Associations between diet, cognitive function and dementia risk in UK adults

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 3 incorporates the work of one jointly-authored publication:

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The candidate has contributed to developing literature search strategies, screening all literatures, extracting information, conducting data analysis, assessing study quality, and preparing the original draft. Conceptualization and design of this work was done by the candidate monitored by supervisors Hardie L and Cade J. All other co-authors contributed to duplicating the work of literature screening, information extraction, and study quality assessment, as well as reviewing and editing the manuscript.

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This publication is a secondary analysis of the UK Women's Cohort Study (UKWCS) dataset. The candidate was not involved in the establishment, data collection, or primary data processing of the UKWCS. The candidate was responsible for the conception and design of the secondary analysis proposal, data cleaning and formatting, data analysis, result interpretation, drafting the original manuscript, and revising all drafts. The other co-authors contributed to the study design, data analysis, findings interpretation, and providing comprehensive feedback throughout the work publication.

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Zhang H, Hardie L, Greenwood D, Cade J. Meat consumption is associated with higher dementia prevalence: a cross-sectional analysis of UK Biobank. *Proceedings of the Nutrition Society* 2021, 80(OCE1), E9.

The published article and conference abstract are secondary analyses of the UKB. The candidate was not involved in the establishment, data collection, or primary data processing of the UKB. The candidate conceived the analysis proposal, and contributed to data cleaning and statistical analyses. The candidate also wrote the first draft of the manuscript and had primary responsibility for final content. All other authors provided critical comments on the scientific interpretation of the results. All authors made substantial contributions to revision of the manuscript throughout the publication of this work.

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Abstract

Cognitive decline and dementia are of increasing concern in aging societies worldwide. Diet, as a modifiable lifestyle factor, represents a target for prevention or limiting progression. However, evidence on associations of cognitive function and dementia with diet remains limited and inconsistent, especially on meat consumption summarized in the systematic review of this project.

Cross-sectional associations of dietary factors with one cognitive test (reaction time) and dementia (ascertained via death registers) were conducted in UK Women's Cohort Study (UKWCS). The results showed that consumption of specific food groups, energy-adjusted nutrient intakes, and adherence to dietary patterns were not statistically associated with reaction time and dementia in the UKWCS. Cross-sectional and longitudinal associations of food consumption, especially meat intakes, with five cognitive tests (visual memory, numeric memory, prospective memory, fluid intelligence, and reaction time) and dementia (ascertained via self-report and linkages to hospital admission data and death registers) were conducted in UK Biobank (UKB). Incident dementia cases occurring within 1-year or 3-year follow-up were excluded due to potential reverse causation, and similar results were observed between the two types of exclusion. The results showed that high consumption of processed meat was associated with increased risks of prevalent and incident dementia; with a non-linear pattern of this association indicated in the UKB. Associations between consumption of other meat types and cognitive performance and dementia risk were not consistent in the UKB. A diet-gene interaction of *APOE* ε4 allele on dementia risk was explored, and all *P* values for interaction were not significant. In addition, high consumption of vegetables, fruits, and fish were observed to be associated with poor cognitive performance and increased risk of incident dementia in the UKB although effect sizes were small.

This project highlights potentially non-linear associations between meat consumption and dementia risk, which may be independent of *APOE* ε4 allele carriage. Findings on consumption of vegetables, fruits, and fish were not consistent with the hypotheses proposed of a protective effect in this thesis. However, the effect sizes were relatively small and therefore need to be interpreted with caution and to be confirmed in other studies.

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List of abbreviations

3MS	Modified Mini Mental State Examination
7MS	seven-minute screening test
95%CI	95% confidence interval
Aβ	Amyloid beta
ACE	Addenbrooke's Cognitive Examination
APP	Amyloid precursor protein
AD	Alzheimer’s disease
ADI	Alzheimer’s Disease International
APOE	apolipoprotein E
BBB	Blood-Brain Barrier
BMI	body mass index
CDT	Clock Drawing Test
CERAD	the Consortiumto Establish a Registry for Alzheimer’s Disease
CRT	choice reaction time
DAG	directed acyclic graph
DAT	Dementia of the Alzheimer type
DASH	Dietary Approach to Stop Hypertension
DSM	Diagnostic and Statistical Manual of Mental Disorders
FFQ	food frequency questionnaire
GPCOG	General Practitioner Assessment of Cognition
GMV	Gray matter volume
HEI	Healthy Eating Index
HR	hazard ratios
ICD	International Classification of Diseases
IIV	intraindividual variability
IPAQ	International Physical activity questionnaire
IQR	interquartile range
LCI	lower confidence interval (95%)
LTM	long-term memory
MCI	mild cognitive impairment
MeDi	Mediterranean diet
MDS	Mediterranean Dietary Score
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
Mini-Cog	Mini Cognitive Assessment Instrument
MIS	Memory Impairment Screen
MMSE	mini mental state examination
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MoCA	Montreal cognitive assessment
MRI	Magnetic Resonance Imaging
MUFA	monounsaturated fatty acids
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association
NA	not applicable
NR	not reported
ONS	UK Office of National Statistics
OR	odds ratios

PC	principal component
PCA	the principal component analysis
PR	prevalence ratio
PRISMA	the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
PUFA	polyunsaturated fatty acids
RCS	restricted cubic spline
RCTs	randomised controlled trials
ref	reference
RT	reaction-time
SD	standard deviation
SES	socio-economic status
SFA	saturated fatty acids
SMD	standardised mean differences
SQL	Structured Query Language
SRB	the standardized regression-based method
SRT	simple reaction time
STM	short-term memory
TBV	total brain volume
TDI	Townsend deprivation Index
UCI	upper confidence interval (95%)
UFA	unsaturated fatty acids
UKB	UK Biobank
UKWCS	UK Women's Cohort Study
VD	vascular dementia
WHO	World Health Organization

CHAPTER I

1. Introduction and Objectives

As becoming more prevalent around the world, dementia is a major public health concern. Dementia typically takes decades to develop which is a complicated process, including but not limited to changes in brain function and structures, cognitive function, and personality as well as emotions [1]. Cognitive decline can occur slowly and progressively for decades before dementia is finally diagnosed. Functional decline can be either a natural process or accelerated through development of diseases such as Alzheimer's disease, but it is difficult to establish the boundary between natural aging and onset of dementia [2]. This process may be influenced independently or interactively by many kinds of internal and external factors including genetic, sex, ethnicity, age, lifestyle behaviours such as smoking status, physical activity level, sleep duration, and dietary behaviours [3,4]. Currently, existing evidence on associations between diet, cognitive aging, and dementia is limited, and findings are inconsistent across studies [5,6].

Alzheimer's disease (AD) is the most common form of dementia and may contribute up to 60–70% of cases [7]. It is notable that less than 5% of AD cases are directly inherited, indicating that environmental factors, and/or gene-environment interactions, are likely to play a major role in initiating and/or promoting the disease [8,9]. The ε4 allele, a variant of the apolipoprotein E (*APOE*) gene, is the most prominent genetic risk factor for sporadic AD, with a three-fold increase in AD incidence for *APOE* ε4 heterozygotes and a more than 10-fold higher risk for *APOE* ε4 homozygotes [10,11]. Therefore, it is important to consider potential interactions between *APOE* ε4 carriage and risk factors in research on dementia.

1.1 Research aim and objectives

The aim of this project is to explore the associations between diet, cognitive aging, and dementia, as well as to explore a potential diet-gene interaction with the *APOE* ε4 allele. To fulfil the aim, some specific objectives in each chapter are proposed as follows.

1.1.1 Chapter 2: Literature review on research background

Generally, related evidence of associations between diet, cognitive aging, and dementia remains limited. It was therefore necessary to conduct a literature review to understand related research progress and limitations in this field. The objectives of this chapter were:

1) To briefly introduce cognitive function including some common cognitive domains as well as related, frequently-used cognitive tests, and discuss cognitive aging and its relationship with dementia.
2) To introduce the general epidemiology, main subtypes, screening tools, diagnostic criteria, and risk factors for dementia.
3) To introduce described associations of cognitive aging and dementia with diet including foods, dietary patterns, and nutrients, and further discuss potential mechanisms underlying the associations.

1.1.2 Chapter 3: Systematic review on meat, cognition, and dementia

The systematic review with meta-analysis focused on the relationships between meat consumption (including processed meat, unprocessed red meat, and poultry, but not fish) and cognition-related outcomes (including cognitive impairment/decline, dementia, Alzheimer's disease) among older adults and elderly people. Currently, the associations of red meat and/or poultry with cognitive function remain controversial where some evidence suggests detrimental effects but other studies showed non-significant results or even protective effects. This chapter was designed to achieve the following objectives:

1) To narratively summarize the existing evidence regarding associations between meat consumption and cognitive disorders especially dementia, and to report the research gaps in this area.
2) To combine results from similar studies with small sample sizes to provide more powerful findings using meta-analysis.
3) To briefly discuss possible mechanisms underlying associations between meat consumption and cognitive disorders.

1.1.3 Chapter 4: Analyses on food consumption, dietary patterns, and nutrient intakes within the UKWCS

The UK Women's Cohort Study (UKWCS) has collected detailed dietary information on over 35,000 UK women including food consumption frequencies, and cooking methods used for several common foods. The UKWCS has a sub-group of participants who performed reaction time tasks as a cognitive test; at the same time, the cohort was updated with death register data which contain dementia diagnosis information. These data made it possible to explore relationships between food consumption, dietary patterns, and nutrient intakes with cognitive function, as well as to investigate the influential dietary factors of dementia mortality among UK women. Specific objectives in this chapter were:

1) To assess consumption of common food groups such as fruit, vegetables, meat, and fish, and to determine dietary patterns and calculate the daily nutrient intakes based on the baseline food frequency questionnaire.
2) To cross-sectionally examine associations between consumption of foods, nutrients, dietary patterns, and cooking methods with reaction times using logistic regression adjusting for age, socioeconomic status, physical activity, and other lifestyle factors within the cognition subgroup of the UKWCS.
3) To explore associations between dementia mortality and dietary factors, specifically consumption of foods, dietary patterns, and nutrients using logistic regression adjusting for age, socioeconomic status, physical activity, and other lifestyle factors in the whole UKWCS cohort.

1.1.4 Chapter 5: Analyses of diet with multi-domain cognitive tests using data from UK Biobank

UK Biobank is a large-scale population-based cohort with over half a million participants. A touchscreen brief food frequency questionnaire was administered at recruitment to collect basic information on food consumption. UK Biobank has administered cognitive function tests including reaction time, visual memory, numeric memory, prospective memory, and fluid intelligence on most participants. The diet and cognition data in UK Biobank can be used to support the research objectives:

1) To cross-sectionally examine associations between food consumption and

cognitive performance within each cognitive test at baseline.

2) To characterise cognitive changes over time and determine cognitive change status including cognition deterioration and improved cognition.

3) To determine associations of food consumption with prospective cognitive changes over a follow-up period.

1.1.5 Chapter 6: Analyses of diet in relation to prevalent and incident dementia in UK Biobank

In UK Biobank, prevalent and incident dementia cases were ascertained via self-report at baseline or data linkages to hospital inpatient admission data and death register data. In addition, genotyping data are also available on most participants. These data are used in this project to achieve the following objectives:

1) To cross-sectionally assess associations between food consumption and prevalent dementia at baseline using logistic regression modelling.

2) To determine longitudinal associations of food intakes, especially meat consumption, with risk of incident dementia during follow-up using survival analysis.

3) To explore potential genetic modification by the *APOE* ε4 allele on the associations between food consumption and risk of dementia.

1.2 Research framework

The whole framework of this thesis is outlined in Figure 1.1. To achieve the aims and objectives, first a literature review was conducted to introduce the background and current research issues in this research field (Chapter 2). During the process of reviewing the literature, meat consumption was found to have the most inconsistent results from individual studies in relation to cognitive aging and dementia. Therefore, a systematic review on meat consumption related to cognitive impairment and dementia was conducted (Chapter 3). The associations between diet, cognitive function, and dementia were firstly examined in the UK Women's Cohort Study (Chapter 4) cross-sectionally using reaction times, and longitudinally using mortality from dementia as outcomes. Then, five tests of cognitive function including reaction time, fluid intelligence, visual memory, numeric memory, and prospective memory were analysed in UK Biobank in relation to food consumption

cross-sectionally and longitudinally (Chapter 5). In addition, associations of food consumption with prevalent and incident dementia were determined in UK Biobank cross-sectionally and longitudinally (Chapter 6). Based on these studies, some conclusions, strengths, and limitations were discussed in the final chapter (Chapter 7).

1.3 Research hypotheses

1) High consumption of fruits, vegetables, and fish individually are hypothesized to be protective against cognitive decline, while high meat consumption is potentially detrimental to cognitive performance.
2) High adherence to Mediterranean diet may be protective against cognitive impairment and dementia.
3) Dietary patterns characterized by high consumption of fruits, vegetables, and fish may be associated with lower risk of cognitive impairment or dementia, while other dietary patterns featuring high meat consumption, especially processed meat, may have higher risk of cognitive impairment and dementia.
4) The *APOE* ε4 carriage may modify the associations between food consumption and dementia risk.

Overall, this thesis will include literature reviews and data analyses based on the UK Women's Cohort Study and the UK Biobank to explore potential associations between diet, cognitive aging, and dementia.

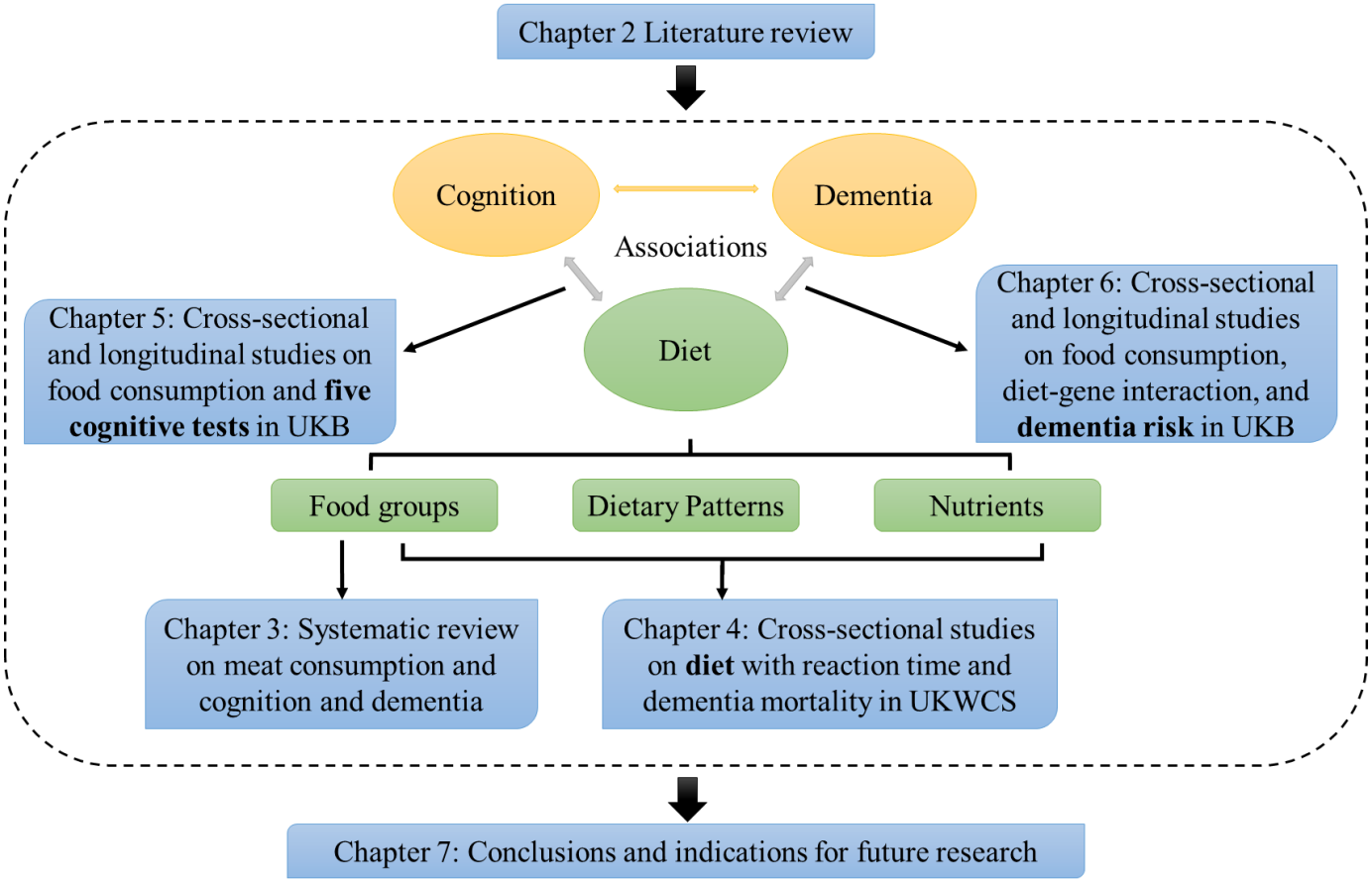


Figure 1.1 The framework of the project

UKB: UK Biobank; UKWCS: UK Women's Cohort Study

CHAPTER II

2. Literature review on cognitive aging and dementia in relation to diet

2.1 Summary

2.1.1 Highlights

- Cognitive impairment and dementia are increasingly important public health issues, as there is no effective treatment established. As such modifiable lifestyle factors may represent potential prevention targets.
- Some dietary factors, such as oily fish consumption, Mediterranean diet, have been linked with decreased risk of cognitive decline or dementia, while other dietary patterns high in saturated fat were associated with increased risks; however, the evidence to date remains limited and inconsistent.
- Potential mechanisms underlying the associations between diet, cognitive aging, and dementia remain unclear but may include antioxidant effects, and providing essential components of neural membranes and neurotransmitters.

2.1.2 Abstract

Cognitive aging can evolve into progressive cognitive decline or even dementia, which has a detrimental impact on the life quality and health for elderly individuals and their caregivers. At present there is still no effective therapy available, and thus it is highly necessary to search for preventive strategies against cognitive decline and dementia. As a modifiable lifestyle-related factor, diet has gained increasing interest in relation to prevention of chronic diseases including dementia. Cumulative evidence has shown that oily fish consumption, high adherence to Mediterranean diet, high intakes of unsaturated fatty acids and antioxidative nutrients are associated with reduced risks of cognitive impairment and dementia. However, these associations are far from conclusive and conflicting findings exist in the literature, possibly reflecting variation in methodology. In addition, evidence on some dietary factors in relation to cognitive aging is limited, such as meat consumption, and some dietary patterns derived from *a priori* or *a posteriori* method. In most cases, these results were from cross-sectional studies with small

sample sizes, and thus evidence from large population-based cohort studies is needed for clarification and confirmation of results from less well-powered studies.

2.2 Introduction

It is believed that cognitive aging and dementia development could occur simultaneously. Cognitive aging may progress at a high rate under some risk factors which could trigger development of dementia, in contrast other protective factors may reduce the rate of cognitive aging and could be preventive or delay dementia. Cognitive decline at a low rate could be considered as "healthy cognitive aging" [12].

Currently, few studies have investigated to what extent cognitive decline could evolve into dementia. Cognitive decline is a condition which is not disease-specific. Therefore, a significant association between a risk factor and cognitive decline is not necessarily observed between that risk factor and any type of dementia in the same population. However, most dementia is accompanied by cognitive decline. Therefore, an association between a risk factor and cognitive decline could be an indication of early dementia in relation to that risk factor [13]. A study comparing the course of changes in everyday tasks between normal aging and dementia showed that cognitive aging was more likely linked to inefficiency of executive functioning, while mild cognitive impairment or dementia was more prone to errors in memory measures, indicating that daily task difficulties may evolve from inefficiencies to inaccuracies in task completion during the progression from healthy aging to dementia compromising ability to live independently [14].

Cognitive training or "brain fitness" interventions have consistently shown preventive effects on cognitive decline in older adults conducted by psychologists, particularly pronounced together with physical exercise [15]. In addition to brain fitness, diet has been given much attention in relation to healthy cognitive aging. The brain is an organ with high metabolic activity which is more sensitive to deficiency or redundancy of nutrients [16]. Since the brain is particularly prone to oxidative stress and has few antioxidant enzymes for neuronal protection [17], antioxidant nutrients could play important roles in the brain aging. At the same time, oxidative damage and neural inflammation are thought to be part of the underlying biological mechanisms of dementia like Alzheimer's disease [18]. Therefore,

cognitive aging and dementia could share similar biological mechanisms, and thus both could be influenced by nutrition such as protective antioxidant nutrients including vitamin E, vitamin C, carotenoids, and flavonoids. However, cognitive aging and dementia may not have similar influential dietary factors; for instance, associations with B-vitamins have produced inconsistent findings from epidemiologic studies. Cohort studies with dementia-free participants showed that low serum levels of both B12 and folate were associated with increased risk of developing dementia over 3–4 years follow-up [19,20], which could be largely explained by the metabolic disorder of hyperhomocysteinaemia related to high risk of dementia [21]. In contrast, a high level of serum folate with a low level of serum vitamin B12 was reported to be associated with cognitive impairment in seniors from the US national health and nutrition examination survey data [22].

This chapter reviews the literature on cognitive aging and dementia in relation to diet. In general, this part focuses on more recent literature reviews, particularly systematic reviews including meta-analyses and pooling studies, to provide a relatively comprehensive summary on this field. Nevertheless, some individual studies that appear to be influential are also referenced; methodology involving study designs, measurement errors, confounding biases, potential strengths and limitations are discussed. In addition, some basic concepts, classifications, types of dementia, prevalence and incidence, as well as social burden related to cognitive aging and dementia are briefly introduced in the first place.

2.3 Overview of cognition

2.3.1 Cognitive functioning

Cognitive functioning involves a process of acquiring knowledge and understanding through experience, thoughts, and senses. It encompasses a variety of neurocognitive and neuropsychological processes including general cognitive or intellectual ability, attention and distractibility, processing speed, executive or visual-spatial abilities, language and communication, and memory acquisition, which were identified by the mental cognitive subcommittee of occupational information development advisory panel (OIDAP) [23]. Since cognitive functioning is a complex, multi-domain, and multi-discipline research field, detailed discussion is beyond the scope of this thesis. Three most investigated

cognitive domains including general cognition, memory, and processing speed are introduced below.

2.3.1.1 General cognition

General cognition or intellectual ability refers to a complex cognition process reflecting general abilities such as reasoning, problem solving, which sometimes involves other cognitive domains e.g., memory, language. It can be divided into two categories: fluid intelligence and crystallized intelligence, developed by Cattell, Hebb, and Horn in 1930s to 1940s [24-26].

Fluid intelligence

Cattell gave an explanation to fluid intelligence as "the ability to perceive relationships independent of previous specific practice or instruction concerning those relationships" [27]. It is mainly related to people's capacity to analyse, reason, and address novel problems which is independent of knowledge or experience from the past. Fluid intelligence reflects the inductive and deductive capacities, and an ability to adapt to novel situations by enabling mechanisms for flexible, intelligent behaviour. It enables a winding path in brain which requires many transitions, namely a difficult-to-reach network state. This state depends on pathways and connections between brain functions which are not well-developed before and require the adaptive selection, actually highly cognitive demands [28].

Crystallized intelligence

Also, according to Cattell [27], crystallized intelligence tends to engage prior knowledge, skills and experience acquired over a lifetime period in daily life. It is usually well-established from learning and experience, and dose rely on processing information from long-term memory. Crystallized intelligence usually reflects in using the extensive vocabulary and grammar to organize languages, taking tests and quizzes with learning capabilities, solving trifles with general knowledge and an array of skills, and so on. Unlike the difficulty in reachable network states underlying fluid intelligence, crystallized intelligence needs a direct path with minimal transitions which is an easy-to-reach network state. Crystallized intelligence mainly relies on the engagement of easily reachable network states to access prior skills, experience and knowledge, for example, "by strongly connected hubs within the default mode network" as Barbey noted [28].

Relevant tests

Tests for general cognition or intellectual functioning, commonly referred to as global cognitive tests or intelligence tests, are widely accepted. Global cognitive examination usually requires a test or a battery of tests that encompass most brain regions involved in cognition to provide more comprehensive assessments. The fluid intelligence test comprising 13 questions in relation to reasoning, calculating, and analysing abilities has been conducted among participants in the UK Biobank (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100027).

The mini mental state examination (MMSE) is another widely used test for global cognitive performance, particularly among the elderly in clinical practice and research fields; the traditional version is a 30-point questionnaire covering several cognitive aspects including orientation, attention, memory, language, and visual-spatial skills [29]. The MMSE and its developed version Addenbrooke's Cognitive Examination (ACE) are common screening tools for cognitive impairment [30]. Other tests are also available currently and emerging in future; however, the validation and accuracy should be taken into consideration when choosing testing tools for global cognitive assessment.

