placing a tick in one of the boxes below, if this exercise was
  - *Vigourous* (breathlessness, heavy sweating, heart pounding)
  - *Moderate* (light sweat, some increase in heart rate) or
  - *Light* (no noticeable physical symptoms)

  You may tick **more than one box** if appropriate.

Frequency	Vigourous activity	Moderate activity	Light activity
1/2 - 1 hour a week			
2 - 3 hours a week			
4 - 7 hours a week			
7 - 14 hours a week			
14 + hours a week			

THANK YOU FOR COMPLETING THE 46 – 60 YRS QUESTIONNAIRE

PLEASE STOP & CONTINUE WITH THE ELDERLY QUESTIONNAIRE TOMORROW.

Questionnaire 5

For ages 61 to 75 (Elderly)

AGE 61 - 75

Between which years were you aged 61 - 75?

Can you recall any significant event(s) that happened either in the world or to you personally during this time? Describe briefly.

Where were you living (e.g. street/suburb, city, country)? Include multiple places if you moved over this period.

Did you do any travel? If so where to?

What hobbies, sports, or interests did you enjoy?

How many people, including yourself, lived in your household?

Who did the shopping and who did the cooking in your household?

Did you make any definite changes to your diet during this period (e.g. become a vegetarian)?

YES NO

If YES, what changes did you make? Please describe.

Elderly

During the period you were aged **61 – 75** years, please indicate how often you ate the following foods by placing a tick in the spaces below. If your diet changed significantly during this period, answer for your most representative diet.

VEGETABLES (Fresh or Juice)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 – 3 TIMES A MONTH**	**RARELY/ NEVER**
Any of the following: Cabbage, Broccoli, Cauliflower, Brussel sprouts				
Spinach, Silverbeet				
Beans, Peas, Corn				
Peppers (Capsicum)				
Aubergines (Eggplant)				
Carrots				
Potatoes				
Parsnips, Turnips, Swedes				
Pumpkin				
Olives				
Tomatoes (fresh or canned)				
Garlic, Onions,				
Beetroot				
Rhubarb				
Lettuce (any variety)				
Parsley				
Fresh herbs				
Vegetable soup				
MILK PRODUCTS				
Cow's milk				
Yoghurt				
Cream				
Cheeses				
Icecream				

Elderly 61 – 75 yrs (continued)

FRUIT (Fresh, tinned or juice)	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Apples				
Pears				
Cherries				
Bananas				
Mangos				
Oranges, Grapefruit, Mandarins, Lemons, Limes				
Blueberries, Blackberries, Cranberries, Strawberries				
Red grapes				
White grapes				
Melon				
Figs				
Apricots, Peaches				
Plums				
CEREALS				
White bread				
Multigrain bread				
Whole grain bread				
High-fibre breakfast cereals (e.g. Weetbix, bran)				
Oats (porridge, muesli)				
Brown pasta or Brown rice				
White pasta or White rice				
TAKEAWAY FOOD				
Any takeaway food				

Elderly **61 – 75 yrs** (continued)

PROTEIN FOODS	DAILY	2 - 3 TIMES A WEEK	2 – 3 TIMES A MONTH	RARELY/ NEVER
Beef/Lamb/Pork				
Chicken				
Sausages/Processed meat (e.g. ham)				
Lentils & Dried peas/ beans (e.g. kidney beans, haricot beans – used in baked beans)				
Eggs				
Tofu				
Soya Milk				
Nuts				
Vegemite				
SEAFOOD (fresh, frozen or canned)				
Any of the following: Salmon, Trout, Sardines, Mackerel, Anchovies, Herring, Pilchards, **Fresh** Tuna				
Other Fish (including canned tuna & takeaway)				
Other Seafood (e.g. oysters, calamari, prawns, mussels, scallops etc.)				
SWEETS				
Sweets/Desserts (other than milk-based) including lollies, cakes, sweet biscuits etc.				
Chocolate				
Soft drinks				
SNACK FOOD				
Any snack foods (e.g. chips, savoury biscuits)				

Elderly 61 – 75 yrs (continued)

FATS & OILS (On bread or in cooking)	**DAILY**	**2 - 3 TIMES A WEEK**	**2 –3 TIMES A MONTH**	**RARELY/ NEVER**
Butter				
Margarine (polyunsaturated; e.g. Meadowlea)				
Oil (vegetable or seed-based; e.g. sunflower)				
Olive oil				
ALCOHOL				
Red wine				
Other wine				
Beer				
Cider				
Spirits				
TEA				
Green tea				
Herbal tea				
Black tea				
White tea				
Sweetened?				
COFFEE				
Black coffee				
White coffee				
Sweetened?				
MULTI-VITAMINS				
Any multi-vitamin supplements				

Elderly **61 – 75 yrs** (continued)

Physical Activity Questions

Please answer the following physical activity questions for the period when you were aged **61 – 75 years**. If your level of activity varied during this time, give an approximation of your activity levels.