2.3.1.2 Memory

All individuals sometimes complain about forgetting something, and when getting older, the frequency of complaints tends to increase as a sign of memory aging. Some psychologists have worked on the definition or categorization of memory, but the issue of memory classification remains controversial. Some theories have proposed that memory includes short-term memory and long-term memory [31]. The short-term memory (STM) is a term referring to the temporary retention of small amounts of material over brief delays, usually periods of a few seconds in psychological field. A similar term involving temporary storage of information is working memory; however, it also involves the manipulation of information compared to STM and is helpful in conducting many complex tasks. On the other hand, the long-term memory (LTM) is a term referring to a system or systems speculated to underpin the capacity to store material over long periods of time. Squire (1992) proposed that the components of LTM broadly included explicit memory (declarative memory), implicit memory (non-declarative memory),

episodic memory, and semantic memory [32]. These kinds of categories could be illustrated in Figure 2.1, and further explanation will not be discussed in the thesis.

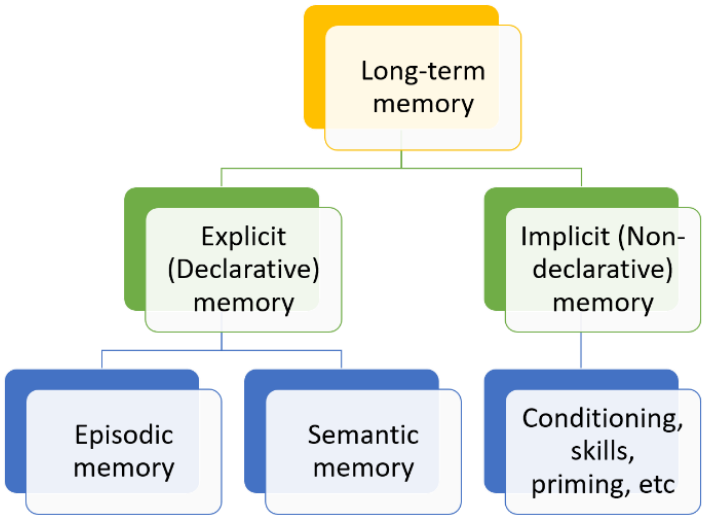


Figure 2.1 Components of long-term memory as proposed by Squire (1992) [32]

Epidemiological studies on memory aging involve two main methods, the cross-sectional and the longitudinal. The cross-sectional design measures the memory performance across the age range on a single occasion. A major drawback is the so-called cohort effect in the cross-sectional design referring to tendency for people born at different time point to differ due to context changes in education, diet, and other social factors. The longitudinal design could avoid this problem since the same participants are successively tested at different ages. However, loss to follow-up, especially atypical drop-out, should be noted gradually resulting in less representativeness of samples. Another problem in longitudinal studies that should be concerned is the practice effect or learning occurring in the repeated memory measurement. Baddeley *et al.* proposed a solution to these problems that is to combine the cross-sectional design and the longitudinal design by adding a new participant cohort at each measuring point [33]. This method has been carried out in the Betula Study and has shown some improvement in memory measurement [34].

Previous studies suggested that both verbal and visual short-term memory tend to slightly decline with age (age effect), and episodic long-term memory steadily declines throughout the adult and elderly years, while semantic long-term memory especially in vocabulary knowledge and implicit memory such as skills are

maintained [33]. Episodic memory is needed when completing dietary assessments using recall tools such as food frequency questionnaires and 24-hour dietary recall. It can be modulated by the level of environmental support provided during retrieval [35]; thus providing necessary amount of retrieval cues as environmental support could improve the accuracy of dietary recalls, such as food images for children and older adults, food groups recall.

Regarding time orientation, memory can be classified into retrospective memory and prospective memory. The former refers to memory for events, people, and words experienced in the past which includes most of the above memory types, while the latter refers to remembering to carry out intended action in the future which includes event-based and time-based prospective memory. Unlike working memory that is susceptible to the age effect, it is not clear whether either or both of two prospective memory types have the age effect, whereas some studies suggested that they are likely to be impaired in older adults [33].

Relevant tests

The memory span is widely measured for assessment, such as the digital span test also known as numeric memory, reading span, counting span, and operation span for working memory, the pairs-matching task and the Corsi block tapping task for spatial memory span [36]. In addition, tests like face recognition, name recognition, and name-face associative recognition are also often used for episodic memory.

In the UK Biobank cohort study, the lights-pattern memory task, digital span task, pairs-matching task, and prospective shape-chose task have been used to assess participants' verbal and visual memory, spatial memory, and prospective memory.

2.3.1.3 Processing speed

Processing speed refers to a pace at which it takes to receive information, make perception, and respond information. The processing speed is an important domain of cognitive ability. Researchers have suggested that processing speed might be a fundamental or even central component of individual differences and may account for variability in how well people perform many daily activities which reflects mental efficiency [37]. Due to the importance of processing speed as a foundation for other cognitive processes and its sensitivity of cognitive constructs to neurological tests, it has been identified as one of the most important aspects in

National Institutes of Health Toolbox for assessment of neurological and behavioural function [38]. It is found that processing speed is an age-related cognitive ability and has a well-defined trajectory which could reflect the cognitive aging [39]. The performance of processing speed showed an inverted U shape over the lifespan which could increase throughout childhood, peak at adolescence or early adulthood, and decline throughout later adulthood and older age [40]. The processing speed is commonly assessed via the amount of time it takes to react to questions and process received information visually (patterns, letters, or numbers), auditorily (language), or in movement.

Relevant tests

Tests for processing speed [41] are digit letters, number comparison, identical pictures, and reaction time tasks, where the latter is commonly used in experimental psychology including the simple reaction time task and the choice reaction time task. Distributions of response time data are usually not normal (non-Gaussian distributions) but have special characteristics. It usually increases rapidly on the left but decreases slowly on the right which is a long positive tail. In general, the genuine reaction times have a range of minimum values since there is a least time period needed for cognitive functioning and physical processing. Thus, some very fast reaction-time outliers could be the result of accidental pressing, or fast guesses, and they are usually excluded from analyses by using cut-offs [42]. The reaction time tasks are usually measured using mean values and standard deviation of reaction times across a range of trials. The latter is also known as intraindividual variability (IIV) referring to the trial-by-trial variation for a speed-related task. It can reflect within-person fluctuations in processing speed and is often used in reaction time measurement [41].

Simple reaction time task

The test of simple reaction time (SRT) requires participants to respond to a simple stimulus (e.g., a shape, a sound, or a signal) as quickly as possible whenever the stimulus appears. Typically, there is just one stimulus that randomly and repeatedly appears throughout an experiment. At the same time, the response is also simple and specific (e.g., pressing the space bar of computer keyboard or pressing a special button). This straightforward task in essence measures the basic cognitive latency

from stimulus perception to response execution which is the pure speed of responding. It is a "baseline" measure of how fast people respond without engaging other complicated cognitive functioning (e.g. discrimination, resisting distraction, response types) [43]. Outcome measures in the SRT task only involve the latency time of reaction. For young healthy college students, the average simple reaction times were around 160 milliseconds (ms) for auditory stimuli and 190 ms for visual stimuli although it seems that they are interestingly increasing throughout different generations [44].

Choice reaction time task

The test of choice reaction time (CRT) requires participants to respond to multiple stimuli as fast as possible anytime one of the stimuli appears, which involves a decision or a choice made during the process in contrast to the SRT task. The CRT task measures general ability of attention focusing and speed of execution. Outcome measures in the CRT task include numbers of correct and incorrect responses, specific incorrect numbers of commission and omission responses apart from the reaction time (response latency). Unlike the SRT task which only concerns response speed, the CRT task involves response speed and response accuracy simultaneously [45]. Clearly, the CRT task is slower than the SRT task, and the more stimuli and responses engaged the longer the reaction time is. Taking a 2-stimuli and 2-responses CRT task (that is the simplest one, e.g. “patterns’ snap” in the UK Biobank cohort study [46], “stop-go” for left and right arrows) as an example, most individuals have an average CRT between 350 and 450 ms, which can be influenced by a range of factors including age, sex, the exact stimulus type and response mode [47].

2.3.2 Cognitive aging and cognitive impairment

Cognition is a fundamental and crucial part of brain function including attention, memory, learning, decision-making, information-processing and so on; Cognitive development is a continuous process which mainly occurs in the childhood and adolescence, and it may cease at different life stages depending on the type of cognitive function [48]. Cognitive aging is believed to be a natural process alongside the functional and structural changes over the brain aging; however, it is still unclear when and how the cognitive aging begins to occur.

Some scholars suggest that cognitive function may start to decline since adulthood, and the most affected function may be those that are dependent on coordination efficiency, volume and speed of functioning, such as attention, reasoning, multi-tasking, verbal recall, working memory, and response inhibition [48]. As mentioned previously, those are more likely to be fluid intelligence which is related to abilities in responding and adapting to changes in the environment less familiar and more challenging to a person [25]. They are likely to be in decline from late adulthood, and some functions related to fluid intelligence tend to decrease as people reach very late adulthood. Cognitive aging may also reflect a slowing of processing or an increase in error rates of responses. Processing speed, and executive function considered as fluid intelligence might decline at an estimated rate of -0.02 standard deviations per year during the later life stage [49]. In contrast, crystallized intelligence referring to the well-practiced and familiar skills or abilities, and knowledge of the world, language, and people, tends to be resilient to brain aging and might be well preserved or even improve over aging. As people getting older and expanding their knowledge, crystallized intelligence might to some extent increase to experiences [50].

Parallel to cognitive function decline, there is a gradual loss of brain mass throughout the brain aging. Certain cortical and subcortical areas related to cognition are particularly susceptible to loss of grey matter over time including prefrontal cortex and the hippocampus [51]. In addition, changes in white matter are also common after late midlife with the volume of white matter declining more significantly in the prefrontal cortex. The decreased integrity of the white matter tracts compromises the connectivity between brain regions resulting in less efficient networks [51].

Cognition forms the basis of capacity for everyday activities and an individual's aging is typically accompanied by declines in cognitive abilities. Although cognitive aging is a normal process and somewhat inevitable, not all cognitive declines are due to natural aging, some could be the onset of dementia. However, it is a big challenge to measure the gap between healthy cognitive aging and dementia development, as it is not immediately clear to what extent the cognitive aging is no longer healthy anymore. As illustrated in Figure 2.2, under some ongoing negative circumstances an individual's cognitive functioning could experience a progressive

decline from prodromal period to mild cognitive impairment stage, then to dementia stage; there should be a measurable gap to alert people some changes needed to be made. Accumulating evidence has linked several modifiable risk factors with the pathological process of cognitive decline; these modifiable factors are mostly lifestyle-related such as smoking, physical activity, diet, social economic status, sleep duration, and obesity [52]. The present project mainly focuses on the associations between dietary factors and risk of cognitive impairment.

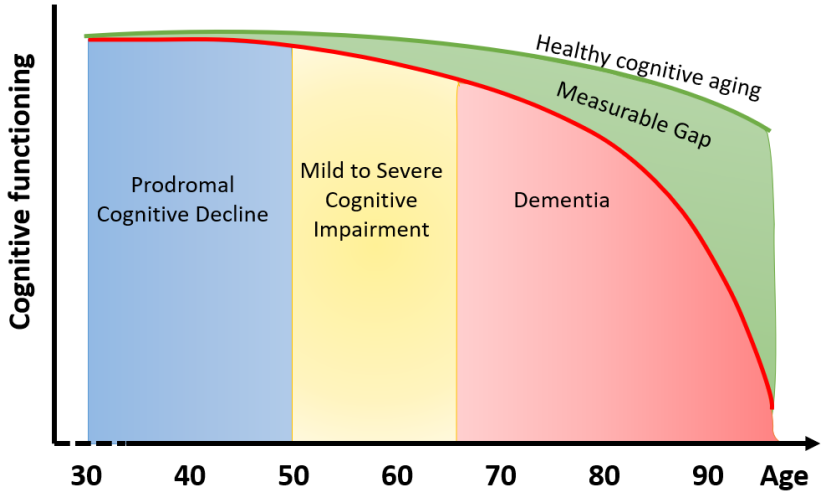


Figure 2.2 Illustrations of changes in cognitive functioning over time

2.4 Overview of dementia

Cognitive decline at a more than normal rate or cognitive impairment that affects independent living can be considered as dementia rather than normal cognitive aging [53]. Dementia is characterized by impairment of several brain domains including memory, comprehension, language, judgement, calculation, learning, and thinking, usually alongside changes in emotional control or social behaviour. In the aging society, it is increasingly of a growing concern.

2.4.1 Epidemiology of dementia

According to the Alzheimer's Disease International (ADI), in 2015 there were around 47 million people living with dementia in the world, and every 3 seconds a new dementia case was diagnosed resulting in that the prevalence would almost double every 20 years. With the situation ongoing, the number of people with dementia is projected to reach 75 million by 2030 and 130 million by 2050 [54,55]. Although there is a low diagnosis rate in low-income countries, dementia cases

from these countries make up a vast part of people with dementia globally. At the same time, the growth rate of dementia is going rapidly around the world, especially in middle and low-income countries as shown in Figure 2.3 [54]. In UK, although the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) found that the prevalence of dementia declined significantly between 1993 and 2011 [56], there still are approximate 0.6–0.8 million people living with dementia and the number is projected to double by 2050 [57]. In terms of age groups, it is estimated one in six people aged 80 years or older living with dementia and one in 14 people over 65 years living with dementia in UK [58]. In addition, around 84% of dementia cases live in England with estimated 66,800 in Scotland, 43,500 in Wales, and 19,800 in Northern Ireland [59].

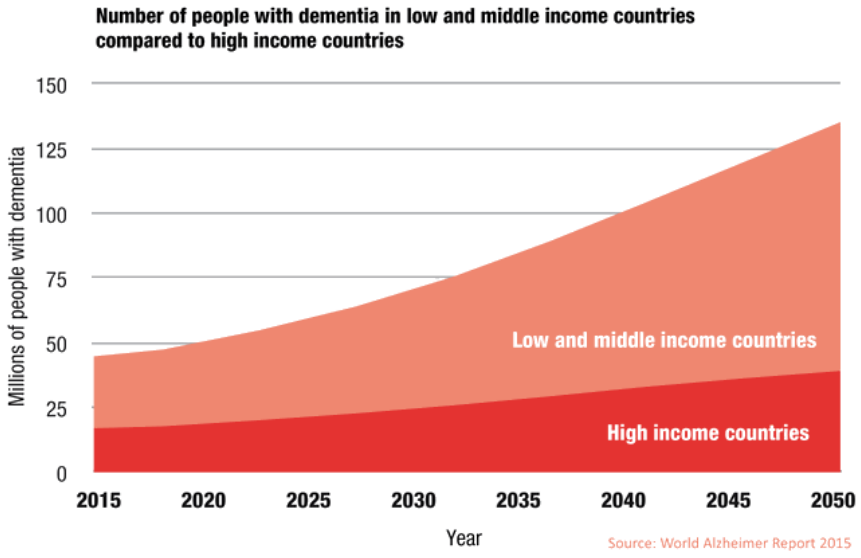


Figure 2.3 Estimated worldwide prevalence of dementia with difference of income [54]

The economic burden of dementia needs much more attention due to high prevalence globally. According to the ADI, in 2010 the global cost of dementia amounted to US$604 billion, and in 2015 this figure rose to US$818 billion, representing a 35% of increase in five years [60]. Under assumptions of diagnostic rates subjected to 10% in the low- and middle-income countries and 50% in high-income countries in 2015 which are expected to rise to 50% and 75% respectively by 2030, the annual costs would come to estimated 0.5% of total expenditure on public healthcare to achieve 50% coverage of comprehensive dementia care in low and middle income countries, and 50% coverage in high income countries [61]. In

UK, it is estimated that dementia costs around £26 billion annually with around £11.6 billion contributed by caregivers (usually family) who are not paid for their time and effort [59]. Therefore, without control or intervention our society would encounter a large number of people living with dementia and a huge financial burden on health systems in the foreseeable future.

2.4.2 Types of dementia

Dementia is a syndrome associated with progressive and irreversible decline of brain function. It always exists with other symptoms or features to form a collection of recognised subtypes. With respect to age of onset, dementia could be classified into the early-onset dementia and the late-onset dementia with 65 years old as the cut point. It is noted that the early-onset dementia, or young-onset dementia, developing before the age of 65 years is mainly caused by genetic factors, while the late-onset dementia mainly results from the environmental factors [62]. Except the age classification, cases with dementia can differ in their aetiology, forms of presentation, associated disorders, and have differences in clinical development course and clinical outcomes, which lead to difficulties in making and unifying diagnostic criteria. Therefore, there are several types of dementia deriving from different diagnostic criteria which have been well-characterised clinically including dementia of the Alzheimer type (DAT), vascular dementia (VD), Parkinson dementia, frontotemporal dementia, dementia with Lewy bodies, alcohol-related dementia, HIV-related dementia, traumatic dementia. This section will briefly introduce several common types of dementia.

2.4.2.1 Dementia of the Alzheimer type (DAT)

Dementia of the Alzheimer type (DAT) is the syndrome of dementia caused by Alzheimer's disease (AD). AD is a neurodegenerative disorder associated with progressive damage in brain function characterised by memory deterioration, cognitive dysfunction, and behaviour disorder [63]. The early-onset AD also named as the familial AD is mainly due to autosomal-dominant genetic mutations accounting for <1% of dementia cases [64], while the late-onset AD also called as the sporadic AD is mainly associated with genes, age, gender, lifestyle factors, and other environmental factors. Because the familial type is relatively rare, the general AD usually means the sporadic type.

In terms of sex differences, women are usually considered at higher risk of developing AD than men, while other less common dementias including vascular dementia, Parkinson dementia, and dementia of Lewy body type do not show sex differences [65]. Kawas and colleagues reported that there was a trend of high incidence of female AD compared with male but the difference was not statistically significant [66]. Another study showed that women had a nonsignificant trend of short doubling time in AD incidence worldwide (5.4 years for women vs. 6.5 years for men) [67]. Therefore, sex difference should be taken into consideration when conducting AD related research and analyses.

Dementia of the Alzheimer type has various symptoms among different individuals and development stages. The Alzheimer's Association has summarized 10 early signs and symptoms of AD [68]. Briefly, one of the most common initial symptoms is memory loss, especially forgetting recently learned information, which could get worse gradually to disrupt the normal daily life. The following common symptoms are challenges in making plans and coping with problems, or even completing familiar tasks from home, work, or leisure activities. More seriously, people with AD can be confused with time, dates, place, and difficulties in discrimination of visual images and spatial relationships. Word misuse, things being misplaced or lost can occur more frequently with decreased judgement and withdrawal from society. Some people with AD can experience changes in mood and personality, such as depression, with anxiety, agitation, and sleep disorders.

With the symptoms progressing, the brain itself is also going through some changes in macro- and micro- structures which might happen before symptoms appear [69,70]. Brain atrophy is the most representative macro-structure change including decreased volume of cortex and hippocampus [71]. Amyloid beta (Aβ) protein is thought to be the metabolite of amyloid precursor protein (APP). In normal brain Aβ is balanced between production and degradation, while under some circumstances it can aggregate and form into senile plaques, an important marker of AD [72]. A micro-structure change is that the microtubule-associated protein tau could get aggregated into neurofibrillary tangles due to the stability of tau protein is reduced. Both senile plaques and neurofibrillary tangles are strong brain biomarkers of AD which have been used in the standardised diagnostic criteria [73].

2.4.2.2 Vascular dementia

Vascular dementia (VD) is the second most prevalent dementia type after Alzheimer's dementia, accounting for 20–30% of dementia cases [74]. It is considered to be mechanically linked to pathological damage caused by cerebrovascular diseases, although there are still uncertainties and difficulties in finding the exact contribution of cerebrovascular pathology in vascular dementia [75]. Highly dependent on the specific brain area affected by the vascular pathology, cognitive changes in vascular dementia are far more varied than in other cognitive disorders such as Alzheimer's disease; for example, one common subcortical vascular pathology can interrupt circuits of the front striatal, frequently resulting in cognitive deficits in attention, executive function, and processing speed [76]. According to the specific brain area and cerebrovascular pathology, VD can be classified into different subtypes including multi-infarct dementia (cortical vascular dementia), small vessel dementia (subcortical vascular dementia), strategic infarct dementia (e.g., thalamus), hypoperfusion dementia, haemorrhagic dementia, hereditary vascular dementia, and Alzheimer's disease with cardiovascular disease (mixture of vascular and degenerative pathology) [75].

Similar to AD, incidence rates of VD rise with age, with prevalence of VD roughly doubling every 5.3 years [77]. In addition, people with a stroke history have high risk of developing dementia in the long term, or post-stroke dementia is considered as a subtype of VD, where around 15–30% of subjects develop dementia three months after a stroke [78]; however, the pathophysiology of this disorder is unclear. At the same time, it is revealed that people with AD are more likely to have a stroke history; therefore, the post-stroke delayed dementia seems to be attributable to degenerative pathology, vascular diseases, or an interaction of the two, which remains unclear [75,78].

The aetiology of VD also remains controversial but can be attributable to genetic factors and environmental risk factors. With regards to genetic factors, there is less genetic related research on VD compared with AD. A systematic review reported six polymorphisms including *APOE*, *MTHFR*, *ACT*, *ACE*, *PON1*, and *PSEN-1* genes associated with vascular cognitive impairment, but only *APOE* ε4 (odds ratio=1.82, P <0.001) and *MTHFR* rs1801133 (odds ratio=1.32, P =0.013) showed significant associations in meta-analyses [79]. At the same time, the *APOE* ε4 was associated with developing AD and cardiovascular diseases; thus, it is plausible

there is a potentially genetic association between VD and AD. In terms of the environmental risk factors, VD shares some common factors with AD including smoking, high alcohol consumption, low education level, inactive lifestyle, unhealthy diet, and presence of stroke [75]. Vascular risk factors seem to be obviously associated with developing VD such as high blood pressure, high plasma cholesterol level, cardiovascular diseases, obesity, and diabetes. Since diet is a factor influencing vascular conditions, for example, high-fat diet is highly associated with risk of obesity and high-sodium diet with risk of high blood pressure [80], diet could be one of the predominant risk factors that is related to vascular dementia.

2.4.2.3 Other types of dementia

Compared with AD and VD, other types of dementia mostly have specific inducing factors, such as, Parkinson dementia caused by Parkinson disease, alcohol-related dementia caused by excessive alcohol consumption, HIV-related dementia and traumatic dementia caused by HIV infection and head injuries respectively. However, cases with dementia in these scenarios are always diagnosed as the specific disease, thereby this thesis will not discuss them in detail.

Since there are difficulties in diagnosis and classification of dementia, there is always an option for undefined dementia in clinical and research practice, for example, the ICD code F03 indicating unspecified dementia. Due to the majority of dementia being caused by AD or VD, this thesis has included those cases with unspecified dementia into all-cause dementia cases for comprehensive investigation of associations between diet and dementia risk as well as potential involvement of genetic factors.

2.4.3 Screening and diagnosis of dementia

So far, there is still no effective treatment for dementia, especially AD. Therefore, it is much more important to prevent, slow and restrain the development of dementia. The key for that is early detection and clear diagnoses which are exceedingly difficult. However, progress in relation to screening and diagnosis of dementia has been made over the past decades.

The most widely used detection tool for dementia is MMSE which is also used to screen cognitive impairment. Meanwhile, there are still many other alternative

screening tools with various diagnostic ability for detecting different types or extents of dementia, such as the Mini-Cog test that is more sensitive screening for dementia, and the Montreal Cognitive Assessment that is more sensitive screening for mild cognitive impairment [81]. In general, cases with poor performance in these screening tests can be classified into mild cognitive impairment, which is considered as a pre-dementia status. Here, several widely used screening tools were summarized to compare their effectiveness and feasibility (Table 2.1).

Table 2.1 Screening tools for detecting dementia

	MMSE [82]	3MS [83]	ACE [84]	MoCA [85]	7MS [86]	CDT [86]	GPCOG [83]	Mini-Cog [86]	MIS [83]
Measuring method	Verbal, Written	Verbal, Written	Verbal, Written	Verbal, Written	Verbal, Written	Written	Verbal	Verbal	Verbal
Completion time	5–12 min	12–15 min	15 min	10 min	7 min	1–4 min	4–5 min	2–4 min	4 min
Items & Scoring	11 items; Score: 0–30	15 items; Score: varied	100 points	13 items; Score: 0–30	4 Tests	Various items; Score: varied	15 items; Score: varied	3-item recall + CDT; Score: 0–3 + CDT	4 items
Sensitivity (%)	86–92	87	85–96	83–94	89.4–92.9	59–74.7	82–85	76–99	80–86
Specificity (%)	92–99	89	63–83	50	93.5	65.5–90	83–86	89–96	96–97
Validity	Adequate	Adequate	—	Adequate	—	Adequate	Adequate	Adequate	Adequate
Reliability	Adequate	High	—	Adequate	High	Adequate	Adequate	Adequate	Adequate
Cognitive domains									
Memory	√	√	√	√	√	√	√	√	√
Language	√	√	√	√	√		√	√	
Attention/ Orientation/Concentration	√	√	√	√	√	√	√	√	
Visuospatial abilities	√	√	√	√		√			
Executive functions	√	√	√	√	√	√			
Different types of dementia	To some degree	Yes	Yes	Yes	Yes	To some degree	Yes	Yes	To some degree
Different education levels	To some degree	To some degree	To some degree	Yes	No	Yes	To some degree	Yes	Yes
Language &cross culture	To some degree	Yes	Yes	Yes	To some degree	Yes	No evidence	Yes	Yes

3MS = Modified Mini Mental State Examination; 7MS = 7 Minute Screen; ACE = Addenbrooke's Cognitive Examination; CDT = Clock Drawing Test; GPCOG = General Practitioner Assessment of Cognition; Mini-Cog = Mini Cognitive Assessment Instrument; MoCA = Montreal Cognitive Assessment; MIS = Memory Impairment Screen; MMSE = Mini-mental State Examination.