- Please circle how much physical activity you did in your **everyday life**.
    - LITTLE physical activity (e.g. reading, watching television, office work)
    - SOME physical activity (e.g. shopping, light cleaning)
    - FREQUENT physical activity (e.g. gardening, minding grandchildren, heavy cleaning)
- IN ADDITION to the physical activity demanded by your everyday life, how often did you engage in walking, or any other exercise, for **greater than 30 mins** at a time?

  Please indicate, by placing a tick in one of the boxes below, if this exercise was
    - *Vigourous* (breathlessness, heavy sweating, heart pounding)
    - *Moderate* (light sweat, some increase in heart rate) or
    - *Light* (no noticeable physical symptoms)

  You may tick **more than one box** if appropriate.

Frequency	Vigourous activity	Moderate activity	Light activity
1/2 - 1 hour a week			
2 - 3 hours a week			
4 - 7 hours a week			
7 - 14 hours a week			
14 + hours a week			

YOU HAVE COMPLETED THE 61 – 75 YRS QUESTIONNAIRE

& FINISHED THE LIFETIME DIET QUESTIONNAIRE

THANK YOU!

APPENDIX C

The design and analysis of the cognitive test battery, which provided the outcome measures in Study 4 and 5, were not encompassed by the scope of this thesis.

The following is a short extract from a submitted publication currently under review with the Journal of Nutrition (Danthiir et al., 2013). It provides additional detail of dthe statistical treatment of the cognitive variables further to the analyses outlined in the EPOCH protocol (Danthiir, V. et al., 2011).

Data screening and transformations

Cognitive variables

The mean correct latencies for the reaction time tasks were inverted, excepting the inhibition tasks' difference scores, to normalise the distributions (Greaud & Green, 1986). The difference scores for Colour Stroop and Spatial Stroop were reflected and then square root transformed, while the difference score for the Simon task was only reflected. Thus, the speed scores for these three inhibition tasks are interpreted as smaller is better, reflecting less interference from irrelevant stimuli, while for all other speed task, a higher score reflects faster performance. The working memory tasks were transformed according to a transformation recommended for severe negative skewness , (NEWX=1/(K-X))(Tabachnick & Fidell, 2007) and, along with the other accuracy based tasks, are interpreted such that higher scores indicate better performance.

Statistical Analyses

Measurement models for the cognitive variables

Confirmatory Factor Analytic models were estimated using AMOS v7 (Arbuckle, 2006) for the speed and accuracy-based tasks separately, in order to derive factor scores representing the latent cognitive constructs to use in subsequent analyses, thereby providing a more reliable and valid measure of the cognitive constructs, as opposed to individual task scores. For the accuracy based tasks, latent variables were specified for Fluid Intelligence (Reasoning), Crystallized Intelligence (Knowledge), Working Memory, Short-term Memory, and Retrieval Fluency, indicated by the tasks specified above for each construct.[31] For the speed-based tasks, the model specified latent variables for Simple/Choice Reaction Time,

[31] Note that Knowledge was indicated by only one task (with the residual variance specified as ((1-reliability)*VAR), and was included only for completeness of the model; scores representing this task will not be used in subsequent analyses.

Reasoning Speed, Inhibition, Speed of Memory Scanning, and Psychomotor Speed, with the indicators for each factor as specified above. All factors were free to co-vary in both models; correlations were all of the expected direction and size, generally moderate to large in magnitude, with none so high as to imply redundancy between constructs. All regression weights were significant, in the expected directions, and moderate to high in magnitude, confirming that all tasks were good markers of their respective cognitive constructs. Both the accuracy-based and speed-based models provided good fit to the data (accuracy-based: $\chi 2$ = 69.3, df = 35, p = .000; Root Mean Square Error of Approximation (RMSEA) = .048, 90%CI [.031, .064]; Comparative Fit Index (CFI) = .974. Speed-based: $\chi 2$ = 156.68, df = 89, p = .000; RMSEA = .042, 90%CI [.031, .053]; CFI = .979). Factor scores were estimated for each construct with more than one indicator, based on the coefficients from these models,

APPENDIX D

Dear Mr/Mrs.....

Thankyou for volunteering to complete the Lifetime Diet Questionnaire. Your time and effort are much appreciated and will make a valuable contribution to this new and exciting research.

The findings from this particular part of the EPOCH study will be made available to you when the main study has concluded.

Best wishes,

Diane (Hosking)

LIFETIME DIET QUESTIONNAIRE

***Information about your Lifetime Diet Questionnaire**.*

Recent research has found associations between eating certain foods and cognitive functioning; that is thinking, reasoning and memory. However, possible relationships between peoples' diet over their lifetime and their cognition have not yet been explored. This is the purpose of the Lifetime Diet Questionnaire. (You might remember from the information sessions that this is a sub-aim of the EPOCH trial.) You will only need to complete the Lifetime Diet Questionnaire ONCE, and that is in the next few weeks (when convenient for you).

You will be asked to remember some of the foods you ate during **a number of different periods** of your life. For each period of time, some autobiographical questions will help 'locate' you in that time and so aid in the recall of your diet; your responses to these questions **will not** be used in the study (and will be discarded on return of the questionnaire) but we do need to check that you have completed this aspect of the questionnaire in order for your results to be valid. Thus the questions are not for any purpose other than to help your memory.

In addition, you will be asked to remember how physically active you were during each life period. As with all our data, all your responses will remain anonymous and will not be linked to your name.

There are 4 to 5 (depending on your age) mini-questionnaires that make up the Life Time Diet Questionnaire. Please complete ONE only of these mini-questionnaires per day over 4 to 5 consecutive days, to minimise the chance of your diet memories from one period of your life influencing diet memories from another period.

When you have completed all of the mini-questionnaires that make up the Lifetime Diet Questionnaire, please place them in the reply-paid envelope and post back to CSIRO at your earliest convenience. If you have any questions regarding the questionnaire please call Diane Hosking on 83038858 or email Diane.Hosking@csiro.au

Before commencing your Lifetime Diet Questionnaire please answer the following questions about your smoking habits (if any) over your lifetime.

Smoking (cigarettes, cigars, pipes)

(PLEASE TICK (✓) ONE BOX)

☐ I don't smoke ☐ Smoke more than 20 per day

☐ Smoke 1-10 per day ☐ Have smoked but given up. Age ceased.....

☐ Smoke 11-20 per day ☐ Other ……

If you used to smoke but have given up please answer the two questions below: (if there's more than one smoking period, please specify for each period)

1. Between which years did you smoke for?

2. How many cigarettes (cigars, pipes), on average, did you used to smoke per day?

PLEASE FILL OUT YOUR FIRST LIFETIME DIET QUESTIONNAIRE NOW FOR THE PERIOD OF YOUR CHILDHOOD.

APPENDIX E

PRELIMINARY MODELS:
ASSOCIATIONS BETWEEN LDQ DIETARY PATTERNS AND 18-MONTH COGNIITVE CHANGE ON ALL CONSTRUCTS.

The following tables present the parameter estimates of LDQ dietary patterns as predictors of all 18-month cognitive change on all constructs. All models controlled for age, Apoe-ε4 status, current diet, and their Time interaction terms. Other potential covariates were included if their correlations with the cognitive construct of interest and dietary pattern variable approached significance which was defined as having a p value of **≤ 0.1.**

In these preliminary models, the parameter estimates have been highlighted for those dietary patterns that approached significance as predicting cognitive change. These models were then re-run including only covariate interaction with Time terms that significantly contributed to the model (See Chapter 8: 8.2.8).

Results presented in Chapter 8 represented significant outcomes from these subsequent models with the addition of the past dietary factors from the other life-periods.