Diagnostic criteria of dementia have been developed for decades, but still there is no unified and standardised criteria available. Most diagnostic criteria and dementia stages were developed based on the symptoms and brain changes. The most widely used diagnostic guideline for AD is Diagnostic and Statistical Manual of Mental Disorders (DSM) [87], initiated by the American Psychiatric Association, with its revised fourth edition (DSM-IV-TR) more specific to Alzheimer's disease [88]. The guideline from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) is another widely used method in the diagnosis of AD [89]. Compared with the DSM-IV-TR, the 5th edition (DSM-V) has been broadened to more subtypes of dementia and weakened the unique status of Alzheimer's disease, more easily used for dementia [90]. The International Classification of Diseases 10th revision (ICD-10), devised by the World Health Organization, has specific items on dementia as well as its subtypes, and also has been used widely [91].

The changes and updating of diagnostic criteria could result in discrepancy in prevalence of dementia even among same population. Wancata and colleagues investigated the influence of different diagnostic systems among a same population of 1019 Swedes aged 70 or older, and found that the prevalence of dementia was 9.6% diagnosed by DSM-IV which was most frequent, followed by DSM-III-R (6.3%), ICD-10 (3.1%), and ICD-9 (1.2%) [92]. It seems that DSM systems have a higher level of sensitivity than ICD systems, and thus differences in diagnostic criteria should be considered when analysing the prevalence of dementia.

2.4.4 Risk factors for dementia

There is little known information about the specific aetiology of dementia with several hypotheses on risk factors emerging over the past decades. The early-onset dementia was postulated to be caused by autosomal dominant mutations of genes such as *APP* (Aβ precursor protein), *PS1* (presenilin 1), and *PS2* (presenilin 2), but the familial form of dementia only accounts for a small proportion of all dementia cases [93]. The remaining non-familial dementia cases are also hypothesized to be influenced by some common gene variants, modifying risks of dementia. One of three allelic forms (ε2, ε3, and ε4) in the apolipoprotein E (*APOE*) gene, the presence of ε4 allele is highly associated with increased risks of dementia, especially for AD [94]. In addition to genetic risk factors, environmental risk factors

have been emerging, identified to be related to modifying dementia risks independently or synergistically.

Increasing with age, the incidence and prevalence of dementia are getting higher among people aged 65 or more; meanwhile, sex-specific incidence also brings sex differences to attention for research [95]. Other environmental risk factors such as low education level, chemical exposure (e.g., aluminium), head trauma, also show some associations with dementia [95]. In addition, it has been recognized that lifestyle factors, including diet, physical activities, sleep, depression, and stress, could be among the modifiable prevention strategies.

2.5 Diet, cognitive performance, and dementia

Emerging evidence has suggested that modifiable behavioural-related factors are associated with cognitive impairment, providing potential targets for prevention of dementia. Diet particularly has gained much interest in relation to cognition. This thesis summarized current findings in the rapidly expanding research field.

Some specific foods or food groups, such as meat and fish, are summarized separately below which have been potentially related to cognition performance. Considering the complexity and interaction of dietary components, specific dietary patterns in relation to cognition, such as the Mediterranean diet that may be more beneficial than individual food items, are introduced in this chapter as well. Some macro- and micro- nutrients, such as calories, vitamins, and fatty acids, have been associated with cognition, and related evidence is summarized below. In addition, some plausible mechanisms, such as inflammation and oxidative stress, are discussed.

2.5.1 Foods and food groups

2.5.1.1 Fruits and vegetables

At least five portions of fruit and vegetables per day are recommended to prevent chronic diseases. Although regular consumption of fruit and vegetables is associated with a lower risk of coronary heart disease [96] and stroke [97], there is no conclusive evidence of associations in relation to age-related cognitive decline. A systematic review of nine cohort studies with a total of 44,004 participants followed up for at least six months showed that higher intakes of vegetables rather

than fruits were related to decreased risk of cognitive decline or dementia in five out of six cohorts, which was also seen in another three cohorts for vegetable and fruit analytically combined; this review also suggested that more cohort studies covering different regions and different life stages are needed in this research field [98].

2.5.1.2 Meat and fish

Detailed information on meat consumption will be discussed in Chapter 3 that is a systematic review on this topic. In brief, meat consumption might be the most debated food group in relation to chronic diseases since the dual characteristics of being high in saturated fat and high in protein are likely to be present simultaneously. Meat consumption generally comprises intakes of processed meat, red meat (unprocessed pork, beef, lamb/mutton, etc.), and poultry (unprocessed chicken, duck, etc.). In the United Kingdom, elderly individuals who had high consumption of red meat were more likely to be associated with poor cognitive performance, but not the rate of cognitive decline over 5-year follow up [99]. However, current evidence on associations between age-related cognitive decline and consumption of meat remains limited, particularly regarding specific meat types and amounts consumed.

Fish consumption has been associated with a reduced risk of age-related cognitive decline. A review showed that high consumption of fish was associated with a significantly decreased risk of dementia (risk ratio=0.4, 95%CI: 0.2, 0.9) in the Rotterdam Study (5386 participants), and associated with an insignificantly reduced risk of cognitive impairment and decline (risk ratio=0.5, 95%CI: 0.2, 1.2) in another Dutch cohort, the Zutphen Elderly Study (476 participants) [100]. Fotuhi and colleagues updated this topic in a systematic review in 2009 and included another two prospective studies that used cognitive decline as an outcome reporting significant benefits from consuming fish meals or high blood levels of unsaturated fatty acids in USA and France [101]. A recent review showed that two meta-analyses supported the protective association between cognitive preservation and higher fish intakes among community-dwelling dementia patients, and one cohort favoured benefits from seafood consumption in relation to less neurofibrillary tangles and neuritis plaques in brain autopsies from the elderly [102]. Similarly, in Asian area individuals who consumed fish ≥1 serving/week had a reduced mean

annual rate of global cognitive decline by 0.35 point (95%CI: 0.13, 0.58) compared with those consuming <1 serving/week among 1566 community-dwelling Chinese adults aged 55+ [103]. Based on previous evidence, fish consumption could be a potential target for prevention of cognitive impairment as a modifiable dietary factor.

2.5.1.3 Milk and other dairy products

Milk and dairy products are recommended to be consumed regularly in many dietary guidelines due to richness in protein, calcium, and vitamin B12. A systematic review on dairy consumption and cognitive function in adults showed that lower consumption of milk or dairy products was associated with poorer cognitive performance, where underlying biological mechanisms are not fully understood but phospholipid in the milk fat globule membrane in relation to good cognitive function was postulated; however, consumption of whole-fat dairy products was found to be associated with risk of cognitive decline in the elderly [104]. By contrast, another systematic review on the same topic did not find sufficient evidence (including one intervention study) regarding the associations between milk consumption and risk of cognitive decline [105]. A recent systematic review also suggested the association cannot be firmly established with contradictory findings from individual studies [106].

2.5.1.4 Other food groups

Consumption of other food groups like alcohol and nuts has also been associated with cognitive performance. A systematic review summarizing 20 cohort studies and 3 nested case-control studies found that small amounts of alcohol intakes did not show significant associations with risk of cognitive decline (risk ratio=0.89, 95%CI: 0.67, 1.17); however, there was obvious heterogeneity in follow-up durations and alcohol measures among studies included [107]. At the same time, a meta-analysis of 15 prospective studies confirmed that compared with non-drinkers, alcohol drinkers also did not have significant changed risks of cognitive decline [108]. However, data analysis from the Whitehall II cohort study with 5054 men and 2099 women suggested that compared with low to moderate drinking (0.1 to 9.9 g/d), both heavy drinking (≥36 g/d) in men and alcohol abstainers in women showed faster cognitive decline after 10 years follow-up [109]. Similarly,

controversial findings were also found in nuts consumption. A review suggested that nuts consumption may contribute to the delay of age-associated cognitive decline [110]. However, consumption of nuts was not associated with significant cognitive changes after median follow-up of 4.1 years among 334 older people in a randomized clinical trial [111].

Evidence in relation to associations between consumption of other single foods or food groups and cognitive function is limited. Often with inconsistent results and unconvincing findings, more related research is needed for prevention and delay of cognitive decline regarding modifiable dietary factors.

2.5.2 Dietary patterns

Due to the complexity of diet, dietary patterns have been broadly used given a combination of food consumption and nutrient intakes. Determination of dietary patterns is generally via two approaches, *a priori* method and *a posteriori* method. The *a priori* method defines dietary patterns based on existing information [112], where some of these patterns are formed among some specific area such as the Mediterranean diet (MeDi), and some are formed to provide a comprehensive diet for disease prevention or treatment such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) [113]. Usually, *a priori* dietary patterns comprise several featured criteria or components, and scores are marked accordingly. The *a posteriori* method empirically derives dietary patterns based on statistical models analysing collected dietary information and characterizing dietary patterns [112]. The widely used statistical approaches include factor analysis, principal component analysis, cluster analysis, and reduced rank regression [113]. The dietary pattern is usually named as the featured food types such as “prudent diet”, “western diet”, “low-fat or high-fat diet”. In contrast to the traditional food analysis used in nutritional epidemiology, dietary pattern analysis takes comprehensive effects of diet into account which may enhance our knowledge in diet. Several common dietary patterns are introduced in relation to cognitive performance.

2.5.2.1 Mediterranean diet

The Mediterranean diet (MeDi) pattern is featured as low consumption of meat, low

to moderate consumption of dairy products, moderate to high consumption of fish, high consumption of unsaturated fat (olive oil as a main source), and high consumption of vegetables, fruits, legumes, nuts, and unrefined cereals, with low-to-moderate wine consumed during meals [114]. The traditional MeDi, firstly described by Professor Trichopoulou in 1960s, is a dietary pattern consumed in Mediterranean countries, and has been advocated by the United Nations Educational Scientific and Cultural Organisation (ENESCO) due to the potential health benefits, including low incidence of chronic diseases, such as cardiovascular diseases, and reduced mortality risk [114].

As an *a priori* approach to defining dietary patterns, the Mediterranean Dietary Score (MDS) was developed according to the main features of the MeDi, and has been increasingly used to classify the degree of adherence to the MeDi in epidemiological studies [115]. The MeDi was evaluated initially with nine components: vegetables, fruit and nuts, legumes, cereals, fish, meat, dairy, alcohol, and the fatty acid ratio of monounsaturated fatty acids (MUFA) plus polyunsaturated fatty acids (PUFA) to saturated fatty acids (SFA) that is MUFA+PUFA : SFA; afterwards poultry was added in separating from meat as the tenth components in the revised MDS version [115].

The MDS is calculated by assigning a value of 0 or 1 to each component of the MeDi with the sex-specific median values consumed in the sampled population as cut-points. For six presumed beneficial components (vegetables, fruit and nuts, legumes, cereals, fish, and the fatty acid ratio), people whose consumption is below the sex-specific cut-point are assigned a value of 0, and those whose consumption is equal to or above the cut-point are assigned a value of 1. For three components traditionally considered to be detrimental in the MeDi (meat, poultry, and dairy products), people whose consumption is below the cut-point are assigned a value of 1, and those whose consumption is equal to or above the cut-point are assigned a value of 0. For alcohol, a value of 1 is assigned to women who have consumption of 5–25 g/d, and to men who daily consume alcohol of 10–50 g. Thus, the total MDS ranges from 0 to 10, where a higher score indicates greater adherence to the MeDi.

The associations between the MeDi and cognitive function has been explored in both observational and interventional studies. A meta-analysis including eight

observational studies showed that high adherence to the MeDi was associated with a reduced risk of cognitive impairment (risk ratio = 0.60, 95%CI: 0.43, 0.83); this association was also observed in moderate adherence [116]. A systematic review on associations between the MeDi and cognitive function in normal aging highlighted that greater adherence to the MeDi was associated with better cognitive performance and less risk of age-related cognitive decline [117]. However, a systematic review including five randomized controlled trials covering 66 cognitive tests on 1888 participants showed conflicting findings, where most data were nonsignificant with small effect sizes, and concluded that there was no benefit of the MeDi for incident cognitive impairment [118]. The controversial results from observational studies and interventional studies suggest that more well-designed research is needed for confirmation of the beneficial effect on age-related cognitive decline.

In terms of the potential biological mechanisms underlying the association between adherence to the MeDi and the reduced risk of cognitive impairment, researchers hypothesized that there might be the transitioning effect of cardiovascular events and the metabolic syndrome (defined as a cluster of cardio-metabolic abnormalities such as high waist circumference, hypertriglyceridemia, low level of high density lipoprotein cholesterol, hypertension, and hyperglycaemia) [114]. Cognitive impairment has been positively associated with vascular risk factors and metabolic syndrome; on the other hand, it is well documented that greater adherence to the MeDi was related to a reduced risk of cardiovascular events and lower incidence of metabolic syndrome [114]. Another potential mechanism has been linked to the anti-inflammatory effect of consuming the MeDi; neuroinflammation was considered as one of pathological changes during the process of cognitive impairment [4]. In addition, protective effects against age-related cognitive decline from single food or food group as one of components of the MeDi have been discussed above. Other potential mechanisms from a perspective of nutrients were introduced in the following section of nutrients.

2.5.2.2 Dietary Approach to Stop Hypertension (DASH)

The DASH diet was proposed as a non-pharmacological method for prevention or treatment to hypertension in 1999 [4]. This dietary pattern is characterized by high intakes of vegetables, fruit, nuts, legumes, and wholegrain products, which is much

like the MeDi; however, the DASH diet has extra emphasis on low-fat or non-fat dairy products and a limited consumption of dietary sodium, and does not recommend consumption of alcohol in contrast to the MeDi [119]. The DASH diet also applies scores to assess the degree of adherence or accordance among the sampled population.

There are two different score systems available for DASH assessment. The Folsom score system [120] comprises 11 dietary components with predefined cut-points. For components of total grains, wholegrains, fruits, vegetables, nuts and seeds and dry beans, and dairy products, a value of 1 is assigned to people with higher intake than cut-offs; for components of meat and fish, sodium, sweets, energy percentage from fat, and energy percentage from SFAs, a value of 1 is assigned to people with lower intake than cut-offs; a value of 0.5 is assigned to intakes equal to cut-offs, and thus total score ranges from 0 to 11 (the higher the greater adherence to the DASH diet). The Fung score system [120] comprises eight dietary components and a value of 1 to 5 is assigned to different quintiles of consumption for each component. For fruits, vegetables, wholegrains, nuts and legumes, and low-fat dairy products, a value of 1 is assigned to people with the lowest quintile, whereas for red and processed meats, sodium, and sweetened beverages, a value of 1 is assigned to people with the highest quintile; thus, total score ranges from 8 to 40 in this assessment system. Not like the MeDi which is the most investigated dietary pattern with most findings supporting protection against cognitive impairment, the number of studies on the DASH diet in relation to cognitive function remains limited, and results have not been consistent so far.

A review including a brief summary of the DASH diet on cognitive health showed promising findings, where higher DASH scores have been related to better cognitive performance and slower cognitive decline although some results were not consistent with these findings [119]. Another review summarized several observational studies showing that greater adherence to DASH has been associated with a lower incidence of cognitive decline among older adults, in particular those at high risk of cardiovascular diseases [121]. Underlying the beneficial effect on cognitive aging, the reduction of blood pressure and reduced risk of cardiovascular events as well as stroke may play a role since the DASH was originally designed to prevent hypertension and the protective effect has been demonstrated in several

randomized trials [121]. A systematic review summarized studies published up to March 2019 within Ovid Medline on associations between the DASH diet and cognitive function, and found that greater adherence to the DASH diet was related to better cognitive performance in one cross-sectional study, two out of five prospective studies, and one intervention study [120], indicating that even a limited number of studies available in this field it is promising to apply the DASH diet to prevention of cognitive impairment.

2.5.2.3 Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

The MIND diet was firstly designed in the Rush Memory and Aging Project (RMAP) by Morris and colleagues for brain health and protection against cognitive decline and dementia [122]. This diet has combined the dietary components which are expected to be neuroprotective from the MeDi and the DASH diet. Generally, the MIND diet emphasizes natural plant-based foods, in particular berries and green leafy vegetables, and specifies limited consumption of animal-based foods and a reduction in intakes of saturated fat [122]. The MIND diet score [120] is developed based on 15 dietary components with predefined cut-points. For nine components including berries, green leafy vegetables, other vegetables, whole grains, nuts, beans, olive oil, fish, and poultry, a value of 1 is assigned to people with consumption above the cut-offs, whereas for five components including red meat and products, fast fried foods, pastries and sweets, butter and margarine, and cheese, a value of 1 is assigned to people with consumption below the cut-offs. For the last component, like the MeDi a value of 1 is assigned to moderate consumption of alcohol, and thus the total MIND diet ranges from 0 to 15 with higher scores meaning greater adherence.

The prospective RMAP cohort study showed that higher MIND diet scores were associated with slower cognitive decline (adjusted $\beta = 0.009$, $P < 0.0001$) among 960 US adults over mean follow-up of 4.7 years, and the greater adherence to the MIND diet indicated a beneficial effect on decline rates [122]. However, the protective effect of the MIND diet against cognitive decline was not observed in another cohort study among 16,058 American women after 12.9 years follow-up [123]. So far, there is only a limited number of studies on the MIND diet in relation to cognitive function available. Van den Brink reviewed there was one cross-sectional study and two out of three longitudinal studies suggesting that higher adherence to

the MIND diet was associated with better cognitive performance and slower cognitive decline [120]. Considering the limited studies and inconsistent results, further research on the MIND diet in relation to cognitive performance and dementia is highly needed.

2.5.2.4 Other dietary patterns

Other *a priori* dietary patterns such as the Healthy Eating Index (HEI), the Recommended Food Score (RFS), and the French National Nutrition and Health Programme Guideline Score (PNNS-GS), and some data-derived dietary patterns such as “healthy diet” and “prudent diet” using *a posteriori* approaches including principal components analysis, factor analysis, and clustering methods, have been found to be associated with good cognitive performance and/or low risks of cognitive decline in some observational studies [124]. However, the evidence for these relationships remains limited which needs to be confirmed in other cohort studies across countries. These dietary patterns do not seem to be consistently related to cognitive function; some observational studies showed no associations or even inverse associations of these dietary patterns with cognitive outcomes, and thus related findings are discordant [124]; research with sound study designs is needed to provide robust evidence in this field.

Diet is a complex exposure variable involving various foods and food groups as well as their potential interactions. The dietary pattern analysis allows taking complex correlations of the foods and food groups into account. In addition, the dietary pattern analysis has a relatively high level of validity and reproducibility [124]. The degree of adherence to some specific dietary patterns can be reflected using predefined score systems which can be reproducible in other studies; thus, the dietary pattern analysis is a good approach to examine associations between diet and outcomes.

Although there are plenty of dietary patterns in relation to cognitive function, comparisons among them suggest that diet rich in vegetables, fruits, beans or legumes, and other plant-based foods could be protective against cognitive impairment. However, the potential mechanisms underlying the relationships remain unclear. At the same time, differences in neuroprotective effects between dietary patterns could not be ignored. Since there is much potential variation in

nutrients between dietary patterns, the dietary pattern analysis cannot be specific about which nutrients are responsible for the observed associations with risk of cognitive impairment. Therefore, the observed relationships should be investigated further in the light of findings from individual nutrients.

2.5.3 Nutrients

Nutrients are substances used by an organism for essential life activities. They are primarily classified into macronutrients and micronutrients based on quantities needed by humans. Macronutrients usually refer to nutrients consumed in large quantities, and some of them can provide energy including carbohydrates, proteins, and fats, while some can be components of tissues such as calcium, potassium, magnesium, and chloride ions. Macronutrients could exert a role in cognition as a result of dietary energy intake. Studies from animal models, epidemiological surveys, and clinical trials suggested adverse effects of excessive dietary energy intake on cognitive function, and dietary energy restriction may be associated with better cognitive performance [125]. Micronutrients consumed in small quantities basically can support metabolism including dietary minerals such as trace elements, copper, iron, and vitamins such as vitamin A and vitamin B family [126]. This section introduces some nutrients in relation to cognitive outcomes.

2.5.3.1 Carbohydrates

The influence of carbohydrates on cognitive function has focused on glucose, since glucose is the main source of energy for the brain. In spite of inconsistency of the evidence, several studies have reported beneficial associations of glucose with good cognitive performance, especially delayed verbal memory [127]. More recently, the carbohydrate quality (e.g., type, nature, source) as well as the quantity are of interest to researchers in this area; however, related studies remain limited. In an intervention study, both a very low-carbohydrate with high-fat diet, and a high-carbohydrate with low-fat diet had similar effects on processing speed and working memory among 106 overweight and obese participants (50 years old, SD=0.8) with 1 year follow-up [128]. Gilsenan and colleagues evaluated eight related studies in a review, and reported that there was an association between food carbohydrate and cognitive function but evidence was insufficient to draw conclusions with much heterogeneity in methodology [127].

2.5.3.2 Protein

Protein is an essential dietary component for maintaining cellular integrity and function (including brain cells). Dietary protein may play an important role in cognition maintenance, particularly for elderly people. Data from the National Health and Nutrition Examination Survey (2011–2014) among free-living US adults aged 60+ years suggested that dietary protein intake was positively associated with cognitive function, and the association was found in some protein sources including total meat, eggs, and legumes, but not milk or milk products [129]. To date, there is a limited number of studies directly linking protein intake to risk of cognitive impairment, and as a result the relationship and underlying mechanisms remain poorly understood. Nevertheless, several studies have suggested that the beneficial effect may be attributed to amino acids; for instance, some amino acids are required for neurotransmitter synthesis (e.g., tryptophan is a serotonin precursor) [130]. However, the role of protein and its constituent amino acids in cognitive health needs more investigation.

2.5.3.3 Fats

Fats or its functional part, fatty acids, can be briefly classified into saturated and unsaturated categories. Saturated fatty acids (SFA) such as stearic acid usually exist in animal food products including meat and dairy products. Unsaturated fatty acids (UFA) include monounsaturated fatty acids (MUFA, e.g., olive oil as a good food source) and a series of polyunsaturated fatty acids (PUFA) comprising n−3 (i.e., α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), fatty fish such salmon and tuna as good sources), n−6 (i.e., linoleic acid, vegetable oils as good sources). In the past decades, an increasing number of epidemiological and clinical studies has investigated associations between dietary fat intake and cognitive impairment. A recent review summarized studies on associations between different types of dietary fat intake and cognitive performance among elderly people, and showed that high SFA intake was associated with an increased risk of cognitive impairment (risk ratio =1.40, 95% CI: 1.02, 1.91) compared with low intake, but total and unsaturated dietary fat intakes were not statistical-significantly linked with cognitive impairment, with nine studies covering 23,402 participants being included [131].

At present, despite some inconsistency among studies, most findings suggested that diet high in SFA could have adverse effects on cognitive function, and high intakes of PUFA and MUFA have been associated with reduced risks of cognitive impairment [132]. In addition, the elevated UFA intake and the lower SFA intake could have synergistic effects on protecting cognitive function. Several hypotheses could potentially explain the relationships between high intake of UFA and protection against cognitive impairment, including the roles of fatty acids in maintaining the membranal integrity of neurons, supporting the membranal fluidity of synaptosomes and thereby regulating neuronal functioning; in modifying the activity of some certain membrane-bound enzymes (e.g. phospholipase A2 and acetyltransferases), and the function of the neurotransmitters' receptors; and in influencing the function of membrane proteins such as permeability of ion channels by free fatty acids, phospholipids, and lipid metabolites [132].

2.5.3.4 Vitamins

Vitamins are organic molecules including water -soluble and -insoluble types, essential for functioning of metabolism in human. The processes of brain aging are considered to be related to a series of oxidative actions; plasma vitamin levels were found to be associated with cognitive functioning among healthy older individuals, and meanwhile it is hypothesized that the antioxidative effect of vitamins plays a key role in protection from cognitive impairment [133]. Some vitamins that may exert an antioxidative effect against cognitive aging are the B, C, D, and E vitamins. Most previous research on vitamins in relation to cognitive aging pertained to the water-soluble B vitamins, especially B12. The deficiency of vitamin B12 (namely cobalamin, serum vitamin B12 levels <150 ρmol/L or homocysteine levels >19.9 μmol/L) was associated with an increased risk of cognitive impairment; administration of vitamin B12 supplements at high dose (1 mg/d) was related to improved cognition only in people with pre-existing vitamin B12 deficiency [134]. Vitamin C is another water-soluble vitamin, and may be involved in neuronal differentiation, myelin formation and modulation of the central nervous system. A review summarized associations between vitamin C and cognitive performance in both cognitively healthy and impaired individuals, and found that compared with cognitively impaired people those with intact cognition had higher serum vitamin C levels but there was no significant correlation between vitamin C levels and

global cognitive function [135].