Associations between LDQ dietary patterns and 18-month cognitive change on Perceptual speed
TIME=CUBIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
PERCEPTUAL SPEED	CHD 'vegetable & non-processed'	Time -.028	0.331	sex, pack years
		Time^2 .040	0.425	
		Time ^{3} -.012	0.579	
	CHD 'traditional Australian'	Time -.001	0.909	sex, pack years, CES-D
		Time^2 -.001	0.946	
		Time ^{3} .003	0.790	
	CHD 'coffee & high sugar, high fat extras'	Time .044	0.183	English as first language
		Time^2 - .065	0.258	
		Time ^{3} .024	0.330	
	EAD 'vegetable'	Time .007	0.746	sex, pack years
		Time^2 - .001	0.981	
		Time ^{3} -.000	0.990	
	EAD 'traditional Australian'	Time .003	0.858	pack years
		Time^2 - .002	0.946	
		Time ^{3} .001	0.909	
	EAD 'non-traditional Australian'	Time .001	0.953	English as first language, pack years
		Time^2 .022	0.644	
		Time ^{3} - .016	0.552	
	AD 'fruit & vegetable'	Time .000	0.982	sex, pack years
		Time^2 - 0.015	0.744	
		Time ^{3} .008	0.666	
	AD 'non-traditional Australian'	Time - .030	0.237	years of education, pack years
		Time^2 .045	0.290	
		Time ^{3} - .018	0.339	
	AD 'Processed high-sugar, high-fat'	Time .051	0.146	English as first language
		Time^2 0.054	0.389	
		Time^3 - .016	0.547	
	MAGE 'fruit, vegetable & non-processed'	Time .006	0.712	sex, pack years
		Time^2 - .012	0.706	
		Time ^{3} .005	0.675	
	MAGE 'non-traditional Australian'	Time .044	0.179	sex, pack years
		Time^2 - .077	0.181	
		Time ^{3} .035	0.166	
	MAGE 'processed, high sugar & high fat'	Time - .062	0.096	sex, pack years
		Time^2 .107	0.156	
		Time ^{3} - .038	0.186	

*CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Psychomotor speed
TIME=CUBIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
PSYCHO-MOTOR SPEED	CHD 'vegetable & non-processed'	Time - .045 Time^2 .063 Time^3 - .022	0.165 0.271 0.372	pack years
	CHD 'traditional Australian'	Time - .024 Time .033 Time - .011	0.175 0.282 0.398	pack years, CES-D
	CHD 'coffee & high sugar, high fat extras'	Time - .016 Time .022 Time - .009	0.657 0.736 0.734	English as first language
	EAD 'vegetable'	Time - .017 Time .027 Time - .025	0.537 0.579 0.556	pack years
	EAD 'traditional Australian'	Time -.006 Time .024 Time - .013	0.778 0.560 0.451	pack years
	EAD 'non-traditional Australian'	Time .008 Time - .008 Time .000	0.787 0.881 0.979	pack years English as first language
	AD 'fruit & vegetable'	Time - .007 Time .016 Time - .009	0.809 0.763 0.693	pack years English as first language
	AD 'non-traditional Australian'	Time - .016 Time .035 Time - .017	0.571 0.472 0.433	pack years
	AD 'Processed high-sugar, high-fat'	Time .038 Time - .069 Time .026	0.347 0.336 0.405	English as first language
	MAGE 'fruit, vegetable & non-processed'	Time .028 Time - .044 Time .017	0.260 0.261 0.361	pack years
	MAGE 'non-traditional Australian'	Time - .005 Time .018 Time .011	0.876 0.781 0.693	pack years
	MAGE 'processed, high sugar & high fat'	Time - .030 Time .057 Time - .028	0.474 0.436 0.378	English as first language

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scal

Associations between LDQ dietary patterns and 18-month cognitive change on Inhibition
TIME=QUADRATIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
INHIBITION (the direction of parameter estimates was reversed so, in accord with other constructs, a higher score equated to better performance)	CHD 'vegetable & non-processed'	Time .005 Time^2 .005	0.836 0.717	N/A
	CHD 'traditional Australian'	Time .010 Time^2 - .002	0.431 0.809	N/A
	CHD 'coffee & high sugar, high fat extras'	Time - .016 Time^2 .013	0.576 0.449	N/A
	EAD 'vegetable'	Time -.003 Time^2 .006	0.882 0.600	N/A
	EAD 'traditional Australian'	Time - .001 Time^2 .000	0.942 0.994	N/A
	EAD 'non-traditional Australian'	Time -.024 Time^2 .018	0.299 0.225	N/A
	AD 'fruit & vegetable'	Time .022 Time ^{2}- .013	0.323 0.355	N/A
	AD 'non-traditional Australian'	Time - .020 Time^2 .016	0.324 0.333	years of education
	AD 'Processed high-sugar, high-fat'	Time - .003 Time^2 .005	0.919 0.788	N/A
	MAGE 'fruit, vegetable & non-processed'	Time - .004 Time^2 .005	0.832 0.651	N/A
	MAGE 'non-traditional Australian'	Time - .016 Time ^{2}.017	0.553 0.578	N/A
	MAGE 'processed, high sugar & high fat'	Time .021 Time^2 - .008	0.491 0.674	N/A