Water-insoluble yet fat-soluble vitamins include vitamin A, vitamin D, and vitamin E. Vitamin D deficiency has been related to a range of non-skeletal conditions including cognitive disorders. Vitamin D receptors (VDR) were found in human brains such as cortex and hippocampus, which are key areas for cognition. At the same time, serum concentrations of 25-hydroxyvitamin D (25OHD), the biologically active status including D3 and D2 forms, were positively associated with global cognitive function; however, there were inconclusive results in some cognitive domains with most non-significant associations [136]. In addition, elder people with severe deficiency of vitamin D (25OHD < 25 nmol/L) had up to four times greater risk of cognitive impairment than those with adequate levels (25OHD ≥ 75 nmol/L); low vitamin D concentrations were associated with increased risks of cognitive decline in prospective studies [137]. However, both reviews indicated that relationships between vitamin D and cognitive performance remain unclear. Vitamin E (tocopherol) plays a key role in protecting brain cells from oxidative stress as an important antioxidant. Due to its antioxidative properties, the link between vitamin E and cognitive aging has been examined in both observational studies and clinical trials. High levels of serum vitamin E were cross-sectionally associated with better cognitive performance; however, inconsistent outcomes were also reported in other population-based studies [138]. Therefore, the beneficial role of vitamin E in cognitive aging is still under debate.

2.5.3.5 Dietary minerals

Dietary minerals usually refer to chemical elements essentially required by organisms to perform biochemical function. Except for five major minerals including calcium, phosphorus, potassium, sodium, and magnesium, all other elements are called trace elements for humans such as iron, copper, zinc, and manganese. These dietary minerals are usually considered beneficial for brain functioning due to their specific biochemical actions such as critical constituents of certain enzymes, inactivating or activating molecules to certain membrane-bound enzymes, preventing oxidative stress as antioxidants [139]. However, the number of studies on dietary intakes of minerals currently is very small in relation to cognitive function; six dietary minerals (Ca, Fe, Zn, Cu, Mn, Mg) are the most investigated elements regarding development disorders and some non-

communicable chronic diseases, and associations with cognitive aging have been emerging. One longitudinal study showed that higher intake of magnesium was related to a reduced risk of mild cognitive impairment, but higher intakes of potassium and iron were associated with an increased risk among 1406 cognitively healthy individuals with eight years follow-up in Australia [140]. Although zinc concentration was found to be elevated in the senile plaques of AD [141], dietary zinc intake was not associated with risk of cognitive decline or AD in randomized controlled trials and observational studies [142]. However, findings are far from conclusive and more well-designed research is needed to examine the potential role of dietary minerals in cognitive aging.

2.5.4 Diet and dementia

Since cognitive impairment or decline is a predominant stage or precursor to dementia or AD, most associations between dietary factors and cognitive aging described above can also be observed in relation to risk of dementia. For example, in terms of single food and food group accumulating evidence suggested a potential association of fish consumption, especially oily fish, with a reduced risk of dementia [143]. High consumption of milk products has been found to be associated with a reduced risk of dementia in the elderly [144]. A limited number of epidemiological studies available on consumption of fruit and vegetables in relation to dementia has generated conflicting findings [143]. Low-to-moderate consumption of alcohol is indicated to be associated with a decreased risk of incident dementia, especially AD; however, some insignificant effects or even conversed findings have emerged [145]. Consumption of meat, especially processed meat and unprocessed red meat, has been debated in relation to dementia risk due to limited evidence and controversial findings available [5]. Evidence on other foods or food groups is scarce so far.

Like the relationships with cognitive aging, associations of dietary patterns with dementia have increasingly become research areas of interest including the MeDi diet, the DASH diet, the MIND diet, and some *a posteriori* healthy patterns [124]. A meta-analysis of five cohort studies showed that individuals with high adherence to the MeDi diet had a 33% reduction in risk of AD compared to those with low adherence [146]; such protective effects also have been observed in other dietary patterns reported by systematic reviews and meta-analyses [6]. Although there are

many encouraging results in observational studies, some intervention studies or clinical trials have failed to confirm the value of some dietary patterns in preventing incident dementia [147]. Based on current inconsistent findings concerning these dietary factors, it is less possible to make definitive dietary recommendations for the public in relation to dementia prevention.

2.5.5 Potential underlying mechanisms

Although there are many uncertainties and underlying mechanisms remain unclear, some hypotheses have been proposed and tested in experiments *in vitro* and *in vivo*.

2.5.5.1 Neuroinflammation and oxidative stress

An inflammatory state is one of features of aging and age-related degenerative diseases; the brain is particularly susceptible to inflammation since it has low antioxidative ability compared with other organs [6]. Increasing evidence has shown that neuroinflammation is a characteristic of dementia pathology, especially AD; accumulating misfolded proteins (e.g., beta-amyloid) activate microglia toll-like receptors (TLRs) and initiate innate immune responses resulting in production of inflammatory mediators [148]. High consumption of fats, particularly saturated fatty acids (SFA), was shown to act on microglia and induce inflammatory responses in animal experiments, leading to production of local cytokines, i.e., hypothalamic nuclear factor kappa B (NF-kB) indicated *in vitro* experiments [149]. On the other hand, frequent consumption of foods or food groups rich in antioxidants and anti-inflammatory compounds has been related to a reduction of systemic inflammation [150].

Some antioxidants may be associated with decreased risks of dementia, including polyphenol compounds (e.g., resveratrol in berries, grapes, and red wine), phytoestrogen compounds (e.g., isoflavones in soy), curcuminoids (e.g., curry as a good source), allium sulphur compounds (e.g., leeks, onions, and garlic), caffeine (e.g., cocoa, coffee, tea), and some vitamins (e.g., beta-carotene in carrots) reported in a review [6]. In addition, foods high in magnesium (Mg), such as dark leafy greens, nuts, whole grains, and fish, may help reduce inflammation; evidence has shown that Mg insufficiency leads to increased production of free radicals, oxygen peroxide and superoxide anion, and decreased expression and activity of antioxidative enzymes, and thus decreased cellular and tissue antioxidative levels

[151].

2.5.5.2 Blood-Brain Barrier (BBB) Disruption

The integrity of BBB is essential for brain function, and increased permeability caused by any damage to the BBB has been strongly associated with the development of AD [152]. An animal study showed that the permeability of the BBB increased and Aβ as the major AD biomarker accumulated in the hippocampus of rabbits after extended exposure to a high cholesterol diet [153]. In addition, Banks and colleagues found that activities of transport systems for some neuroendocrine signals through the BBB were impaired in obese rodents after having a high fat diet, resulting in the molecules with neuroprotective function reduced in the brain and may contribute to cognitive impairment [154]. Neuroinflammation can also damage the integrity or permeability of the BBB, and thus foods with anti-inflammatory properties might play a role in BBB protection which might ultimately lead to protection from cognitive impairment and dementia onset.

2.5.5.3 Influencing the integrity and function of neurons

The integrity and fluidity of neuronal cell membranes are important for the synaptic vesicle fusion as well as communication between neurons via neurotransmitters; the PUFAs are essential components of cell membranes and also can be used to synthesize substances for lipid messengers in signalling processes, influencing neural function [155]. The long-chain ω-3 PUFAs, mainly coming from fish consumption, have been widely investigated, and a systematic review supported a role of ω-3 PUFA in the protection from cognitive impairment [156]. The PUFAs deficiency has been observed in the cortex and hippocampus of the brain aging, and this deficiency has been found to be worse in brains with AD in particular [157]. On the other hand, higher intakes of SFAs and simple sugars were considered to alter the neuronal integrity and communication resulting in compromised neural function, which was hypothesized to be caused by metabolites from the breakdown of digestions of SFAs and simple sugars [158].

2.5.5.4 Induction of pathological amyloidosis

Amyloid-β (Aβ) plaques are a major hallmark in Alzheimer's pathology. Research has shown that high consumption of SFAs was associated with increased levels of

circulating plasma Aβ which might accumulate in brain areas resulting in dysfunction [159]. Studies using mice models suggested that a high-fat feeding had induced increased secretion of β-amyloid from the small intestines absorptive epithelial cells compared with mice given a low-fat diet [160]. Additionally, the elevated Aβ might enter the rodent brain via an impaired BBB and in turn could disrupt the BBB in rodents [161].

2.5.5.5 Others

Other potential mechanisms linking diet to dementia have also been indicated; for example, obesity related to high consumption of caloric-rich foods or overeating behaviour in midlife has been associated with an increased risk of late-onset dementia [162]; high vitamin D intake has been related to low dementia risk potentially due to widespread distribution of Vitamin D receptors in brain tissue and a neuroprotective effect via clearance of amyloid plaques by 25-hydroxyvitamin D [137]. However, those putative mechanisms have not been fully confirmed, and more specific hypotheses explaining the association between diet and dementia need to be tested in future research.

In conclusion, there are still many uncertainties in the research field of diet, cognitive function, and dementia; for example, few studies have been conducted on whether cooking methods play a role in cognitive decline, and what the most influential type and amount of food consumption in relation to cognitive function and dementia. Based on these inconsistent and limited findings, this present project was conducted with specific objectives, scientific hypotheses, and sound study designs.

CHAPTER III

3. Meat consumption, cognitive function, and dementia: A systematic review and meta-analyses

3.1 Summary

3.1.1 Highlights

- Meat consumption may be not associated with cognitive function and dementia risk in older adults.
- Evidence on associations between cognitive disorders and consumption of specific amounts and types of meat remain limited, and additional research is needed.

3.1.2 Abstract

Background: Cognitive impairment, Alzheimer's disease, and other forms of dementia are increasing in prevalence worldwide, while global dietary patterns are transitioning to a 'western type' with increasing meat consumption. However, evidence linking meat intake with these cognitive disorders remains inconsistent.

Objective: To systematically review studies which have explored associations between meat consumption, cognitive function, and risk of cognitive disorders.

Methods: Five electronic databases were searched—MEDLINE, EMBASE, The Cochrane Library, Web of Science, and Scopus, up to 21 January 2019. This review included original research studies, written in English, with full texts available, reporting information on meat intake (all types but not fish) and cognitive function or disorders among older adults. Narrative synthesis was conducted with meta-analysis where odds ratios or mean differences were pooled using a random-effects model. The I^2 statistic and contour-enhanced funnel plots were used to detect heterogeneity and publication bias separately in meta-analyses.

Results: Twenty-nine studies were retrieved including twelve cohort, three case-control, thirteen cross-sectional studies and one intervention study. The majority (21/29) showed that meat consumption was not significantly associated with cognitive function or disorders. Meta-analysis of five studies showed no significant

differences in meat consumption between cases with cognitive disorders and controls (overall pooled standardised mean difference = -0.36, 95%CI: -1.12, 0.39); however, there was considerable heterogeneity. In contrast, a meta-analysis of seven studies showed reduced odds of cognitive disorders by consuming meat weekly or more (overall pooled odds ratio = 0.85, 95%CI: 0.70, 0.99); however, potential publication bias was noted in relation to this finding.

Conclusions: There was no strong association between meat consumption and cognitive disorders. However, the evidence base was limited requiring more studies of high quality to isolate the specific effect of meat consumption from dietary patterns, to confirm these associations.

3.2 Introduction

Red meat and processed meat are usually defined as unprocessed mammalian muscle meats and meats transformed through salting, smoking, curing, or other processes, respectively [163]. According to the International Agency for Research on Cancer (IARC), consumption of red meat (unprocessed) was classified as "probably carcinogenic to humans", whereas consumption of processed meat as "carcinogenic to humans" [164]. In addition, consumption of red and processed meat has been associated with an increased risk of all-cause and cardiovascular mortality in a meta-analysis of prospective cohort studies [165]. However, evidence on associations between meat consumption and cognitive decline or development of dementia remains inconsistent.

As the most prevalent type of dementia, Alzheimer's disease (AD) is clinically characterized by chronic and progressive memory loss, cognitive decline and other neurodegenerative symptoms [166]. The cause of AD is poorly understood but research has highlighted diet as a potentially modifiable risk factor for AD [167]. The most studied dietary factor in relation to dementia is the role of Mediterranean diet (MeDi) which has been detailed in Chapter 2. Accumulating studies reveal that higher adherence to the MeDi was associated with better cognitive performance and reduced risks of mild cognitive impairment (MCI) and Alzheimer's disease (AD) [146,168]; however, it is unclear whether the MeDi exerts its effects as a whole, or via its individual characteristics. As one characteristic of MeDi, the contribution of meat avoidance remains unclear in relation to cognitive disorders.

Meat consumption has been increasing globally; with regards to red meat, the global annual average consumption is forecast to reach 45 Kg per capita per annum by 2030, which is almost twice as high as the respective assessment during the 1970s [169]. In addition, according to the latest data from World Health Organization (WHO), around 50 million people worldwide have dementia with an annual incidence of nearly 10 million [170]. In Japan the prevalence of AD rose from 1% in 1985 to 7% in 2008 during the nutrition transition from the traditional Japanese diet to the Western diet [171]. Another ecological study analysed dietary supply data 5, 10, and 15 years before AD prevalence data from 10 countries (Brazil, Chile, Cuba, Egypt, India, Mongolia, Nigeria, Republic of Korea, Sri Lanka, and the United States), and found that dietary meat supply 5 years before the prevalence data had the highest correlations with AD prevalence [172]. Therefore, it is important to explore associations between meat consumption, cognitive function, and dementia especially AD.

As mentioned in Chapter 2, cardiovascular factors are part of dementia risk factors; since meat consumption has been associated with an increased risk of cardiovascular events [165], meat consumption is hypothesized to be a risk factor of dementia in this project. In the Newcastle (northeast UK) 85+ Cohort Study a dietary pattern high in red meat was associated with poor cognitive performance among 791 individuals born in 1921 over a five-year follow up [173]. Data from 194 cognitively healthy individuals who took part in the Uppsala Seniors cohort study confirmed that low consumption of meat and meat products was linked with higher cognitive scores [174]. The Chinese Longitudinal Health Longevity Study (CLHLS) investigated 6911 residents aged 65 or older and found no significant association between higher meat consumption and risk of dementia after three years of follow up [175]. The Maine-Syracuse longitudinal study even showed that higher intakes of meat were prospectively associated with higher cognitive scores among 333 participants free of dementia and stroke [176]. Although conducted among a similar age group (≥65 years old), these studies reported different directions of associations between meat consumption and cognitive function. It is noted that there was a high level of heterogeneity between studies. Differences in the adjustment set may have caused the heterogeneity; for example, the *APOE* ε4 status was adjusted for as a confounding factor in the Newcastle 85+ Cohort Study but

not in other cohorts [173]; and a homeostasis model assessment of insulin resistance was only adjusted for in the Uppsala Seniors cohort study [174]. In addition, all cohort studies list above did not consider the reverse causation which may also have made the findings unstable and inconsistent.

As a modifiable factor, diet might potentially support primary prevention related to senile dementia or AD. However, current recommendations on meat are unclear in relation to dementia, and some countries do not have specific recommended daily allowances for the elderly. Current information on a healthy diet from WHO only specifies that 'less than 30% of total energy intake is from fats containing saturated and trans-fats (mainly found in fatty meat and sweet foods)' [177]. Some key recommendations of the Healthy US-Style Eating Pattern at the 2000-calorie level only stipulate a variety of protein foods including lean meat and limited saturated fats and trans-fats in the 2015–2020 dietary guidelines [178]. Both guidelines refer to limiting saturated fats and trans-fats from meat but do not provide specific daily recommendations for meat intake. In the United Kingdom, a healthy daily portion of red and processed meat was reduced from more than 90g (cooked weight) to 70g per day in the 2011 report from the Scientific Advisory Committee on Nutrition (SACN) [179,180]. In China, the 2016 dietary guidelines for Chinese population recommend 'consumption of an appropriate amount of fish, poultry, eggs, and lean meat with 280~525g red meat and poultry per week' [181]. Although these dietary guidelines contain recommended intake allowance of meat, few of them have specific recommendations of meat for elderly people, let alone in relation to cognitive aging. Reasons why these dietary guidelines are limited in specific recommendations on meat may be a lack of reports synthesising the relevant studies systematically.

For the above-mentioned reasons it was important to perform a systematic review to summarize current evidence regarding associations between meat consumption and cognitive function or AD risk among old adults. In addition, possible biological mechanisms underpinning these relationships were also briefly discussed.

3.3 Methods

This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement

[182]. The review was reported based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [183], and a completed MOOSE checklist can be seen in Appendix A. The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020173687).

3.3.1 Search scope, terms, and strategies

A systematic literature search was conducted by investigators using search strategies reviewed by a librarian from University of Leeds in five major databases including EMBASE OVID (1947 onwards), MEDLINE OVID (1946 onwards), Web of Science, Scopus, and the Cochrane Library, up to 21 January 2019. The search was limited to human subjects, using the following terms: (‘meat’ or ‘poultry’ or ‘lamb’ or ‘beef’ or ‘pork’ or ‘mutton’) and (‘cognition’ or ‘dementia’ or ‘Alzheimer’ or ‘AD’ or ‘neurodegeneration’). The specific search terms and strategies are shown in Table 3.1.

Table 3.1 Searching terms and strategies

Research components	Searching terms
Meat	Subject heading searching: meat/ meat products/ or processed meat/ or poultry/ red meat/ or beef/ or lamb meat/ or mutton/ or pork/ or rabbit meat/ or veal/ or venison/ Keyword searching: meat* or lamb or beef or pork or mutton
Alzheimer’s disease	Subject heading searching: Alzheimer disease/ dementia/ degenerative disease/ (for EMBASE) neurodegenerative diseases/ (for MEDLINE and the Cochrane library) Keyword searching: Alzheimer* dementia neurodegenerati*
Cognition	Subject heading searching: cognition/ cognitive disorders/

cognitive dysfunction/ cognitive defect/ cognitive assessment/ Keyword searching: cogniti*

* the wildcard character was used to search for all terms that begin with a word; Combining search terms were ‘OR’ between same research components and ‘AND’ between different research components.

The search was performed using free text searches in Web of Science and Scopus; and with subject heading searches in EMBASE, MEDLINE and the Cochrane Library databases. An additional search via reference lists of each eligible study was conducted manually to identify any missing publications.

3.3.2 Inclusion and exclusion criteria and screening process

Articles were included if they fulfilled the following criteria:

1) original research studies;

2) human studies performed in older adults or the elderly rather than children or youth;

3) studies that provided a description about consumption of meat comprising red meat, processed meat, poultry, but not fish;

4) studies that gave information about methods used for assessing cognitive function, dementia, AD, or other cognition-related health outcomes such as cognitive impairment and cognitive decline;

5) studies written in English with full texts available.

Studies were excluded according to the following criteria:

1) reviews and book chapters, or secondary-research evidence such as meta-analysis;

2) non-individual studies such as ecological methods;

3) for overlapping studies, the study with the smaller sample size was excluded.

Screening was undertaken by different researchers who independently assessed texts according to the inclusion and exclusion criteria and a pre-made diagram (Figure 3.1). Screening results from different researchers were merged and

inconsistencies were discussed between the researchers to reach an agreement.

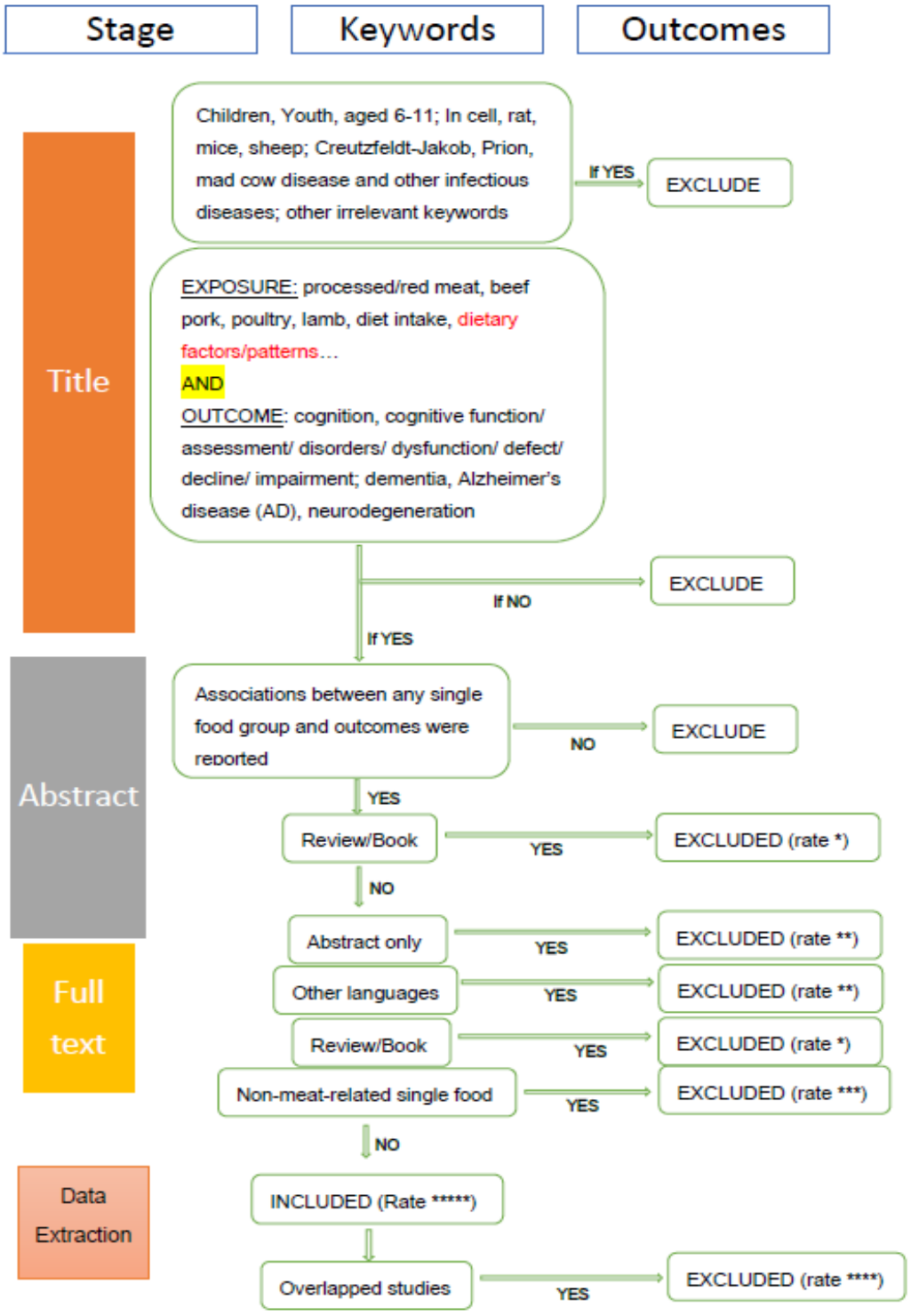


Figure 3.1 Diagram for screening process

3.3.3 Information extraction and Quality assessment

Related data and information were extracted into a pre-made summary table. Since the included studies consist of longitudinal studies, cross-sectional studies, case-

control studies and intervention studies, an adapted quality assessment scale was created according to the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [38] and the Study Quality Assessment Tools (SQAT) for controlled intervention studies, observational cohort and cross-sectional studies [184]. Briefly, the adapted scale consists of ten items covering the rationale, sampling, exposure, outcomes, covariates, statistical methods, and potential bias, with detailed instructions for reviewers (Appendix B). Each item of the scale was given 1 if the answer was "Yes", or 0 if the answer was "No" or "Not Reported". Thus, the total quality score ranged from 0 to 10, with higher scores indicating greater quality as scores 0–4 (Low quality), 5–7 (Moderate quality), and 8–10 (High quality). Data extraction and quality assessment were performed by two reviewers independently.

3.3.4 Narrative synthesis and Meta-analysis

Due to the considerable heterogeneity in study designs, exposure and outcome measures, and analytical methods, it was not statistically appropriate to combine all the included studies in a meta-analysis. Therefore, a formal narrative synthesis on quantitative studies was undertaken according to the reporting guidelines of the synthesis without meta-analysis (SWiM) [185,186]. Briefly, nine items were followed in the reporting of this systematic review, including:

1) a. grouping studies via study designs was applied considering the different effect estimates and potential bias from various study designs; b. reasons and changes were reported where specific studies were not grouped.

2) The direction of effect and its *P* values were used as the standardized metric and the transformation methods were reported where used.

3) Methods of vote counting based on direction of effect were applied since the most studies included were observational study with great potential heterogeneity making it difficult to use data synthesis on all included studies.

4) Quality assessments on studies included were considered when interpreting findings. Studies with higher study quality were prioritized for reporting the synthesis findings considering the higher the study quality is the more robust the results are.

5) Methods of ordering tables by publication years of studies among same group of study design were applied to detect potential publication bias.

6) The synthesis method of vote counting made this project difficult to assess the certainty of synthesis findings.