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Simple/Choice reaction time
TIME=QUADRATIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
SIMPLE/CHOICE REACTION TIME	CHD 'vegetable & non-processed'	Time - .007 Time² .010	0.569 0.222	N/A
	CHD 'traditional Australian'	Time - 008 Time² .009	0.225 0.045	CES-D
	CHD 'coffee & high sugar, high fat extras'	Time - .007 Time² .012	0.607 0.186	English as first language
	EAD 'vegetable'	Time -.000 Time² .004	0.939 0.540	N/A
	EAD 'traditional Australian'	Time .002 Time² .001	0.809 0.759	N/A
	EAD 'non-traditional Australian'	Time .020 Time² - .011	0.110 0.151	English as first language
	AD 'fruit & vegetable'	Time .007 Time² - .004	0.556 0.534	N/A
	AD 'non-traditional Australian'	Time .005 Time2 - .002	0.620 0.760	N/A
	AD 'Processed high-sugar, high-fat'	Time - .003 Time² .003	0.850 0.751	English as first language
	MAGE 'fruit, vegetable & non-processed'	Time -.001 Time² .000	0.864 0.902	N/A
	MAGE 'non-traditional Australian'	Time .002 Time² .001	0.892 0.867	N/A
	MAGE 'processed, high sugar & high fat'	Time -.019 Time² .014	0.253 0.235	English as first language

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Reasoning speed
TIME=LINEAR

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
REASONING SPEED	CHD 'vegetable & non-processed'	Time .003	0.487	sex
	CHD 'traditional Australian'	Time .002	0.297	sex, CES-D
	CHD 'coffee & high sugar, high fat extras'	Time - .002	0.668	N/A
	EAD 'vegetable'	Time .006	0.117	sex
	EAD 'traditional Australian'	Time .003	0.298	N/A
	EAD 'non-traditional Australian'	Time .002	0.680	N/A
	AD 'fruit & vegetable'	Time .002	0.622	sex
	AD 'non-traditional Australian'	Time - .002	0.629	N/A
	AD 'Processed high-sugar, high-fat'	Time .005	0.411	sex
	MAGE 'fruit, vegetable & non-processed'	Time .001	0.760	sex
	MAGE 'non-traditional Australian'	Time - .001	0.794	sex
	MAGE 'processed, high sugar & high fat'	Time .008	0.198	sex

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Memory scanning speed
TIME=LINEAR

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
MEMORY SCANNING SPEED	CHD 'vegetable & non-processed'	Time .011	0.024	N/A
	CHD 'traditional Australian'	Time .005	0.073	CES-D
	CHD 'coffee & high sugar, high fat extras'	Time .001	0.818	N/A
	EAD 'vegetable'	Time .006	0.152	N/A
	EAD 'traditional Australian'	Time .003	0.347	N/A
	EAD 'non-traditional Australian'	Time .000	0.846	N/A
	AD 'fruit & vegetable'	Time .001	0.778	N/A
	AD 'non-traditional Australian'	Time - .002	0.564	N/A
	AD 'Processed high-sugar, high-fat'	Time .001	0.833	N/A
	MAGE 'fruit, vegetable & non-processed'	Time .000	0.840	N/A
	MAGE 'non-traditional Australian'	Time -.002	0.718	N/A
	MAGE 'processed, high sugar & high fat'	Time .005	0.432	N/A