7) Tables presenting first author, publication year, country, cohort name and follow-up period (cohort studies applicable), sample size, age, exposure measures, outcome measures, effects, and quality assessment were used for data presentation.

8) The synthesis findings of counting number of negative or positive associations between meat consumption and cognitive disorders were reported with quality assessment of each study.

9) Limitations of the vote counting based on direction of effect, heterogeneity among studies, and inclusion of low-quality studies were discussed in reporting.

The same types of data with similar methodologies from individual studies were synthesized via meta-analysis using random-effects models (inverse variance method) due to potential heterogeneity across studies. For studies reporting the number of participants who consumed any type of meat (fish not included) weekly or more (that is, ‘always’) both in cases diagnosed with cognitive disorders and controls, odds ratios (ORs) and 95% confidence interval (95% CI) were extracted or calculated to compare the difference in odds of consuming meat weekly or more vs less frequently between cases and controls. For studies reporting continuous measures such as grams per day or frequency of meat consumed, the standardised mean differences (SMDs) and 95% CI were calculated using Glass’s methods [187,188] due to very different independent means and SDs of meat intake. This meta-analysis was to compare differences of meat consumption between cases with cognitive disorders and controls. Study heterogeneity was assessed using Chi^2 test of homogeneity, where *P* values of less than 0.10 indicate significant heterogeneity, together considering I^2 statistics of 50% or higher representing considerable heterogeneity [189]. The contour-enhanced funnel plots were created to explore publication bias with Egger's regression model to detect small-study effects ($P < 0.05$). Meta-analyses and other tests were conducted in Stata/IC, version 16.1 (Stata Corp LP, College Station, TX).

3.4 Results

3.4.1 Characteristics of studies and quality assessment

In total, 3158 records were identified through database and reference list searches. Due to duplication 1559 records were removed, and then 1530 unrelated records were excluded based on title/abstract screening, leaving 69 records. Applying the inclusion and exclusion criteria, a further 11 reviews and 11 records without full texts available were excluded. After reviewing full texts, one record written in Japanese, four records with overlapping studies, two ecological studies, three records with changes of brain structure or β-amyloid (Aβ) deposit as outcomes, and eight records combining meat, fish, and other food together as exposures were excluded including one paper with an unclear description on meat by Heys et al. (2010) [190] without any reply from two authors contacted. Therefore, 29 eligible records were included in the review: twelve cohort [174-176,191-199], three case-control [200-202], thirteen cross-sectional studies [203-215], and one intervention study [216] (Figure 3.2).

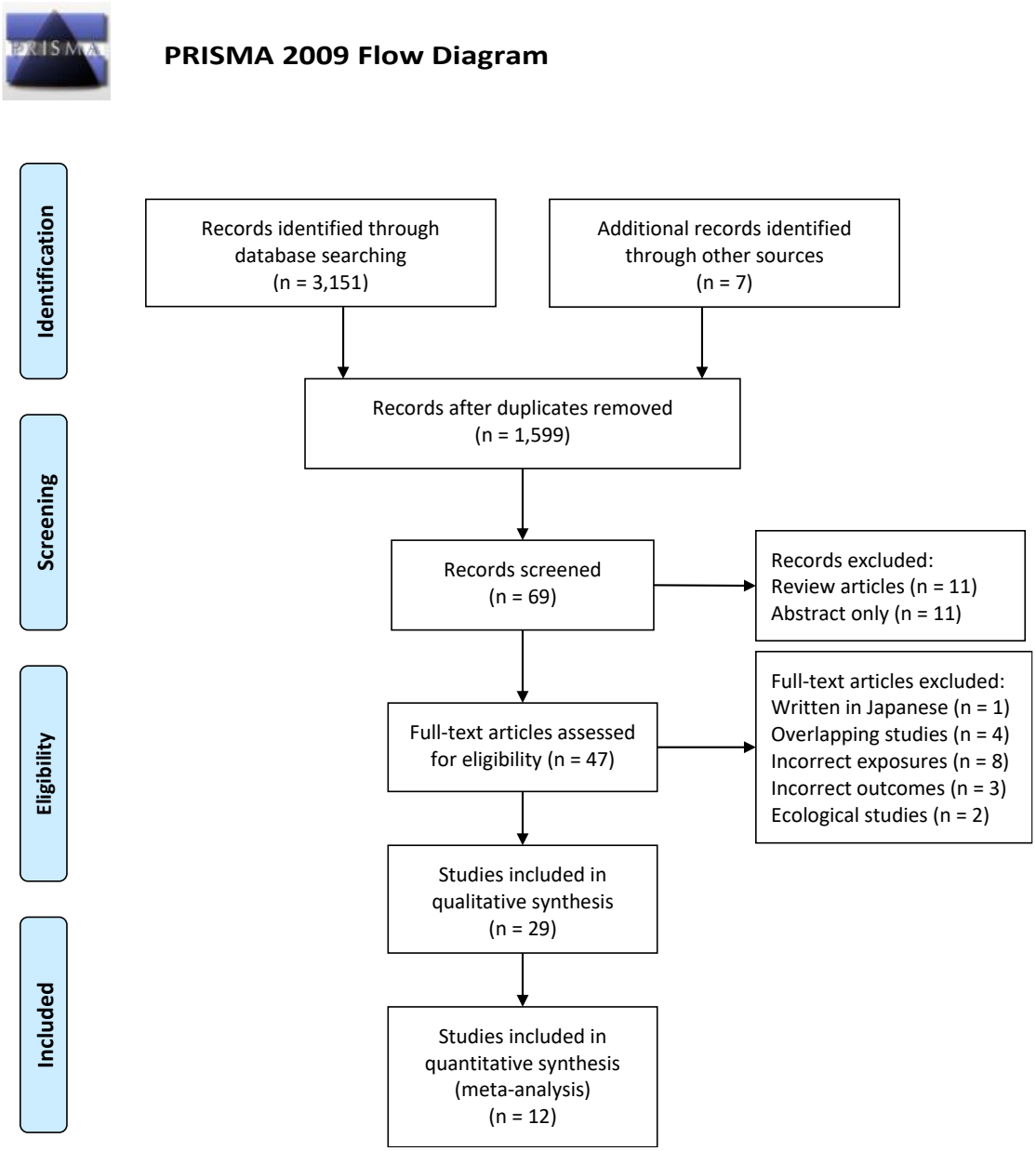


Figure 3.2 Flowchart of the literature screening process for a systematic review of associations between meat consumption and cognitive disorders using PRISMA 2009 flow diagram [217]

Table 3.2 Characteristics of 29 studies included in the systematic review on associations between meat consumption, cognitive function, and dementia

Author, Year [Ref]	Country, Study Name	Follow-Up, Year	Sample Size (Female/Male)	Age [1] (Mean ± SD/Range)	Exposure Measures	Outcomes (Measure Methods)	Effects	Quality Scores
Cohort studies								
Barberger-Gateau et al., 2002 [191]	France, PAQUID	7	1416 (Not Reported)	≥ 68	Frequency of consumption of meat	Dementia (MMSE), AD (DSM-III-R)	No significant association between meat consumption and risk of dementia (P_{trend} = 0.59, adjusted HR = 0.56, 95%CI 0.26–1.20, for weekly consumers).	6
Barberger-Gateau et al., 2007 [192]	France, The Three-City cohort study (3C)	4	8085 (Not Reported)	≥ 65	FFQ including meat	Dementia (neuropsychological tests and DSM-IV), AD (NINCDS-ADRDA)	No association between risk for all cause dementia and meat consumption ($p > 0.25$) adjusted for age.	7
Vercambre et al., 2009 [193]	France, Etude Epidemiologique de Femmes de la Mutuelle Generale de Education Nationale (E3N)	13	4809 (4809/0)	65.5 ± 1.8	208-item FFQ including red meat, offal, processed meat, poultry	Recent cognitive decline (Deterioration Cognitive Observee questionnaire (observed cognitive deterioration), DECO)	High intake of poultry reduced risk of recent cognitive decline (>median consumption vs. no consumption: aOR = 0.73, 95%CI, 0.58–0.91, P_{trend} = 0.004); but offal, red or processed meat did not.	7
Chen et al., 2012 [175]	China, The Chinese Longitudinal Healthy Longevity Study (CLHLS)	3	5691 (4302/1389)	82.94 ± 11.03	Frequency of meat intake (pork, beef, mutton, and poultry)	Cognitive decline (MMSE)	Always meat intake (around daily) could reduce the risk of cognitive decline in bivariate regression model (unadjusted OR = 0.71, 95%CI 0.56–0.89, P = 0.0029), but no significant	6

							associations emerged for meat intake in adjusted models.	
Samieri, et al., 2013 [194]	USA, Women's Health Study	4	6174 (6174/0)	71.9 ± 4.1	131-item FFQ including meat	Global cognitive score (telephone adapted MMSE), verbal memory (the East Boston memory test)	No significant association between red and processed meat consumption and mean score of global cognition ($P_{trend} = 0.16$) or verbal memory ($P_{trend} = 0.15$).	6
Titova et al., 2013 [174]	Sweden, Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)	5	194 (93/101)	70	7-day dietary records including amounts of meat	Cognitive score (seven-minute screening, 7MS)	A low consumption of meat and meat products was linked to a better performance on the 7MS test (β coefficient = −0.26, $P < 0.001$).	5
Wengreen et al., 2013 [195]	USA, The Cache County Memory Study (CCMS)	11	3580 (Not Reported)	≥65	142-item FFQ over past year including meat	Cognitive score (modified MMSE, 3MS)	No significant association between increasing quintiles of red and processed meat and higher 3MS scores (P-linear trend = 0.2796).	5
Ashby-Mitchell et al., 2015 [196]	Australia, AusDiab study	12	577 (284/293)	66.07 ± 4.85	101-item FFQ over past year including meat	Cognitive impairment (MMSE)	No association between odds of cognitive impairment and meat consumption (aOR = 1.005, 95%CI 0.964–1.048).	5
Crichton et al., 2015 [176]	USA, The Maine Syracuse Longitudinal Study (MSLS)	18 ± 5.3	333 (Not Reported)	60.5 ± 12.8	37-item FFQ including meat	Cognitive score (the Wechsler adult intelligence scale, WAIS)	Higher WAIS Scores at baseline were prospectively associated with higher intakes of meats (β coefficient = 0.062, se = 0.012, $P < 0.001$).	8
Trichopoulou et al., 2015 [197]	Greece, the European Prospective Investigation into Cancer and	6.6	401 (257/144)	Mean = 74	FFQ including meat	Improved or unchanged score (cMMSE ≥ 0), mildly lower score (cMMSE −4 to −1),	No significant odds of having mildly lower score (aOR = 1.14, 95%CI 0.89–1.47) or substantially lower score (aOR = 1.09, 95%CI 0.71–1.69) for	5

	Nutrition (EPIC) - Greece cohort					substantially lower score (cMMSE ≤ −5)	an increment of one SD of meat intake.	
Fischer et al., 2018 [198]	Germany, The German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe)	4.5	2622 (1712/910)	81.2 ± 3.4	Single-food-questionnaire on frequency of use of red meat and sausages	AD (DSM-IV and ICD-10), memory decline (CERAD neuropsychological assessment battery)	No significant association was detected between frequency of meat and sausage with incident AD (adjusted HR: 1.09, 95%CI 0.94–1.26, $p = 0.236$) or memory decline (adjusted β = 0.01, 95%CI −0.11 −0.14, $p = 0.845$)	9
Zhu et al. 2018 [199]	China, The Shanghai Women's Health Study and Shanghai Men's Health Study (SWHS and SMHS)	14.4	30,484 (18,458/12,026)	70–86	FFQ over past year including meat	Questions on memory, and decision-making ability: no, minor, or serious impairments	High red meat intake (fourth quintile: 44.7–64.3 g/d for women, 52.9–75.8 g/d for men) was associated with a lower likelihood of impairments in memory (aOR = 0.86, 95%CI: 0.75, 0.99), and decision-making (aOR = 0.82, 95%CI: 0.72, 0.93).	6
Case-control studies								
Baker et al., 1993 [200]	USA	—	72 (50/22)	75.4	Frequency of beef or pork intake	Clinically diagnosed AD cases (McKnann criteria)	No association between the daily or weekly use of beef or pork with a risk for clinically diagnosed AD (aOR = 4.0, CI = 0.30–∞, $p = 0.37$).	5
Zhao et al., 2015 [201]	China	—	404 (Not Reported)	60–90	FFQ including meat	MCI (Montreal cognitive assessment, MoCA)	No difference ($P > 0.05$) in meat intake (pork, beef and mutton) between MCI cases (45.8 ± 3.9 g/d) and controls (52.5 ± 3.4 g/d).	4
Dong et al., 2016 [202]	China	—	894 (604/290)	62.9 ± 5.25	41-item FFQ including meat and poultry	Cognitive score (Montreal cognitive assessment, MoCA)	No significant association was detected between intake of poultry, red meat with MoCA ($P > 0.05$).	5

Cross-sectional studies								
Lee et al., 2001 [203]	Korea	—	449 (239/210)	60–83	24 h dietary recall	Cognitive score (MMSE for Korea)	No significant correlations between MMSE score and meat intake (Correlation coefficients: −0.004 for men 0.096 for women)	6
Requejo et al., 2003 [204]	Spain	—	168 (Not Reported)	65–90	7-day food record	Cognitive decline (MMSE)	No significant difference in meat consumption between MMSE ≥ 28 group and MMSE < 28 group with being stratified by age ($p > 0.1$).	5
Rahman et al., 2007 [205]	USA	—	1056 (708/348)	69 ± 8.9	Frequency of consumption of meat	Cognitive decline (mental status questionnaire, MSQ)	No association between risk of cognitive impairment and intakes of meat (aOR = 0.11, 95%CI: 0.67, 1.84).	9
Albanese et al., 2009 [206]	Latin America, China, and India	—	14,960 (Not Reported)	≥65	Frequency of average weekly meat intake	Dementia (the 10/66 diagnostic algorithm)	A less-consistent, dose-dependent, direct association between meat consumption and prevalence of dementia (adjusted PR: 1.19; 95%CI: 1.07, 1.31).	10
Aránzazu et al., 2010 [207]	Spain	—	178 (Not Reported)	65–97	7 consecutive days food record	Cognitive score (short portable mental state questionnaire, SPMSQ)	The intake of meat correlated with a greater number of errors incurred (Correlation coefficient: $r^2 = 0.1086$; $p < 0.001$).	3
Wang et al., 2010 [208]	China, Project of Longevity and Aging in Dujiangyan (PLAD)	—	364 (204/160)	93.02 ± 3.01	Frequency of consumption of meat	MCI (MMSE)	No significant association was detected in both unadjusted and adjusted models (aOR = 1.01, 95%CI 0.92–1.10).	7

Katsiardanis et al., 2013 [209]	Greece	—	557 (320/237)	>65	157-item FFQ	Cognitive impairment (MMSE)	No association between meat and meat products with the presence of cognitive impairment (aOR = 0.96, 95%CI 0.81–1.16 for women; aOR = 1.03, 95%CI 0.84–1.27 for men).	6
Crichton et al., 2013 [210]	Australia	—	1183 (751/432)	40–65	215-item FFQ	Cognitive failures questionnaire (CFQ); Memory Functioning Questionnaire (MFQ)	No associations between CFQ score and MFQ score with consumption of meat ($P > 0.05$).	6
Bajerska, et al., 2014 [211]	Poland	—	87 (Not Reported)	≥60	Frequency and potion size of meat and meat products intake over the last month	Global cognitive (MMSE), executive function (cognitive test battery)	The consumption of red meat and meat products was negatively related to executive function (β = −0.02, 95%CI: −0.03–−0.007, standardized β = −0.33, $p = 0.01$) and global cognition (β = −0.02, 95%CI: −0.04–−0.007, standardized β = −0.25, $P = 0.01$).	6
Franca et al., 2016 [212]	Brazil, The EpiFloripa Elderly survey	—	1197 (778/419)	73.9 ± 19.3	Habitual intake of red meat with fat or chicken with skin (yes/no)	Cognition score (MMSE)	No significant association was detected between intake of red meat with fat or chicken with skin and MMSE scores both in women and men ($P \geq 0.057$).	7
Brouwer-Brolsma et al., 2018 [213]	Netherlands, Nutrition Questionnaires plus (NQplus) study	—	1607 (770/837)	Mean = 52.9	183-item FFQ over past 4 weeks	Semantic memory and language production (letter fluency test, LFT; processing speed (symbol digit modalities test, SDMT);	The meat intake was negatively related to LFT score (β = −0.006, se = 0.002, $p = 0.007$), SDMT score (β = −0.011, se = 0.005, $p = 0.02$), and SRT score (β = −0.003, se = 0.002, $p = 0.14$) in unadjusted model but not in adjusted models.	6

						everyday memory (story recall test, SRT)		
Rocaspana-García et al., 2018 [214]	Spain	—	111 (70/41)	78.5 ± 6.4	45-item FFQ	AD patients diagnosed in hospital	Almost half of the AD patients (46.8%) ate more meat than recommended.	3
Franca et al., 2018 [215]	Brazil	—	400 (288/112)	≥60	Habitual intake of red meat with fat or chicken with skin (yes/no)	Cognition deficit (MMSE)	No significant association was detected between cognitive deficit and intake of red meat with fat (aOR = 1.053, 95%CI 0.568–1.952) or chicken with skin (aOR = 0.952, 95%CI 0.505–1.793).	6
Intervention studies								
Charlton et al., 2016 [216]	Australia	12 weeks	31 (Not Reported)	78.0 ± 6.2	Intervention: Pork meals; Control: chicken meals	Cognitive score (cognitive test battery)	No significant cognition changes in the pork intervention group over the 12 weeks, while the chicken group had improved verbal learning and memory at six weeks ($p < 0.001$).	4

[1] Age is when the outcomes were measured.

Abbreviations: SD, standard deviation; PAQUID, Personnes Agées QUID epidemiological study of cognitive and functional ageing; MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; HR, Hazard ratio; CI, confidence interval; FFQ, food frequency questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria; aOR, adjusted OR; cMMSE, change of Mini-Mental State Examination; ICD, international classification of disease; CERAD, the Consortiumto Establish a Registry for Alzheimer's Disease; MCI, Mild cognitive impairment; PR, Prevalence ratio.

Table 3.3 Quality assessment results of studies included using a 10-item assessment scale*

Study	Study design	1	2	3	4	5	6	7	8	9	10	Total
Baker et al., 1993	Case-control study	N	NR	NR	NR	Y	Y	Y	Y	N	Y	**5**
Lee et al., 2001	Cross-sectional study	Y	NR	Y	NR	N	Y	Y	Y	Y	NR	**6**
Barberger-Gateau et al., 2002	Longitudinal study	Y	NR	Y	Y	Y	N	Y	Y	N	N	**6**
Requejo et al., 2003	Cross-sectional study	Y	N	Y	Y	Y	Y	N	N	N	N	**5**
Barberger-Gateau et al., 2007	Longitudinal study	Y	Y	Y	Y	Y	Y	N	Y	N	N	**7**
Rahman et al., 2007	Cross-sectional study	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**9**
Albanese et al., 2009	Cross-sectional study	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Vercambre et al., 2009	Longitudinal study	Y	N	Y	Y	N	N	Y	Y	Y	Y	**7**
Aránzazu et al., 2010	Cross-sectional study	Y	NR	Y	NR	Y	N	N	N	N	N	**3**
Wang et al., 2010	Cross-sectional study	Y	NR	Y	NR	Y	Y	Y	Y	N	Y	**7**
Chen et al., 2012	Longitudinal study	Y	N	Y	Y	N	Y	Y	Y	N	N	**6**
Crichton et al., 2013	Cross-sectional study	Y	N	Y	Y	N	N	Y	Y	NR	Y	**6**
Katsiardanis et al., 2013	Cross-sectional study	Y	N	Y	Y	N	Y	Y	Y	N	N	**6**
Samieri, et al., 2013	Longitudinal study	Y	N	Y	Y	N	Y	Y	N	Y	N	**6**
Titova et al., 2013	Longitudinal study	N	N	Y	Y	Y	N	Y	Y	N	N	**5**
Wengreen et al., 2013	Longitudinal study	Y	N	Y	Y	N	Y	Y	N	N	N	**5**
Bajerska, et al., 2014	Cross-sectional study	Y	NR	Y	NR	Y	Y	Y	Y	N	N	**6**
Ashby-Mitchell et al., 2015	Longitudinal study	Y	N	Y	N	N	Y	Y	Y	N	N	**5**
Crichton et al., 2015	Longitudinal study	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	**8**

Trichopoulou et al., 2015	Longitudinal study	Y	N	N	N	N	Y	Y	Y	Y	N	**5**
Zhao et al., 2015	Case-control study	Y	NR	Y	NR	N	Y	N	Y	N	N	**4**
Charlton et al., 2016	Intervention study	Y	Y	Y	N	Y	N	N	N	N	N	**4**
Dong et al., 2016	Case-control study	Y	NR	Y	NR	N	Y	Y	Y	N	N	**5**
Franca et al., 2016	Cross-sectional study	Y	Y	Y	Y	N	Y	Y	Y	N	N	**7**
Brouwer-Brolsma et al., 2018	Cross-sectional study	Y	NR	Y	NR	Y	N	Y	Y	Y	N	**6**
Fischer et al., 2018	Longitudinal study	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	**9**
Franca et al., 2018	Cross-sectional study	Y	Y	Y	NR	N	Y	Y	Y	N	N	**6**
Rocaspana-García et al., 2018	Cross-sectional study	Y	N	Y	NR	N	N	N	Y	N	N	**3**
Zhu et al. 2018	Longitudinal study	Y	NR	NR	Y	N	N	Y	Y	Y	Y	**6**

*Items:
1 Was the research question or objective in this paper clearly stated?
2 Was the sample size clearly defined, calculated and powerful to detect the association of interest?
3 Did this paper describe the eligibility criteria, and the sources and methods of selection of participants?
4 Was the participation rate of eligible persons at least 50% (Response rate or completion rate)? Was loss to follow-up after baseline 20% or less for longitudinal or cohort studies?
5 Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
6 Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
7 Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? Or matched for case-control studies?
8 Did this paper describe all statistical methods and interpret the results clearly?
9 Did this paper report proportions of missing data and explain how missing data were addressed?
10 Was any potential bias reported and did this paper describe any efforts to address potential sources of bias?

Characteristics of included studies are summarized in Table 3.2. The publication year ranges from 1993 to 2018 and the sample size varies between 48 and 30,484. The mean age of participants was more than 60 years except for two studies, one with a mean age of 52.9 years [213] and one with a range of 40–65 years [210]. Of twenty-nine eligible studies, twenty-four measured consumption of total meat based on a food frequency questionnaire (FFQ) and/or dietary records; one study reported consumption of beef and pork as the exposure [200]; one specified frequencies of use of red meat and sausages as the exposure [198]; two investigated whether participants had habitual intake of red meat with fat or chicken with skin (Yes/No) [212,215]; and one intervention study used pork-containing meals as the exposure [216]. Among the studies included, five of them used Alzheimer's disease and/or dementia as outcomes [191,192,200,206,214]; twenty-three measured cognitive function via one or a series of cognitive tests; and one reported both AD and cognitive function [198].

The quality score of each study included is listed in Table 3.2. In total, twenty-one out of twenty-nine studies were of moderate quality; four studies were of high quality; and four were of low quality. These low-quality studies [201,207,214,216] were mainly limited in response rate or follow-up rate, outcome measures, and adjustment for confounding variables compared with other higher-quality studies, resulting in more caution needed when interpreting those findings. The specific assessment information is shown in Table 3.3.

3.4.2 Observational evidence

Twenty-eight articles reported observational studies: twelve cohort, three case-control, and thirteen cross-sectional studies. One of the twelve cohort studies reported an inverse association between consumption of meat and meat products and cognitive performance using the seven-minute screening (7MS) test (β coefficient = -0.26, $P < 0.001$) after five years of follow-up in Sweden [174]. Three longitudinal studies observed a protective association after 13–18 years of follow-up. Of these studies, one conducted in France with a 13-year follow-up found that compared with non-consumers, poultry eaters who consumed more than the median (17 g/d) had a reduced risk of recent cognitive decline (adjusted OR= 0.73, 95% CI: 0.58, 0.91); but this was not seen for eaters of offal, red meat, or processed meat [193]. One cohort study showed that high meat intake was associated with low risk

of impairment in memory (adjusted OR = 0.86, 95% CI: 0.75, 0.99) and decision-making (adjusted OR = 0.82, 95% CI: 0.72, 0.93) after a 14-year follow-up in China [199]. The last cohort conducted in the USA also reported high meat intake related to better cognitive scores (β coefficient = 0.062, standard error = 0.012, $P < 0.001$) after an 18-year follow-up [176]. In addition, one longitudinal study showed that 5691 Chinese people who exposed to an "always meat intake" (around daily) had a reduced risk of cognitive decline in unadjusted regression model (OR= 0.71, 95%CI: 0.56, 0.89, $P= 0.0029$) compared with "not always meat intake" (less than daily) after three years follow-up, but this association was not seen in adjusted models [175]. The remaining seven cohort studies did not find any significant associations between meat consumption and cognitive function, risk of AD and other forms of dementia. These studies had follow-up periods ranging from 4 to 12 years.

All three case-control studies included, with one conducted in USA and two in China, did not observe significant associations between meat intake and either Montreal cognitive assessment (MoCA) score or clinical diagnosis of AD.

One of the thirteen cross-sectional studies demonstrated that meat consumption was negatively related to executive and global cognition function in Poland [211]. One Spanish cross-sectional study used error numbers in tests as outcomes and found that higher meat intake correlated with a greater number of errors incurred ($r^2 = 0.109$, $P < 0.001$); however, the quality of this study was low (score three out of ten) and more attention should be given when considering conclusions [207]. With dementia or AD as outcomes, one cross-sectional study with higher research quality score showed that meat consumption was associated with increased prevalence of dementia (adjusted PR =1.19, 95% CI: 1.07, 1.31) in Latin America, China and India [206], and another Spanish study with a poor research quality found that 47% of AD patients consumed a higher level of meat than the recommended level [214]. In addition, one cross-sectional study conducted in Netherlands demonstrated that consumption of meat was negatively related to memory; however, the significant association only existed in unadjusted models but not in adjusted models [213]. The remaining eight cross-sectional studies which were performed in Korea, China, Netherland, Spain, Greece, Australia, the USA, and Brazil respectively did not find any statistically significant associations.

3.4.3 Interventional evidence

The only trial that compared effects of pork-containing meals with chicken-containing meals (the control group) was conducted in sixty participants aged 60 or older in Australia [216]. During the 12-week intervention, twenty-nine participants dropped out. The remaining twelve participants in the chicken-eating group had improved verbal learning ability and memory at six weeks ($P < 0.001$), while the nineteen participants in the pork-consuming group did not have significant changes in cognitive function over the 12 weeks; however, the study quality was low (score three out of ten).

3.4.4 Meta-analysis

There were five studies reporting continuous amounts of meat consumed between cases with cognitive disorders and controls; two reported eating frequency of meats (e.g. pork, beef and mutton) [208,209], and three reported grams per day of meat or red meat [201-203]. In terms of study design and case definition, three were cross-sectional studies with cognitive impairment cases assessed by the mini-mental state examination (MMSE) [203,208,209]; two were case-control studies with cases assessed by the MoCA [201,202] (more details can be seen in Table 3.4).

Due to the considerable heterogeneity ($I^2 = 99\%$), subgroup analysis by outcome measures or study design was applied. As can be seen in the pooled forest plot (Figure 3.3), meat consumption in cases with cognitive impairment did not significantly differ from that in controls either in the overall pooled results (SMD = -0.36, 95%CI: -1.12, 0.39) or in the subgroups using different outcome measures (SMD = -0.04, 95%CI: -0.15, 0.07 for MMSE; SMD = -0.85, 95%CI: -2.93, 1.22 for MoCA). In addition, the subgroup analysis showed that the heterogeneity mainly came from studies with the MoCA measurement. The contour-enhanced funnel plot was asymmetric with studies mostly located in the area of P >10% (Figure 3.4), indicating potential publication bias. The Egger's regression test showed a P value of 0.042 indicating that there were small-study effects in the publication bias.

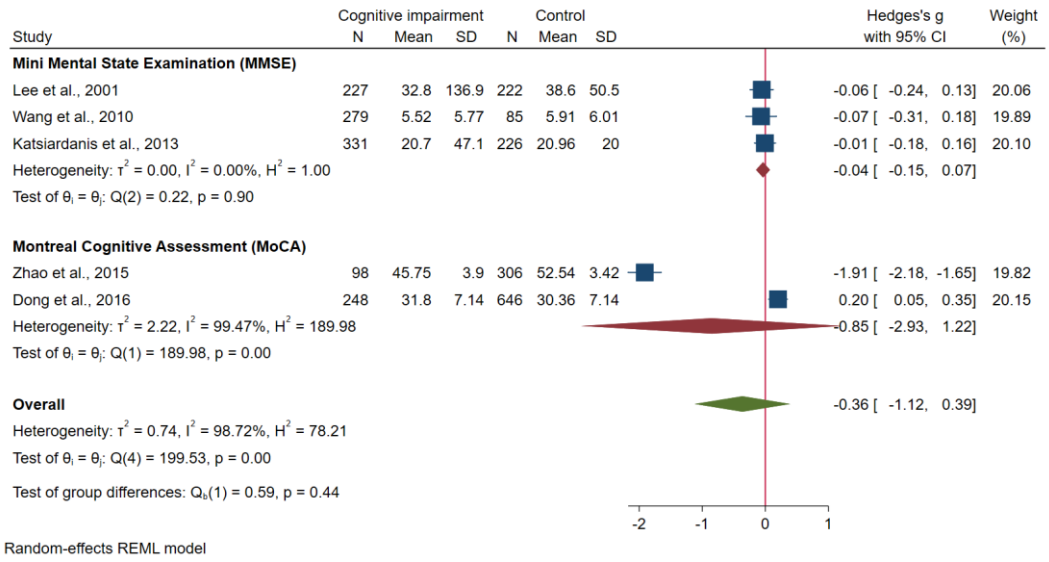


Figure 3.3 Forest plot of studies with continuous amounts of meat consumed between cases with cognitive impairment and controls for meta-analysis

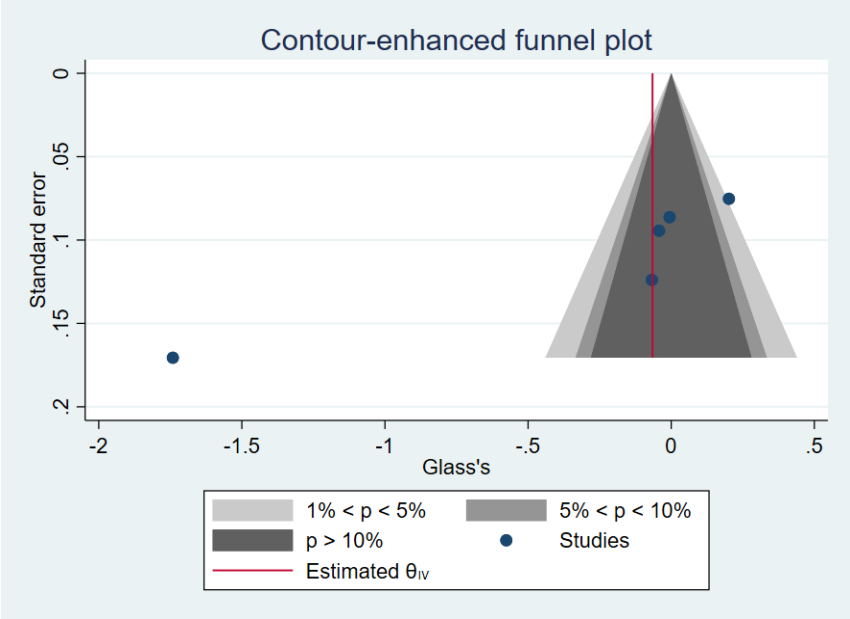


Figure 3.4 Contour-enhanced funnel plot assessing publication bias reporting meat intake levels in cases with cognitive disorders compared to in controls

Table 3.4 specific information of included studies with continuous outcomes for meta-analysis

Author, Year	Study design	Continuous exposure	Case definition	Cases			Controls		
				Num.	Mean	SD	Num.	Mean	SD
Lee et al., 2001	Cross-sectional	Meats (g/d)	Cognitive impairment (MMSE)	227	32.8	136.9	222	38.6	50.5
Wang et al., 2010	Cross-sectional	The frequency of meats (pork, beef, and mutton) (times per week)	Cognitive impairment (MMSE)	279	5.52	5.77	85	5.91	6.01
Katsiardanis et al., 2013	Cross-sectional	The frequency of meats and meat products (times per month)	Cognitive impairment (MMSE)	331	20.7	47.1	226	20.96	20
Zhao et al., 2015	Case-control	Meats (g/d)	Mild cognitive impairment (MoCA)	98	45.75	3.9	306	52.54	3.42
Dong et al., 2016	Case-control	Red meats (g/d)	Mild cognitive impairment (MoCA)	248	31.8	7.14	646	30.36	7.14

Abbreviations: MMSE, mini-mental status examination; MoCA, Montreal Cognitive Assessment.

Table 3.5 Specific information of included studies with categorical outcomes for meta-analysis

Author, Year [Ref]	Study design	Categorized exposure	Case definition	Odds Ratio	Confidence interval 95%		Adjustment factors	statistics
					Lower	Upper		
Baker et al., 1993	Case-control	Weekly or more vs. less than weekly use of beef/pork	Alzheimer's disease	2.74	0.41	30.4	Age within 5 years, sex, race, marital status, status at time of surrogate interview (alive or dead)	Conditional logistic regression
Barberger-Gateau et al., 2002	Cohort	Weekly or more vs. less than weekly use of meat	Alzheimer's disease	0.73	0.25	2.92	Without adjustment	
Barberger-Gateau et al., 2007	Cohort	Weekly or more vs. less than weekly use of meat	Alzheimer's disease	0.53	0.22	1.69	Without adjustment	
Rahman et al., 2007	Cross-sectional	Weekly or more vs. less than weekly use of meat (pork, beef, lamb)	Alzheimer's disease	1.11	0.67	1.84	Adjusted for age, sex, education, and other dietary factors	Multiple logistic regression
Vercambre et al., 2009	Cohort	Consumption>median vs. No consumption of beef, pork, and lamb	Cognitive decline	0.87	0.66	1.15	Adjusted for age, education level, BMI, physical activity, supplement consumption, medical history including	Multiple logistic regression
Chen et al., 2012	Cohort	'Always' vs. 'not always' use of meats	Cognitive decline	0.71	0.56	0.89	Without adjustment	
Zhu et at., 2018	Cohort	Quintile 5 vs. Quintile 1 of consumption of meats	Serious memory impairment	0.95	0.81	1.10	total energy intake, sex, age, marital status, occupation, annual income, education,	Logistic regression

There were seven studies with OR values of those who consumed any-type meat (fish not included) weekly or more (that is, ‘always’) vs less frequently (‘not always’) in cases diagnosed with cognitive disorders compared to controls (Table 3.5); four reported consuming meat (e.g. beef/pork/lamb) weekly or more vs less frequently [191,192,200,205], two reported highest-frequency consumption of meat vs lowest-frequency [193,199], and one reported ‘always’ vs ‘not always’ intake of meat [175]. In terms of study design and case definition, four studies comprising two cohort [191,192], one case-control [200] and one cross-sectional [205] study reported AD as cognitive disorders, while three studies reporting cases diagnosed with cognitive decline were cohort [175,193,199].

The meta-analysis showed that people with cognitive disorders were 15% less likely than controls to consume meat weekly or more (overall pooled OR = 0.85, 95%CI: 0.70, 0.99) (Figure 3.5). The subgroup analysis by outcomes showed that cases diagnosed with cognitive decline had significant odds of consuming meat less frequently than controls (pooled OR = 0.84, 95%CI: 0.69, 1.00), but this was not seen for AD cases (pooled OR=0.87, 95%CI: 0.41, 1.32). Heterogeneity was not detected in the overall group and both subgroups ($P \geq 0.10$). Visual inspection of the contour-enhanced funnel plot shown in Figure 3.6 suggested no presence of publication bias, together with quantitative assessment by Egger's regression test showing no significant presence of small-study effects ($P = 0.63$).

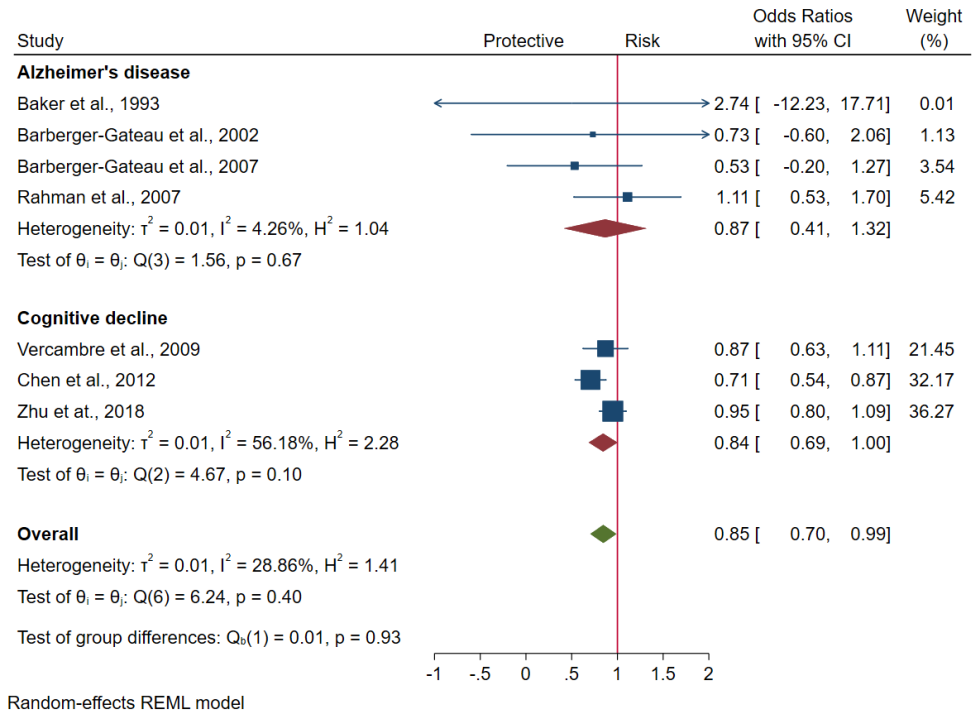


Figure 3.5 Forest plot of studies reporting odds ratios of those who consumed meat (fish not included) weekly or more (‘always’) vs less frequently (‘not always’) in cases diagnosed with cognitive disorders compared to controls

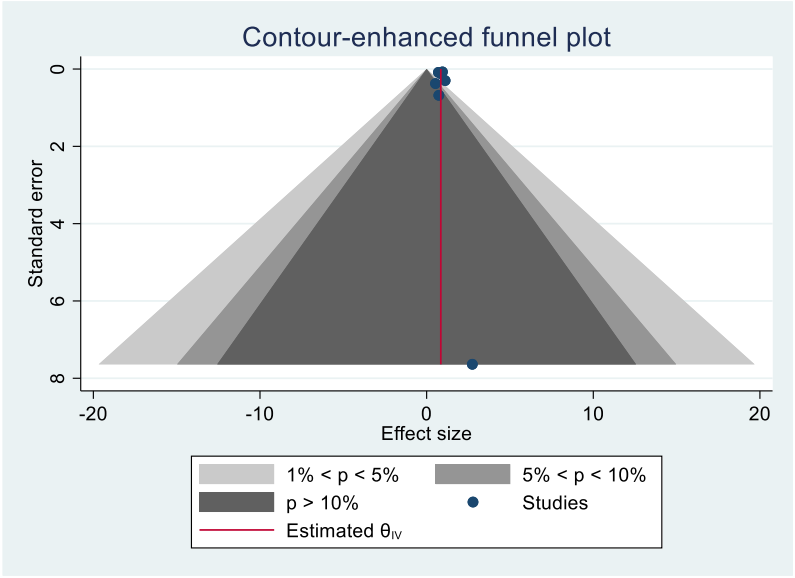


Figure 3.6 Contour-enhanced funnel plot assessing publication bias reporting ORs of meat consumed weekly or more vs less frequently in cases with cognitive disorders compared to in controls

3.5 Discussion

Current existing evidence was reviewed including twenty-eight observational studies and one intervention trial on meat consumption in relation to cognitive function, and cognitive disorders such as cognitive decline and AD. Meta-analysis was only possible on a small number of the studies. The majority of studies included (21/29) showed no statistically significant associations between meat consumption and cognitive outcomes: eight out of twelve cohorts, nine out of thirteen cross-sectional, all three case-control studies, and one intervention trial. Interestingly, only one out of the twelve cohorts showed a negative association, while three observed a protective effect of meat intake. By contrast, four out of thirteen cross-sectional studies suggested that high meat intake was associated with poor cognitive performance, and increased odds of AD and dementia; however, cross-sectional studies are limited in terms of potential reverse causality and selection bias. It indicates the study design may play a role in these associations where selection bias, loss to follow-up, and other biases should be considered when interpreting results.

The meta-analysis of seven studies with OR values showed a potentially protective effect of meat intake weekly or more ('always') on risk of cognitive disorders which mainly existed in the subgroup of cognitive decline, where the subgroup analysis was stratified by outcome types. However, it only involved several relevant studies where data available, and thus the representativeness of the meta-analysis should be taken into consideration. In addition, a meta-analysis of five studies reporting continuous amounts of meat intake showed no difference in meat consumption between cases with cognitive disorders and controls no matter whether stratified by cognition assessment methods (study designs); however, there was considerable heterogeneity and potential publication bias. It should be noted that in this meta-analysis one paper by Zhao et al. (2015) reported very narrow standard deviations of meat intake which appears to be an outlier of the funnel plot. Considering that not all studies retrieved from databases were included in these meta-analyses, together with the publication bias and heterogeneity such as in study designs and confounding factors adjusted for, more cautions should be taken into consideration when evaluating the importance of these findings.

Currently, only a few previous reviews have described associations between meat consumption, cognitive function, and dementia. A systematic review (1999) on diet

and dementia only reported one study showing a positive but weak association between meat consumption and dementia incidence [218]. Other recent reviews have presented similarly mixed effects of meat consumption on cognitive function, brain structure, and risk of AD/dementia [219,220]; however, none of them were systematic reviews and thus no convincing conclusions have been reached so far.

In addition, some interesting studies that were retrieved during the screening process and relevant to the topic but failed to meet the criteria were discussed here. As shown in Table 3.6, two ecological studies examined associations between dietary meat supply and AD prevalence in Japan and other 10 countries (Brazil, Chile, Cuba, Egypt, India, Mongolia, Nigeria, Republic of Korea, Sri Lanka, and the United States), and showed that high meat supply consistently correlated with high AD prevalence especially under a lag of 15–25 years in Japan [171] and five years in other 10 countries [172]. However, two out of three studies taking changes of brain morphology as cognitive outcomes did not show significant associations between meat consumption and brain volume changes or Aβ abnormality which are biomarkers of AD, consistent with findings of the narrative synthesis. Brain morphology assessed by high-tech equipment has been increasingly of interest in relation to cognitive disorders due to high accuracy [221]; however, relevant studies related to meat consumption are rare so far.

Table 3.6 Extra relevant studies with brain morphology as outcomes or with ecological design

Author, Year [Ref]	Study design	Country, Study name	Follow-up, y	Sample size (Female/Male)	Age (Range/ Mean ± SD)	Exposure measures	Outcome measures	Effects
Luciano et al., 2017 [222]	Longitudinal studies	Scotland, The Lothian Birth Cohort of 1936	7	562 (269/293)	72.6 ± 0.72	168-item FFQ	Cortical thickness and volume measures by MRI	No associations between meat intake with TBV (β=-0.282, se=1.496, p=0.850) and GMV (β=-0.509, se=1.236, p=0.681).
Gu et al., 2015 [223]	Cross-sectional studies	USA, WHICAP	—	674 (NR)	80.1 ± 5.6	FFQ	Cortical thickness and volume measures by MRI	Lower meat intake was associated with larger total GMV (β=8.42, p=0.002) and larger TBV (β=12.20, p=0.02).
Vassilaki et al., 2018 [221]	Cross-sectional studies	USA, MCSA	—	278 (123/155)	77.7 ± 7.9	128-item FFQ over past 12 months	β-amyloid (Aβ) PET imaging	No association between red meat consumption and Aβ abnormality (aOR=1.02, 95%CI 0.79-1.31, P=0.88).
Grant, 2014 [171]	Ecological studies	Japan	—	—	≥ 65	Dietary supply data from the FAO of UN	AD prevalence data for Japan came from a review	Meat supply correlated highly with AD prevalence data, with the strongest correlation for a lag of 15–25 years in Japan.
Grant, 2016 [172]	Ecological studies	10 countries	—	—	—	Dietary supply data from the FAO of UN	Age-adjusted AD prevalence data published in peer-reviewed journals	Dietary supply of meat 5 years before AD prevalence had the highest correlations with AD prevalence in Brazil, Chile, Cuba, Egypt, India, Mongolia, Nigeria, Republic of Korea, Sri Lanka, and the United States

Abbreviations: AD, Alzheimer's disease; aOR, adjusted OR; FAO, the Food and Agriculture Organization; FFQ, food frequency questionnaire; GMV, grey matter volume; MCSA, Mayo Clinic Study of Aging; MRI, Magnetic Resonance Imaging; NR, not reported; PET, Positron Emission Tomography; TBV, total brain volume; UN, United Nations; WHICAP, the Washington Heights/Hamilton Heights Inwood Columbia Aging Project.

3.5.1 Possible mechanisms

In general, the associations between meat consumption and cognitive disorders remain debatable with inconsistent findings and unclear potential mechanisms. The specific mechanisms underlying this association remain undetermined partly because it is particularly challenging to isolate the effect of red meat and processed meat from complex dietary patterns. Here, several possible mechanisms were hypothesized that might explain the mixed effects of consumption of meat on cognitive function and dementia.

Firstly, it may be due to the complexity of nutrient composition that meat exerts mixed effects. Meat, especially lean meat, is high in protein and essential amino acids which are important nutrients for humans. Van de Rest and colleagues systematically reviewed the role of dietary protein and amino acids in cognitive function among the elderly, and revealed that six out of eight observational studies demonstrated a protective effect of dietary protein and a key role of tryptophan and tyrosine in relation to cognitive function [224]. However, meat contains much saturated fat and cholesterol which are risk factors for hypertension related to an increased risk of AD [225]. In addition, there is a hypothesis that an increased risk of cognitive impairment in relation to red meat consumption could be due to the copper toxicity, where copper can be absorbed easier from meat compared to vegetables and it may penetrate the blood/brain barrier for neurotoxicity [226]. Increased copper absorption from increased meat intake together with increased dietary fat may result in over-consumption of copper-2 which may play a key role in the current AD epidemic [227]. On the contrary, heme accounting for 95% of functional iron in humans is concentrated in red meat; heme deficiency is potentially associated with AD incidence [228], indicating that low intake of red meat may be related to an increased risk of Alzheimer's disease.

Secondly, meat consumption may exert its effects on cognitive function or dementia via functional alterations to brain structures assessed by brain imaging biomarkers. Brain volume changes and β-amyloid (Aβ) deposition, as imaging biomarkers, were found to be associated with cognitive impairment and AD measured by magnetic resonance imaging and Positron emission tomography imaging respectively [229-231]. Staubo et al. observed an inverse association of red meat intake with cortical thickness among older adults in a cross-sectional study in the United States [232].

Another cross-sectional study showed that lower meat intake was related to larger grey matter volume and total brain volume [223], indicating higher meat intake may be related to reduced brain sizes and further affect cognitive function in an indirect way. However, Luciano et al. found no associations of meat intakes with cortical thickness and volume in the Scottish Lothian birth cohort with following up for 7 years [222]. In addition, the Mayo clinic study of aging (MCSA) observed no associations between meat consumption and Aβ abnormality among 278 older participants [221]. Therefore, whether meat intake is in relation to changes of brain volume or Aβ deposit remains unclear.

Other potential mechanisms may include meat preparation using different cooking methods, where some meat cooking methods may produce harmful by-products. For example, high-temperature cooking methods such as frying and BBQ/grilling may generate benzo[α]pyrene (BαP) during the incomplete oxidation process of protein which is found to be associated with detrimental changes of neurobehavioral function [233,234]. However, these associations are weak and unconvincing at present and more evidence is required.

3.5.2 Strengths and limitations

There are several limitations that need to be taken into consideration when interpreting the findings. Firstly, due to challenges in isolating the specific contributing role of dietary factors, this review did not include dietary patterns rich in meat (i.e., western diet) or low-meat intake (i.e., vegetarians). However, these studies are relevant, for example, Granic reported a dietary pattern high in red meat was associated with poor cognitive function [173]. At the same time, relevant studies always involve various aspects of diet such as foods, nutrients, dietary patterns, rather than specific in meat intake, where some negative or insignificant data often remain unpublished or unreported. In addition, relevant studies written in other languages were not included in this review. All these limitations could have resulted in potential publication bias. Secondly, different data types and statistical methods impede the combination of evidence in a quantitative method (e.g., meta-analysis). Here, of the twenty-nine included studies, three reported hazard ratios, ten odds ratios, eleven β-coefficients and five used other statistical methods. Thirdly, studies included in this review mainly consist of observational studies which have limits in interpretation of the causality between meat consumption and cognitive

disorders.

Another limitation of this review is the considerable heterogeneity of studies included. The differences in cognition measures and diagnostic criteria related to dementia and AD could ultimately influence the homogeneity. For example, some studies used the Diagnostic and Statistical Manual of Mental Disorders (DSM), third revised version (that is DSM-III-R), to evaluate dementia or AD, while others used the DSM-IV criteria or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria, raising issues of heterogeneity. It is important to note various cut-offs, specificity, and sensitivity in different cognitive assessment tools (i.e., MMSE, MoCA). In addition, the use of various cognitive tests to diagnose dementia or AD should be interpreted with caution, since these tests are not gold standard diagnostic criteria. The heterogeneity was not only in definitions of cognitive disorders, but also in measures of meat consumption (e.g., FFQ, 24h recall, or unvalidated dietary questionnaires).