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Working memory
TIME=LINEAR

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
WORKING MEMORY	CHD 'vegetable & non-processed'	Time -.003	0.442	N/A
	CHD 'traditional Australian'	Time .095	0.515	CES-D
	CHD 'coffee & high sugar, high fat extras'	Time .006	0.483	English as first language
	EAD 'vegetable'	Time - .001	0.606	N/A
	EAD 'traditional Australian'	Time - .001	0.654	N/A
	EAD 'non-traditional Australian'	Time .000	0.841	English as first language
	AD 'fruit & vegetable'	Time .001	0.754	years of education
	AD 'non-traditional Australian'	Time -.002	0.339	English as first language
	AD 'Processed high-sugar, high-fat'	Time - .002	0.650	N/A
	MAGE 'fruit, vegetable & non-processed'	Time .002	0.444	income level
	MAGE 'non-traditional Australian"	Time .005	0.279	English as first language
	MAGE 'processed, high sugar & high fat'	Time .004	0.371	English as first language

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Retrieval fluency
TIME=CUBIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
RETRIEVAL FLUENCY	CHD 'vegetable & non-processed'	Time .043	0.174	pack years, sex
		Time^2 -.085	0.131	
		Time^3 .037	0.134	
	CHD 'traditional Australian'	Time -.016	0.322	pack years, sex
		Time^2 .025	0.394	
		Time^3 - .010	0.444	
	CHD 'coffee & high sugar, high fat extras'	Time .030	0.400	English as first language
		Time ^{2} -.055	0.379	
		Time^3 .023	0.401	
	EAD 'vegetable'	Time - .010	0.683	pack years, sex
		Time^2 .022	0.639	
		Time^3 - .010	0.825	
	EAD 'traditional Australian'	Time - .027	0.233	pack years
		Time^2 .050	0.211	
		Time^3 - .005	0.206	
	EAD 'non-traditional Australian'	Time .009	0.765	pack years, English as first language
		Time^2 -.009	0.865	
		Time^3 .002	0.910	
	AD 'fruit & vegetable'	Time -.012	0.659	sex
		Time^2 .032	0.528	
		Time^3 -.015	0.491	
	AD 'non-traditional Australian'	Time .045	0.098	income, pack years
		Time ^{2} -.065	0.174	
		Time^3 .025	0.237	
	AD 'Processed high-sugar, high-fat'	Time -.046	0.238	sex, English as first language
		Time^2 .072	0.302	
		Time^3 -.030	0.324	
	MAGE 'fruit, vegetable & non-processed'	Time - .014	0.540	N/A
		Time^2 .022	0.601	
		Time^3 - .008	0.964	
	MAGE 'non-traditional Australian'	Time - .065	0.068	pack years, sex, income
		Time^2 .136	0.031	
		Time^3 -.060	0.031	
	MAGE 'processed, high sugar & high fat'	Time .006	0.884	English as first language, sex
		Time^2 - .043	0.552	
		Time^3 .024	0.444	

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Short-term memory
TIME=CUBIC

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates (including their Time interaction terms)
SHORT-TERM MEMORY	CHD 'vegetable & non-processed'	Time -.029	0.356	pack years, sex
		Time^2 .058	0.300	
		Time^3 -029	0.240	
	CHD 'traditional Australian'	Time -.009	0.586	pack years, sex, CES-D
		Time ^{2} .024	0.420	
		Time^3 -.013	0.315	
	CHD 'coffee & high sugar, high fat extras'	Time .001	0.970	English as first language
		Time^2 -.028	0.647	
		Time^3 .021	0.439	
	EAD 'vegetable'	Time .000	0.983	pack years, sex
		Time^2 -.002	0.984	
		Time .014	0.915	
	EAD 'traditional Australian'	Time -.011	0.433	pack years,
		Time^2 .030	0.338	
		Time ^{3} - .016	0.581	
	EAD 'non-traditional Australian'	Time .047	0.121	pack years, English as first language
		Time^2 -.028	0.255	
		Time^3 .022	0.355	
	AD 'fruit & vegetable'	Time .001	0.954	sex
		Time ^{2}-.016	0.757	
		Time^3 .011	0.621	
	AD 'non-traditional Australian'	Time .060	0.031	income, pack years
		Time^2 -.020	0.086	
		Time^3 .012	0.151	
	AD 'Processed high-sugar, high-fat'	Time -.053	0.177	sex, English as first language
		Time ^{2} .093	0.182	
		Time^3 -.042	0.174	
	MAGE 'fruit, vegetable & non-processed'	Time -.018	0.442	sex, pack years
		Time^2 .042	0.335	
		Time ^{3} -.020	0.290	
	MAGE 'non-traditional Australian'	Time -.045	0.205	sex, pack years, income
		Time .112	0.076	
		Time^3 -.054	0.053	
	MAGE 'processed, high sugar & high fat'	Time -.005	0.904	sex, English as first language
		Time^2 .000	0.920	
		Time^3 -.003	0.920	