Despite many limitations in this review, some strengths should be noted. Firstly, to the best of my knowledge, this study is the first systematic review to specifically explore associations of meat intake with cognitive function, AD, and other forms of dementia. Most recent reviews and meta-analyses assessed effects of specific dietary patterns such as Mediterranean diet, Dietary Approach to Stop Hypertension (DASH) diet on cognition or dementia [112,235-237]; these patterns represent broad nutritional profiles. By contrast, this review focused on the consumption of meat. In addition, this systematic review covered not only Alzheimer’s disease but cognitive function and other forms of dementia. The development of AD is a long-lasting process with a chronic, yet progressive decline of cognitive function. It is not clear at which stage of disease development diet in particular meat intake may be involved.

3.5.3 Conclusions

Overall, twenty-nine studies reported an individual association of meat intake with cognitive function, AD, and other forms of dementia showing inconsistent findings, and most of them could not be combined in a meta-analysis. The majority of studies included showed no strong associations between meat intake and cognitive disorders. Meta-analysis of seven studies suggested that meat intake was protective

against cognitive disorders; however, this was limited with representativeness and potential publication bias.

Based on the present systematic review, there are numerous challenges with regards to establishing a conclusive association and providing dietary recommendations on meat to the public. The heterogeneity of study designs, exposure and outcome measures calls for additional research on the association between meat intake and cognitive disorders. Further studies are necessary to clearly isolate the contributions of meat consumption with well-designed study types. Since randomized controlled trials would be extremely time-consuming and expensive to conduct, use of existing large-scale and long-term cohort studies with clearer definitions of meat exposures and cognitive health outcomes may be highly informative.

CHAPTER IV

4. The associations of foods, nutrient intakes, and dietary patterns in midlife with cognitive function and dementia in the UK Women's Cohort Study

4.1 Summary

4.1.1 Highlights

- No significant associations were indicated between dietary factors in midlife including food consumption, energy-adjusted nutrient intakes, and dietary patterns, with reaction ability or dementia mortality in the UK Women's Cohort Study.

4.1.2 Abstract

Background: Associations between diet and some cognitive function in the elderly have been documented; however, evidence on the association between midlife diet, reaction ability and dementia risk remains poorly explored.

Methods: The UK Women's Cohort Study (UKWCS) collected dietary information from 35,372 middle-aged women (35–69, 52±9.4 years old) using a validated 217-item food frequency questionnaire in 1995–98. Two sub-studies were conducted separately within the UKWCS. The first one is the reaction-time sub-study. In 2010–11, a sub-group of 664 participants completed online reaction time tests including simple reaction time and choice reaction time; 503 participants were eligible for analysis. Participants were grouped into fast and slow groups by their median reaction times. The intakes of particular foods, nutrients, adherence to Mediterranean diet (MeDi), and other dietary patterns, as well as cooking methods (roasting/baking, frying, and BBQ/grilling) were explored in relation to reaction times. The second sub-study explored risk of dementia mortality in relation to the dietary factors similar as the first sub-study. The UKWCS has 283 dementia death cases accruing up to January 2018. The associations between diet and dementia mortality were fitted in Cox regression models.

Results: In the reaction-time sub-study, no significant associations between reaction

times and investigated foods, nutrients, the MeDi or other eating patterns were observed in adjusted models. However, consumers of fried vegetables were associated with higher odds of having slower simple reaction time (adjusted OR=1.64, 95% CI: 1.12, 2.39, *P*=0.010) compared with non-consumers of fried vegetables. In the dementia cases of death sub-study, cases dying of dementia were much older (66 vs. 52 years of mean age), had lower educational attainment and a lower proportion who were married or living as married than controls. Regression results showed that no significant associations were observed between investigated dietary factors and risk of dementia mortality.

Conclusions: The findings suggest that some foods, nutrient intakes, adherence to the MeDi, and other dietary patterns were not associated with reaction ability or dementia mortality in the UKWCS. However, limitations should be noted in both sub-studies, and further research is needed in other large cohort studies.

4.2 The UK Women's Cohort Study (UKWCS)

The UK Women's Cohort Study (UKWCS) [238] was initiated in 1995 to explore potential associations between diet and chronic diseases, and recruited 35,372 women aged 35–69 years at the baseline data collection (1995 to 1998, Figure 4.1). At recruitment, the baseline survey collected food frequency questionnaires (FFQs), lifestyle behaviours, demographic, and anthropometric information. The dataset in the UKWCS comprises a wide range of variables including food consumption, anthropometric measures, socioeconomic status, lifetime lifestyle and health outcomes. The phase II survey was conducted in the cohort collecting a one-day activity diary, a four-day diet diary, cooking styles, and other lifestyle as well as demographic information with 13,406 women's responses in 1999 to 2002. A reaction time sub-study was conducted among women who have completed the phase II data collection in the UKWCS. The whole participants were updated with death registration data. Detailed information can be seen in each sub-study below.

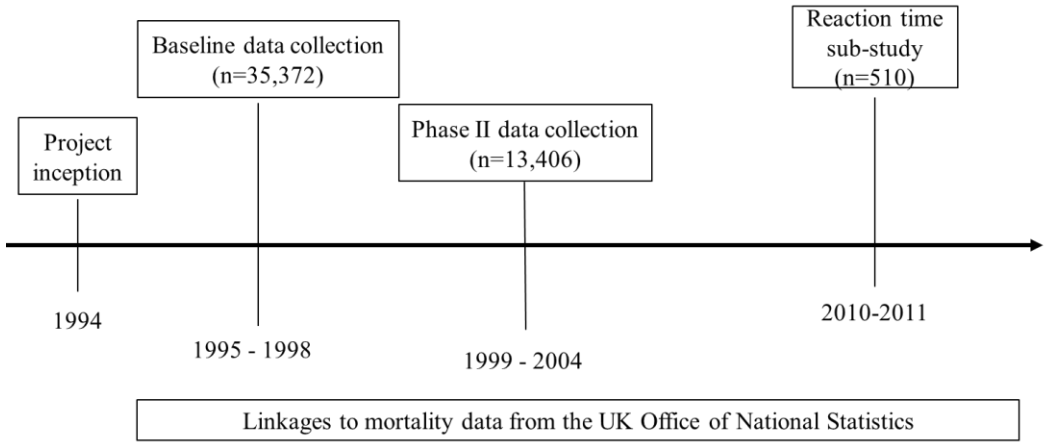


Figure 4.1 Timeline of data collection in UK Women's Cohort Study in relation to sub-studies in the thesis

4.2.1 Ethical approval

Ethical approval was granted from the National Research Ethics Service (NRES) Committee for Yorkshire & the Humber – Leeds East (Ref: 15/YH/0027) at the cohort's initiation in 1993; now covered by Health Research Authority REC Reference: 17/YH/0144. No further ethical approval is required for these sub-studies.

4.2.2 Calculation of nutrient intakes and classification of food groups

Dietary information at baseline was obtained from self-administered FFQs with 217 British food items that was developed based on the FFQ used in the UK for the European Prospective Investigation into Cancer and Nutrition (EPIC) study [239]. The baseline FFQ was compared against four-day weighed food diaries and a second FFQ collected at the same time as the diary, on 283 women three years after the baseline. Whilst accepting that each tool type is measuring different aspects of diet, correlations between the two dietary assessment methods were comparable to those found in other studies; for example, the correlation coefficients between the FFQ and the four-day weighed food diaries were 0.39 for carbohydrate, 0.35 for fat, 0.43 for calcium and 0.62 for vitamin C [240,241]. An example of the FFQs used in the UKWCS can be seen in Appendix C. The food intake frequency was converted into daily portions for each item (Table 4.1), followed by calculation for weight of each food consumed per day (gram/day, g/d) based on standard portion weights from the Food Standards Agency portion sizes book [242]. For any missing food frequency information, it was assumed that the missing item had not been

consumed.

Table 4.1 Transformation from intake frequencies to portion servings per day

Frequency of intake	Portion servings per day (formula)
Never	0
Less than once a month	0.02 (0.5/30)
1-3 per month	0.07 (2.0/30)
Once a week	0.14 (1.0/7)
2-4 per week	0.40 (3.0/7)
5-6 per week	0.80 (5.5/7)
Once per day	1.00 (1.0/1)
2-3 per day	2.50 (2.5/1)
4-5 per day	4.50 (4.5/1)
6+ per day	6.00 (6.0/1)

Classification of food groups and derivation of nutrient intakes were detailed in previous studies [243,244]. A total of 217 food items was classified into 20 main food groups detailed in the A-Table 4.1 of Appendix D: 1) Wholegrain products & cereals; 2) Refined grain products; 3) Plain Potatoes; 4) Potatoes with added fat; 5) Low-fat dairy products; 6) High-fat dairy products; 7) Low-fat dressing, spread, sauce; 8) High-fat dressing, spread, sauce; 9) Eggs & Egg dishes; 10) Soybean products; 11) Pulses & Legumes; 12) Fish & fish dishes; 13) Red & processed meat, offal; 14) Poultry; 15) Vegetables; 16) Fruits; 17) Nuts & Seeds; 18) Refreshments & snacks; 19) Alcohol; 20) Beverages; those items were combined based on similar food types and nutrient profile (e.g. fat or fiber content).

Energy and nutrient intakes of each food item were determined by multiplying the consumed food weight by the standard nutrient composition of foods derived from McCance & Widdowson's the Composition of Foods (5th Edition) [245]. Then energy and nutrient intakes per day were calculated by summing nutrient contents of each food item for each participant. In this thesis, nutrients provided by supplements were not included in the nutritional analysis. Nutrient intakes were adjusted for total energy using the nutrient density method [246] (for protein, carbohydrates, and fat, the percentage of total energy being provided by each energy containing nutrients; for other nutrients or foods, the ratio of selected nutrient intake to per 1000 kcal (4186 kJ) of total energy intake). Each energy-adjusted intake of foods and nutrients was entered in a multiple logistic regression model with total energy intake as a covariate using the multivariate nutrient density method recommended by Willett *et al.* [246]. To obtain interpretable results, the ten times

unit intakes of foods and some energy-adjusted nutrients were used in the regression models.

4.2.3 Dietary pattern identification

In this chapter, two approaches were used to derive dietary patterns, *a priori* method (Mediterranean diet and customized eating patterns) and *a posteriori* method (principal component analysis) as detailed in Chapter 2.

4.2.3.1 Mediterranean diet

To quantify adherence to Mediterranean diet (MeDi), a variable of MeDi score was created based on the 217-item FFQ. The MeDi score was derived from a modified 10-point version of the MeDi covering 10 food/nutrient components consumed in grams per day [247,248]. Of the ten components, six traditionally consumed in the MeDi (vegetables, legumes, fruits and nuts, cereals, fish, and fatty acid ratio of monounsaturated plus polyunsaturated fatty acids to saturated fatty acids, namely MUFA+PUFA: SFA), considered beneficial were assigned 1 if consumed at or above the median. Another three foods (meat, poultry, and dairy) considered detrimental were given a score of 1 for consumption below the median. Regarding alcohol, a score of 1 was given to women who had intakes of between 5 and 25 g per day. The specific values of cut-points in each MeDi component in the two sub-studies were shown in Table 4.2. Thus, the total MeDi score ranges from a minimal adherence score of 0 to a maximal adherence score of 10, with higher scores indicating greater dietary adherence. Further the total MeDi score was divided into three groups: scores 0–3 (Low adherence), 4–6 (Moderate adherence), and 7–10 (High adherence).

Table 4.2 The specific values of cut-points in the two sub-studies

	Indicator values			
	The reaction-time sub-study (n=503)		**The dementia cases of death sub-study (n=35,372)**	
MeDi components	**1**	**0**	**1**	**0**
Vegetables (g/day)	≥280	<280	≥275	<275
Legumes (g/day)	≥32	<32	≥25	<25
Fruit & nuts (g/day)	≥274	<274	≥289	<289
Cereals (g/day)	≥242	<242	≥209	<209
Fish (g/day)	≥21	<21	≥27	<27
MUFA+PUFA: SFA[a]	≥2	<2	≥1	<1
Meat (g/day)	<28	≥28	<48	≥48
Poultry (g/day)	<11	≥11	<11	≥11

Dairy (g/day)	<95	≥95	<110	≥110
Alcohol (g/day)	5–25	<5 or >25	5–25	<5 or >25

[a] Fatty acid ratio of monounsaturated plus polyunsaturated fatty acids to saturated fatty acids

4.2.3.2 Customized eating patterns

To investigate the associations of meat and fish with cognitive function and dementia risk, four commonly recognized eating patterns were defined based on frequencies of consumed meat and fish items on the FFQ: red-meat eaters, poultry eaters, fish eaters and meat/fish non-eaters. Red-meat eaters consumed red meat (including processed and unprocessed red meat such as pork, beef, lamb/mutton, offal, and other livestock) at least once a week no matter how much poultry and fish were consumed. Poultry eaters consumed poultry (such as chicken, duck, goose) at least once a week and may eat fish but not red meat, while fish eaters consumed fish or seafood at least once a week but not poultry or red meat. Meat/fish non-eaters are participants who consumed any kind of meat or fish less than once a week.

4.2.3.3 Dietary patterns from *a posteriori* method

To further summarise the eating patterns within the sub-study, the principal component analysis (PCA), a statistical method that groups dietary variables, was applied to derive dietary patterns based on the 20 collated food groups from the 217-item FFQ. The Kaiser-Meyer-Olkin measure of sampling adequacy (0.65) and Bartlett's test of sphericity (P <0.001) were applied to confirm PCA to be an appropriate dimension reduction method [249]. Eigen values (>1.0), as well as their visualised scree plot, and percentages explaining the total variance (50%) were considered for determining the number of retained components. Where possible, orthogonal (varimax method) rotation was used to simplify structure, obtain uncorrelated factors, and interpret results clearly. The loading factor describes the contribution of the food or food group to the dietary pattern, with a higher loading indicating a greater contribution. Foods or food groups that had absolute rotated factor loading scores ≥0.2 were referred to as 'characteristic foods' and used to define dietary patterns [250]. Dietary pattern scores were calculated for all participants by multiplying factor loadings by standardised intakes of corresponding food/food groups and then summing. The mean value of pattern scores for each participant was zero with positive and negative scores representing

high and low adherence to each dietary pattern respectively [251]. All retained components were regressed in one at a time in multivariate models for mutual adjustment in this study.

4.2.4 Covariate assessments

Baseline socio-demographic information, including age, ethnicity (white, Asian, African, and others), educational level (no qualifications, O-level or equivalent, A-level or equivalent, and university degree or above), marital status (married or living as married, separated or divorced, single or widowed), physical activity (hours/day), smoking status (current, former, and never) and other factors, was collected by self-report. Body mass index (BMI) was calculated from self-reported height and weight by the formula of "weight/height^2 (kg/m^2)". Socio-economic status (SES) was derived from the United Kingdom National Statistics-Socio-Economic Classification (NS-SEC), where participants are classified into three categories (routine/manual, intermediate, or managerial/professional) [252]. Due to overlapping properties among socioeconomic indicators (education, social class, income, or employment) [253], only SES was used as the adjustment factor in this study. Physical activity was assessed as self-reported time spent on activities vigorous enough to cause sweating or a faster heartbeat (hours/day). In addition, sleep duration (hours/day) was the weighted mean value calculated from self-reported sleep durations of weekdays and weekends.

A directed acyclic graph (DAG) was plotted using the online DAGitty tool (http://www.dagitty.net) to determine the minimally sufficient set of confounding adjustments for the exposure-outcome relationship [254]. Confounding factors, that are potentially related to the exposure (diet) and the outcome (cognitive function/dementia), were considered in the DAG. Relationships among the exposure, the outcome, and potential confounding factors were built based on *a priori* knowledge from the literature. As shown in Figure 4.2, factors that are associated with the exposure as well as the outcome, were automatically labelled as pink ovals if they are not in the middle biological path of the exposure to the outcome; or were automatically labelled as blue ovals if they are in the middle biological path of the exposure to the outcome. Factors labelled as pink ovals were included in the minimal adjustment set. The minimally sufficient adjustment set was age, ethnicity, SES, marital status, physical activity, sleep duration, smoking

status, and alcohol consumption. BMI and total energy intake were additionally adjusted for. The amount of energy intake may be one of determinants of some certain diseases; even it is not a direct cause, the effects of specific dietary factors may be distorted or confounded by total energy intake [246]. The BMI can reflect the between-person variation in body size which was found to be associated with dementia risk [255]. Also, it is a common practice to adjust for BMI and total energy intake in nutritional studies [246,256,257].

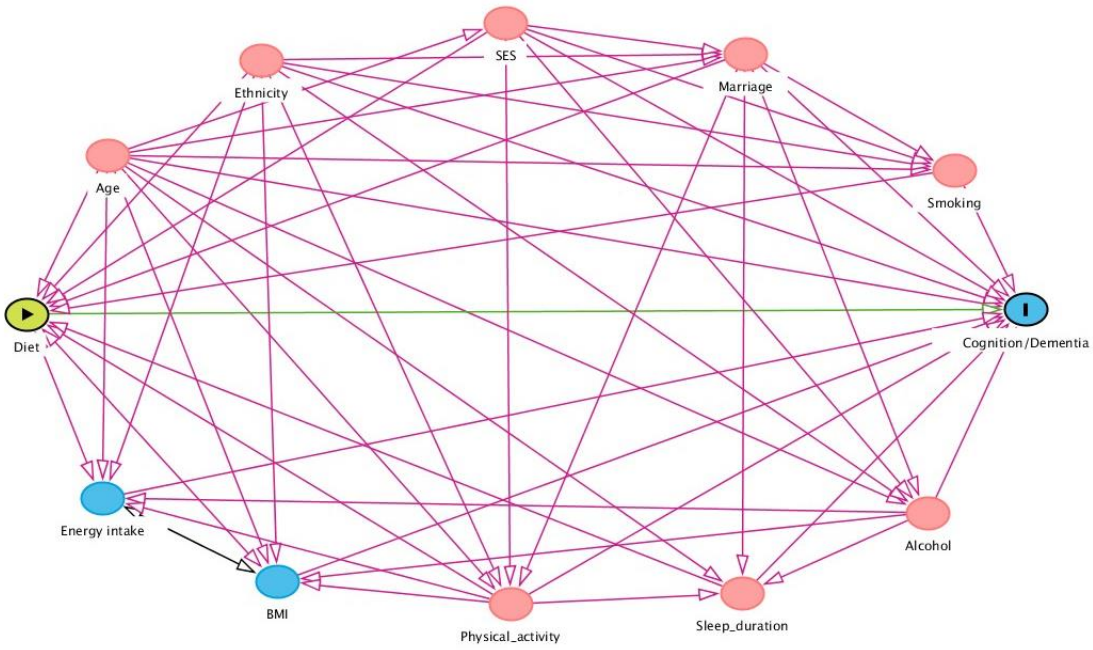


Figure 4.2 Directed acyclic graph (DAG) showing the relationships among the exposure, the outcome, and the covariates.

The exposure (Diet) is represented by the green oval with the triangle, while the outcome (Cognition/dementia) is represented by the blue oval with the line. Variables represent as pink ovals are ancestors of exposure and outcome while variables represent as blue ovals (BMI, Energy intake) are ancestors only of the outcome. Pink lines are biasing paths and the green line between the exposure and outcome is the causal path of interest. SES, social economic status; BMI, body mass index.

4.2.5 Statistics

Given the small percentage of missing data (≤3% for all the covariates), covariates with missing values were imputed with the median for continuous variables, or with the most common category for categorical variables [258]. A significance level of P <0.01 was used due to the potential for multiple testing in regression models [259]. All analyses were conducted using Stata version 16.1 (StataCorp LLC, College

Station, Texas).

Characteristics such as demographics and dietary consumption were summarized. For continuous variables the mean and standard deviation (Mean $\pm$ SD) were displayed, while for categorical variables characteristics were presented as percentages (%). The Student's t-test was used to compare normally distributed continuous variables, while the Wilcoxon rank-sum test and Chi-square test were used to compare non-normally distributed continuous and categorical variables respectively.

4.3 The reaction-time (RT) sub-study

4.3.1 Participants

The sample size to investigate the association between diet and reaction ability in the UKWCS, was estimated using the mean choice reaction time (CRT). A sample size of 530 women was computed from the estimation of the mean CRT using comparison of one mean to a reference value with the two-sided significance level of 0.05, marginal error of 15 milliseconds (ms), and power of 0.8. This estimation was calculated using a reference mean CRT of 628 ms (SD: 123 ms) from a British study in which simple and choice reaction times were tested using the Deary-Liewald reaction time task for residents aged between 61 and 80 in the City of Edinburgh [47]. There were no previous studies of diet and reaction time on which to base a sample size calculation.

In 2010/11, a subset of 664 women was involved in the pre-designed online reaction-time tests. Among them, 510 women had complete dietary records and cognitive testing results. Exclusion criteria were applied among individuals with unlikely fast reaction times (simple reaction time <200ms; choice reaction time <250ms) prior to analyses as these were likely to represent accidental screen presses, and was adapted from a previous study [260]. Participants with reported energy intake outside 1% of the population distribution (<500 kcal/day or 25 MJ/day and >6,000 kcal/day or 0.2 MJ/day) were excluded following previous studies [261]. Participants with a stroke history were also excluded because stroke could significantly impair cognitive function including the reaction time ability [262]. Of 510 women with complete records, one participant with an unlikely fast choice reaction time (64 ms), two individuals with extremely high energy intake (6293

kcal/day that is 26 MJ/day, and 7780 kcal/day that is 33 MJ/day), and four participants with self-reported stroke history were excluded. Therefore, 503 women were considered eligible for analysis (Flowchart, see Figure 4.3).

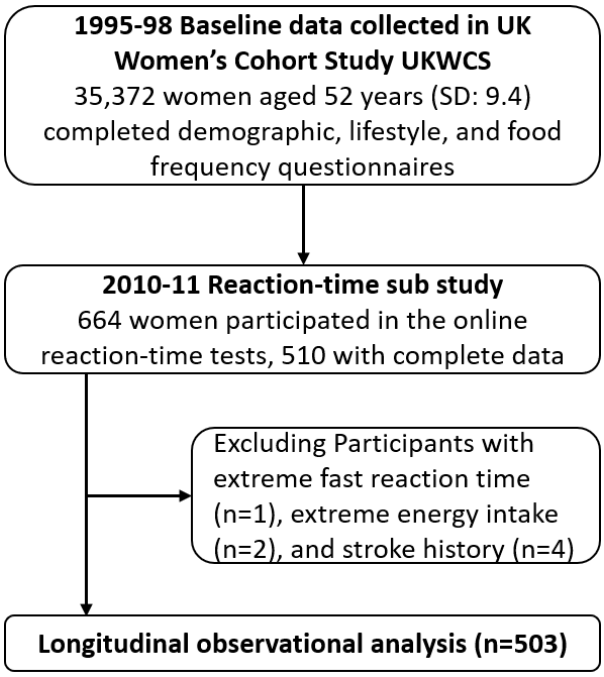


Figure 4.3 Flowchart of the reaction-time sub-study data collection and exclusion criteria within the UK Women's Cohort Study (UKWCS)

4.3.2 Reaction-time tests

The web-based cognitive measurement tasks (www.uk-wcs.co.uk) test participants' reaction ability including simple reaction time and choice reaction time described previously [47,263]. Each test was recorded as a code in the questionnaire which scrambled their reaction time scores. For example, W237P29GL824A1912S represents a simple reaction time mean of 237ms (SD =29) and a choice reaction time mean of 824ms (SD =191), with two errors. The mean values of reaction time were analysed as the outcome to reflect the participants' cognitive ability. Due to skewed distributions, the two reaction time variables were dichotomously categorized taking the median values as cut points, where the slow group was defined as less than the median and the fast group equal to or above the median. The median was used here to reduce the impact of outliers and skewed data. In analyses, the fast groups were treated as the reference group while the slow groups were treated as the case group, and logistic regression was conducted to identify

potential associations between diet and reaction ability.

4.3.2.1 Simple Reaction Time

The simple reaction time (SRT) task requires participants to respond to a letter appearing on the screen. A letter “Y” appears irregularly on the screen and participants should press the “Y” key on the keyboard as soon as it appears for 20 trials (Figure 4.4). At the end of the task, the mean (unit: ms) and standard deviation (SD) of SRT are calculated automatically and appear on the screen as a code.

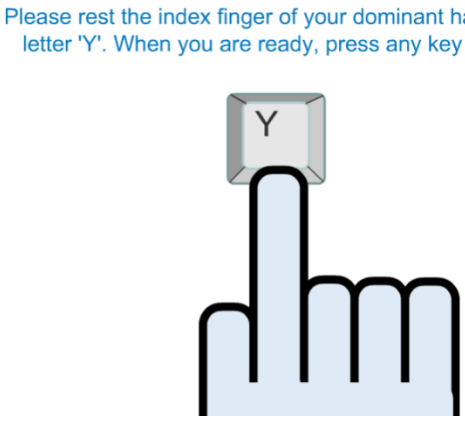


Figure 4.4 Illustration of the Simple Reaction Time task

4.3.2.2 Choice Reaction Time

The choice reaction time (CRT) task requires participants to respond to one of four numbers (5, 6, 7 or 8) appearing randomly on a screen by pressing the corresponding number on the keyboard as soon as it appears for 40 trials (Figure 4.5). At the end of the task, the mean (unit: ms) and standard deviation (SD) of CRT are calculated automatically and appear on the screen as a code ending with the error times.