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

Associations between LDQ dietary patterns and 18-month cognitive change on Reasoning
TIME=LINEAR

Cognitive construct	Dietary pattern	Parameter estimate	P value	Additional covariates* (including their Time interaction terms)
REASONING	CHD 'vegetable & non-processed'	Time - .004	0.263	N/A
	CHD 'traditional Australian'	Time .002	0.341	CES-D
	CHD 'coffee & high sugar, high fat extras'	Time -.008	0.078	English as first language
	EAD 'vegetable'	Time -.002	0.408	English as first language
	EAD 'traditional Australian'	Time -.001	0.535	N/A
	EAD 'non-traditional Australian'	Time -.003	0.370	English as first language
	AD 'fruit & vegetable'	Time .002	0.581	N/A
	AD 'non-traditional Australian'	Time -.001	0.576	years of education
	AD 'Processed high-sugar, high-fat'	Time -.002	0.569	English as first language
	MAGE 'fruit, vegetable & non-processed'	Time .001	0.639	N/A
	MAGE 'non-traditional Australian'	Time .005	0.198	income
	MAGE 'processed, high sugar & high fat'	Time -.001	0.727	N/A

CHD childhood; EAD early adulthood; AD adulthood; MAGE middle-age
CES-D: Score on the Centre for Epidemiologic Studies Depression scale

APPENDIX F:

Published manuscripts: Study 2 (Chapter 4) and Study 3 (Chapter 5), and Statements of Authorship.

Statement of Authorship

Title of Paper	Assessing lifetime diet: reproducibility of a self-administered non-quantitative FFQ
Publication Status	☒ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	Public Health Nutrition 14(5) 801-808

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Diane Hosking		
Contribution to the Paper	Development of questionnaire, concept and design of study, data collection, conducting statistical analyses, and writing the manuscript		
Signature		Date	30-9-2013

Name of Co-Author	Vanessa Danthiir		
Contribution to the Paper	Questionnaire concept and development concept and design of study, statistical analysis, and manuscript revision and approval		
Signature		Date	30-9-2013

Name of Co-Author	Ted Nettelbeck		
	Study concept and design, manuscript review and approval		
Signature		Date	30-9-2013

Name of Co-Author	Carlene Wilson		
Contribution to the Paper	Study concept and design, manuscript review and approval		
Signature		Date	27-9-2013

Statement of Authorship

Title of Paper	Retrospective lifetime dietary patterns are associated with demographic and cardiovascular health variables in community-dwelling older Australians
Publication Status	☒ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Diane Hosking		
Contribution to the Paper	Study concept and design, collected lifetime dietary data, conducted statistical analyses, and wrote the manuscript		
Signature		Date	30-9-2013

Name of Co-Author			
Contribution to the Paper	Concept and design of the Epoch trial and of the present study, statistical analyses, and manuscript revision and approval		
Signature		Date	30-9-2013

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Statement of Authorship

Title of Paper	Retrospective lifetime dietary patterns and cognitive performance in community-dwelling older Australians
Publication Status	O Published, O Accepted for Publication, ☒ Submitted for Publication, O Publication style
Publication Details	British Journal of Nutrition

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Diane Hosking		
Contribution to the Paper	Designed and conducted research, performed statistical analyses, wrote the paper		
Signature		Date	30-9-2013

Name of Co-Author	Vanessa Danthiir		
Contribution to the Paper	Designed research, performed statistical analyses, read and approved final manuscript		
Signature		Date	30-9-2013

Name of Co-Author	Ted Nettelbeck		
Contribution to the Paper	Designed research, approved final manuscript		
Signature		Date	30-9-2013

Name of Co-Author	Carlene Wilson		
Contribution to the Paper	Designed research, approved final manuscript		
Signature		Date	27-9-2013

Hosking, D., Danthiir, V., Nettlebeck, T. & Wilson, C. (2010) Assessing lifetime diet: reproducibility of a self-administered, non-quantitative FFQ.
Public Health Nutrition, v. 14(5), pp. 801-808

Hosking, D. & Danthiir, V. (2013) Retrospective lifetime dietary patterns are associated with demographic and cardiovascular health variables in an older community-dwelling Australian population.
British Journal of Nutrition, v. 110(11), pp. 2069-2083