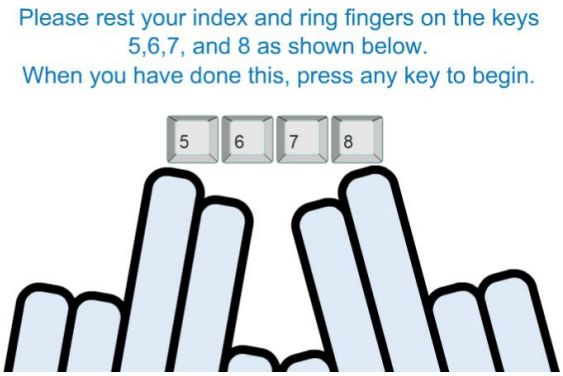


Figure 4.5 Illustration of the Choice Reaction Time task

4.3.3 Cooking methods and doneness of foods

In the phase II of the UKWCS, cooking methods of several common foods including meat, fish, vegetables, and potatoes, have been investigated by asking 'How often do you eat foods cooked by the following methods?' The specific cooking methods included roasting/baking, frying, and BBQ/grilling, and the consumption frequencies ranged from never to more than once a day containing eight categories. Participants with the frequencies of never and less than once a month were treated as non-consumers of specific cooked food item, while others with the frequencies of once a month or more were considered as consumers of that food item. The consumption frequency of each cooking method was treated as a dichotomous variable: non-consumers and consumers. This was included in the regression models with non-consumers as the reference group.

Further, the doneness of several common food and food groups were surveyed using the question 'On average how well cooked do you like the following foods?'. The answers include 'Never eat this food', 'Lightly cooked, very pale brown', 'Medium slightly browned', 'Medium to well done, mid-dark brown', 'Very well done, dark brown & crispy', which were scaled as '0–4'. Through summing each food category, a score was obtained to reflect the degree of food doneness eaten by participants which was used as a continuous variable in regression models.

4.3.4 Regression models

Generalized linear models were fitted to identify the associations between dietary consumption and reaction ability. Logistic regression analyses were conducted for categorical dependent variables such as slow simple reaction time. Unadjusted model and adjusted model were conducted separately, where the adjustment set of potential confounding factors was detailed above.

4.3.5 Results from the reaction time sub-study

4.3.5.1 Baseline characteristics of participants among the fast group and the slow group of two reaction times

The baseline characteristics of women who participated in the reaction-time sub-study are summarized in Table 4.3. Participants who took part in reaction time tests had a mean age of 62 years old (SD =6.6). Women in slow groups were significantly older and had lower educational levels than women in fast groups (64 vs 61 years

old for both SRT and CRT; 35% vs 40% university degree for SRT; 34% vs 41% university degree for CRT). Among the women, 97% were of White ethnicity, 83% were married or living as married, 74% had a higher level of social economic status (professional or managerial), 67% were non-smokers. The participants had a mean BMI of 23.5 kg/m^2, a mean sleep duration of 7.6 hours, and 0.25 hours per day of vigorous activities. With regards to alcohol consumption, 60% of the women drank less than once a day but more than once a month, while 20% consumed alcohol once a day or more and for the remaining 20% consumption was once a month or less.

4.3.5.2 Comparisons of main foods and nutrient intakes between women in fast groups and slow groups

As shown in Table 4.4, the daily energy intake was 2334 kcal (SD: 645 kcal/day) which was slightly higher than the average requirements of energy for 45+ year-old British adults or elderly women (1840–2103 kcal/day) [264]. The daily protein intake of the 503 women was 87 g/day (SD: 26 g/day), while the daily fat intake was 85 g/day (SD: 30 g/day) including 30±13 g/day of saturated fat. The energy-unadjusted intakes of most nutrients were similar between women in fast groups and slow groups. Women who had a fast choice reaction time consumed slightly more polyunsaturated fatty acids than women who had a slow choice reaction time (17 g/day for the fast CRT group vs. 16 g/day the slow CRT group); however, this difference was removed following energy adjustment. Overall, there was no statistically significant difference in daily consumption of some common foods, and total energy intake, as well as energy-adjusted nutrient intakes between fast groups and slow groups for both SRT and CRT (Table 4.4).

4.3.5.3 Associations of main foods, energy-adjusted nutrient intakes, and cooking methods with reaction times

Taking the median reaction time as the cut point, the fast group whose reaction time was less than the median was treated as the reference group, while the slow group whose reaction time was more than the median as the case group. The logistic regression results with or without adjustment for age, ethnicity, marital status, SES, BMI, physical activity, smoking status, alcohol consumption, sleep duration, and total energy intake, were summarized in Table 4.5 and Table 4.6. Multivariate

logistic regression results show that associations between reaction ability and main foods as well as energy-adjusted nutrient intakes were not statistically significant (Table 4.5). As shown in Table 4.6, consumers of fried vegetables were 64% more likely to be in the slow SRT group (adjusted OR = 1.64, 95% CI: 1.12, 2.39; *P* =0.010) with adjustment for confounding factors. However, the consumption of fish or vegetables cooked by any of these three methods did not change the risk of being in slow CRT groups. In addition, neither meat nor potatoes consumption cooked by any of these three methods changed the likelihood of being in slow groups for both SRT and CRT. As shown in the bottom of Table 4.6, the doneness of foods consumed did not have any associations with the SRT or CRT.

4.3.5.4 Adherence to Mediterranean diet, eating patterns and their associations with reaction times

Distribution of adherence to Mediterranean diet (MeDi) and its association with reaction ability are summarized in Table 4.7. Most women included in this analysis had moderate adherence to the MeDi (53%) and the percentage distribution of adherence was similar between fast groups and slow groups for SRT and CRT. Logistic regression results show that SRT or CRT was not associated with adherence to the MeDi either in unadjusted or adjusted models. With regards to the eating patterns, 23% were meat/fish non-eaters, 15% were fish-eaters, 3% were poultry-eaters, and 60% were red-meat eaters of the 503 participants. These percentages were similar between women in fast groups and slow groups (Table 4.8). From the logistic regression results we can see that compared with meat/fish non-eaters, not any of the fish eaters, poultry eaters, or red-meat eaters showed significant odds of being in slow reaction time groups.

4.3.5.5 Analyses of dietary patterns derived from the principal component analysis

The eigenvalues of the first seven components were more than 1. Considering there is no rapid decline between the sixth component and the seventh component in the scree plot of eigenvalues (Figure 4.6), and the percentage of total variance explained has reached 50% by the first six components (50.7%), so the first six components were retained in this sub-study (Table 4.9). The first principal component (PC) featured high factor loadings for red & processed meat, offal, poultry, and potatoes with added fat alongside intake of fish, snacks and eggs which was labelled as the

"Western pattern" (12.3% variance). The second PC, defined as the "Prudent pattern" (11.4% variance), had high factor loadings of vegetables, legumes & pulses, fruits, whole grains & cereals, and low-fat spread alongside intake of plain potatoes, eggs, fish, and low-fat dairy. The third PC was characterized by high-fat foods such as high-fat spread, high-fat dairy, nuts & seeds, snacks, and refined-grain products, and therefore was labelled as the "High-fat pattern" (8.6% variance). The fourth PC was defined as the "Whole dairy & fish" (6.8% variance) due to its main factor loading on high-fat dairy, fish & fish dishes, while the fifth PC was labelled as the "More-alcohol type" (6.2% variance) due to its main factor loading on the alcohol group. The sixth PC was characterized by high factor loadings in Eggs & Egg dishes, whole grain products, and therefore was labelled as the "Egg and grain type" (5.5% variance). The logistic regression results showed that none of these six dietary patterns were significantly associated with the odds of being in the slow groups (Table 4.10).

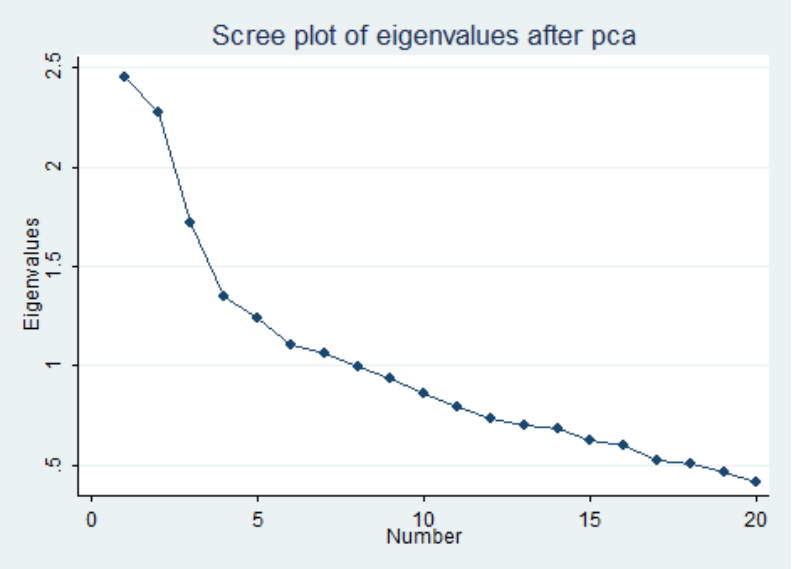


Figure 4.6 The scree plot of Principal Component Analysis on food groups

Table 4.3 Demographic characteristics of participants between fast groups and slow groups for simple and choice reaction times

		Simple Reaction Time			Choice Reaction Time			Total
		Fast group (N=252)	Slow group (N=251)	*P*	Fast group (N=252)	Slow group (N=251)	*P*	(N=503)
Age (years)	Mean (SD)	61 (5.9)	64 (7.1)	<0.001	61 (5.7)	64 (7.2)	<0.001	62 (6.6)
Ethnicity (%)	white	98.4	96.4	0.114	98.4	96.4	0.200	97.4
	Asian	0.4	0.0		0.0	0.4		0.2
	other	1.2	3.6		1.6	3.2		2.4
Educational Level (%)	No qualifications	2.8	9.9	0.009	3.2	9.6	0.023	6.3
	O-level or equivalent	30.6	28.6		29.2	29.9		29.6
	A-level or equivalent	26.6	27.0		26.9	26.7		26.8
	University degree	40.0	34.5		40.7	33.9		37.3
Marital status (%)	Married or living as married	85.7	81.0	0.341	87.0	79.7	0.083	83.3
	Separated or divorced	6.0	8.3		5.1	9.2		7.1
	Single or widowed	8.3	10.7		7.9	11.2		9.5
Socio-economic status (SES) (%)	Routine and manual	4.4	4.4	0.109	4.0	4.8	0.876	4.4
	Intermediate	17.4	25.0		21.7	20.7		21.2
	Professional and managerial	78.2	70.6		74.3	74.5		74.4
Daily exercise (h)	Mean (SD)	0.24 (0.4)	0.27 (0.4)	0.386	0.23 (0.3)	0.28 (0.5)	0.153	0.25 (0.4)
BMI (kg/m^2)	Mean (SD)	23.5 (3.8)	23.5 (3.3)	0.976	23.5 (3.6)	23.6 (3.6)	0.777	23.5 (3.6)
Sleep duration (h)	Mean (SD)	7.6 (0.9)	7.6 (0.9)	0.535	7.7 (0.9)	7.5 (0.9)	0.070	7.6 (0.9)
Smoking status (%)	Never	68.6	66.3	0.817	66.4	68.5	0.708	67.5
	Former	26.2	28.6		28.9	25.9		27.4
	Current	5.2	5.1		4.7	5.6		5.1
Alcohol (%)	Once a month or less	20.6	19.9	0.843	16.2	24.3	0.043	20.2
	Less than daily	60.7	59.5		61.3	59.0		60.1
	Once a day or more	18.7	20.6		22.5	16.7		19.7

Table 4.4 Profiles of main foods and nutrients intake comparing women with fast and slow reaction time

		Simple Reaction Time				Choice Reaction Time				Total
		Fast group (N=252)	Slow group (N=251)	Difference (95% CI)	*P*	Fast group (N=252)	Slow group (N=251)	Difference (95% CI)	*P*	(N=503)
Main food consumption: Mean (SD)										
Vegetables	(g/day)	307 (169)	312 (159)	-5 (-34, 24)	0.724	310 (164)	309 (164)	1 (-27, 30)	0.923	310 (164)
Fruits	(g/day)	313 (205)	296 (194)	16 (-19, 51)	0.364	298 (204)	311 (195)	-13 (-48, 22)	0.476	305 (199)
Oily fish	(g/day)	8 (13)	9 (11)	-0.4 (-3, 2)	0.682	8 (12)	8 (12)	0.3 (-2, 2)	0.748	8 (12)
Total fish	(g/day)	23 (23)	25 (21)	-2 (-6, 2)	0.272	25 (23)	23 (22)	2 (-2, 6)	0.357	24 (22)
Processed meat	(g/day)	10 (13)	11 (13)	-1 (-4, 1)	0.253	10 (12)	11 (14)	-0.2 (-3, 2)	0.844	11 (13)
Unprocessed red meat	(g/day)	31 (46)	29 (35)	3 (-5, 10)	0.494	32 (43)	28 (39)	4 (-3, 11)	0.239	30 (41)
Unprocessed poultry	(g/day)	15 (19)	17 (20)	-1 (-5, 2)	0.406	16 (20)	15 (18)	1 (-2, 4)	0.508	16 (19)
Total meat	(g/day)	57 (67)	58 (58)	-0.5 (-11, 10)	0.933	60 (64)	55 (60)	5 (-6, 16)	0.354	58 (62)
Nutrient intakes: Mean (SD)										
Energy intake	(kcal/day)	2326 (614)	2343 (676)	-17 (-130, 96)	0.770	2375 (601)	2293 (685)	82 (-31, 195)	0.154	2334 (645)
	(MJ/day)	10 (3)	10 (3)	0 (-0.5, 0.5)	0.770	10 (3)	10 (3)	0 (-0, 1)	0.154	10 (3)
Protein	(g/day)	86 (27)	88 (26)	-2 (-6, 3)	0.446	89 (25)	85 (27)	3 (-1, 8)	0.174	87 (26)
	(%energy)	15 (3)	15 (3)	-0.3 (-0.8, 0.1)	0.175	15 (3)	15 (3)	0 (-0.5, 0.5)	0.981	15 (3)
Carbohydrate	(g/day)	311 (93)	309 (99)	3 (-14, 19)	0.759	314 (88)	306 (103)	7 (-9, 24)	0.380	310 (96)
	(%energy)	54 (7)	53 (7)	1 (-0.4, 2)	0.183	53 (7)	53 (7)	-0.2 (-2, 1)	0.703	53 (7)
Fat	(g/day)	84 (29)	87 (31)	-2 (-8, 3)	0.391	88 (30)	83 (30)	4 (-1, 10)	0.104	85 (30)
	(%energy)	32 (6)	33 (6)	-1 (-2, 0.5)	0.258	33 (6)	33 (6)	0.2 (-1, 1)	0.740	33 (6)
SFAs	(g/day)	29 (13)	30 (13)	-1 (-3, 1)	0.476	30 (13)	29 (13)	1 (-1, 3)	0.330	30 (13)
	(%energy)	11 (3)	11 (3)	-0.2 (-1, 0.4)	0.451	11 (3)	11 (3)	-0.1 (-1, 1)	0.853	11 (3)
PUFAs	(g/day)	16 (6)	17 (6)	-0.3 (-1, 1)	0.556	17 (6)	16 (6)	1 (0, 2)	0.029	16 (6)

	(%energy)	6 (2)	6 (2)	-0.1 (-0.4, 0.2)	0.514	6 (2)	6 (2)	0.1 (-0.2, 0.5)	0.357	6 (2)
MUFAs	(g/day)	28 (10)	28 (11)	-1 (-2, 1)	0.463	29 (10)	27 (10)	2 (-0.2, 3)	0.081	28 (10)
	(%energy)	11 (3)	11 (2)	-0.2 (-1, 0.3)	0.509	11 (2)	11 (3)	0.1 (-0.4, 0.5)	0.711	11 (3)
Vitamin C	(mg/k kcal)	74 (33)	73 (32)	1 (-5, 6)	0.822	72 (32)	75 (33)	-3 (-9, 2)	0.254	73 (33)
Vitamin B1	(ug/k kcal)	1281 (810)	1228 (634)	53 (-74, 180)	0.414	1294 (842)	1215 (588)	79 (-48, 206)	0.224	1255 (727)
Vitamin B2	(ug/k kcal)	1075 (289)	1100 (254)	-25 (-72, 23)	0.314	1086 (275)	1088 (271)	-3 (-50, 45)	0.918	1087 (273)
Vitamin B6	(ug/k kcal)	1176 (264)	1171 (223)	4 (-38, 47)	0.839	1172 (254)	1175 (235)	-4 (-46, 39)	0.871	1173 (244)
Vitamin B12	(ug/k kcal)	2 (1)	2 (1)	-0.1 (-0.3, 0.1)	0.154	2 (1)	2 (1)	0 (-0.2, 0.2)	0.908	2 (1)
Folate	(ug/k kcal)	170 (39)	172 (40)	-2 (-9, 5)	0.608	169 (41)	172 (37)	-3 (-10, 4)	0.366	171 (39)
Vitamin A	(ug/k kcal)	392 (179)	416 (188)	-23 (-55, 9)	0.156	392 (178)	416 (189)	-24 (-56, 8)	0.146	404 (184)
Vitamin D	(ug/k kcal)	1 (1)	1 (1)	0 (-0.1, 0.1)	0.763	1 (1)	1 (1)	0.1 (-0.1, 0.2)	0.351	1 (1)
Vitamin E	(ug/k kcal)	4135(1380)	4287(1266)	-152 (-384, 80)	0.199	4249(1244)	4173(1403)	77 (-156, 309)	0.517	4211(1325)
Calcium	(mg/k kcal)	486 (116)	505 (131)	-20 (-41, 2)	0.074	488 (114)	503 (132)	-14 (-36, 7)	0.196	496 (124)
Iron	(mg/k kcal)	8 (3)	8 (2)	0.3 (-0.2, 1)	0.238	8 (2)	8 (2)	-0.1 (-1, 0.3)	0.605	8 (2)
Zinc	(mg/k kcal)	5 (1)	5 (1)	-0.1 (-0.2, 0.1)	0.494	5 (1)	5 (1)	0 (-0.2, 0.2)	0.856	5 (1)

Abbr.: SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids.

Table 4.5 Associations between dietary factors and reaction times with odds ratios of being in slow groups

		Simple Reaction Time			Choice Reaction Time		
		Unadjusted	Adjusted*	*P**	Unadjusted	Adjusted*	*P**
Main foods (OR, 95%CI)							
Vegetables	per 10g/1000kcal	1.01 (0.99, 1.04)	1.00 (0.98, 1.04)	0.458	1.01 (0.99, 1.04)	1.00 (0.98, 1.03)	0.742
Fruits	per 10g/1000kcal	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.327	1.02 (0.99, 1.04)	1.00 (0.98, 1.03)	0.718
Oily fish	per 10g/1000kcal	1.17 (0.83, 1.66)	1.11 (0.78, 1.59)	0.557	1.02 (0.72, 1.44)	0.98 (0.68, 1.40)	0.903
Total fish	per 10g/1000kcal	1.15 (0.95, 1.38)	1.11 (0.91, 1.34)	0.306	0.99 (0.82, 1.19)	0.96 (0.79, 1.17)	0.685
Processed meat	per 10g/1000kcal	1.17 (0.84, 1.62)	1.17 (0.82, 1.67)	0.375	1.12 (0.81, 1.55)	1.24 (0.86, 1.78)	0.242
Unprocessed red meat	per 10g/1000kcal	0.96 (0.86, 1.07)	0.92 (0.82, 1.04)	0.182	0.95 (0.85, 1.06)	0.95 (0.85, 1.07)	0.421
Unprocessed poultry	per 10g/1000kcal	1.08 (0.87, 1.33)	1.07 (0.85, 1.34)	0.570	0.98 (0.79, 1.21)	0.98 (0.79, 1.23)	0.893
Total meat	per 10g/1000kcal	1.00 (0.93, 1.07)	0.98 (0.91, 1.06)	0.634	0.98 (0.91, 1.05)	0.99 (0.91, 1.07)	0.746
Nutrient consumption (OR, 95%CI)							
Energy intake	per 1000kcal	1.04 (0.79, 1.37)	1.10 (0.83, 1.47)	0.501	0.82 (0.62, 1.08)	0.87 (0.65, 1.17)	0.360
Protein	per %energy	1.05 (0.98, 1.12)	1.04 (0.97, 1.12)	0.276	1.00 (0.94, 1.07)	0.99 (0.92, 1.06)	0.770
Carbohydrate	per %energy	0.98 (0.96, 1.01)	0.98 (0.95, 1.01)	0.130	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	0.801
Fat	per %energy	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	0.217	1.00 (0.97, 1.02)	1.01 (0.98, 1.04)	0.690
SFAs	per %energy	1.02 (0.97, 1.08)	1.02 (0.97, 1.08)	0.428	1.01 (0.95, 1.06)	1.03 (0.97, 1.09)	0.305
PUFAs	per %energy	1.03 (0.94, 1.14)	1.05 (0.95, 1.16)	0.374	0.95 (0.87, 1.05)	0.96 (0.87, 1.06)	0.443
MUFAs	per %energy	1.02 (0.96, 1.10)	1.03 (0.96, 1.11)	0.430	0.99 (0.92, 1.06)	1.01 (0.94, 1.08)	0.807
Vitamin C	per 10mg/1000kcal	0.99 (0.94, 1.05)	0.99 (0.93, 1.05)	0.741	1.03 (0.98, 1.09)	1.01 (0.95, 1.07)	0.842
Vitamin B1	per 10μg/1000kcal	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.819	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.300
Vitamin B2	per 10μg/1000kcal	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	0.294	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.773
Vitamin B6	per 10μg/1000kcal	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.845	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.549
Vitamin B12	per μg/1000kcal	1.12 (0.96, 1.31)	1.09 (0.92, 1.30)	0.304	0.99 (0.85, 1.16)	0.97 (0.82, 1.15)	0.728
Folate	per 10μg/1000kcal	1.01 (0.97, 1.06)	1.02 (0.97, 1.07)	0.460	1.02 (0.98, 1.07)	1.01 (0.96, 1.06)	0.826
Vitamin A	per 10μg/1000kcal	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	0.308	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)	0.398
Vitamin D	per μg/1000kcal	1.04 (0.79, 1.37)	0.97 (0.73, 1.29)	0.832	0.88 (0.67, 1.15)	0.86 (0.64, 1.15)	0.310
Vitamin E	per 10μg/1000kcal	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0169	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.401
Calcium	per 10mg/1000kcal	1.01 (1.00, 1.03)	1.01 (1.00, 1.03)	0.111	1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	0.489
Iron	per mg/1000kcal	0.96 (0.89, 1.03)	0.95 (0.88, 1.03)	0.225	1.02 (0.95, 1.10)	1.00 (0.93, 1.08)	0.966
Zinc	per mg/1000kcal	1.07 (0.89,1.28)	1.02 (0.84, 1.23)	0.876	1.02 (0.85, 1.22)	0.96 (0.79, 1.17)	0.693

[*] *P* values were for the adjusted models with adjusting for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, sleep duration, smoking status, alcohol consumption, and total energy intake. *Abbr.*: SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids.

Table 4.6 Comparison of reaction times between consumers and non-consumers of specific foods cooked by roasting/baking, frying, and BBQ/grilling

Cooking methods	Number of Consumers	Number of Non-consumers	Simple Reaction Time Odds Ratios of being in slow groups (95%CI)			Choice Reaction Time Odds Ratios of being in slow groups (95%CI)		
			Unadjusted	Adjusted[*]	*P*[*]	Unadjusted	Adjusted[*]	*P*[*]
Roasted/Baked meat	292	211	1.11 (0.78, 1.59)	1.05 (0.68, 1.61)	0.824	0.89 (0.62, 1.26)	0.89 (0.57, 1.37)	0.586
Fried meat	123	380	1.22 (0.81, 1.83)	1.11 (0.71, 1.74)	0.637	0.94 (0.63, 1.42)	0.91 (0.58, 1.42)	0.669
BBQ'd/Grilled meat	273	230	0.99 (0.70, 1.41)	0.95 (0.63, 1.45)	0.819	1.03 (0.72, 1.46)	1.13 (0.74, 1.73)	0.570
Roasted/Baked fish	271	232	1.51 (1.06, 2.14)	1.46 (1.00, 2.13)	0.049	1.06 (0.75, 1.50)	0.99 (0.68, 1.45)	0.953
Fried fish	144	359	1.27 (0.86, 1.87)	1.12 (0.75, 1.69)	0.579	0.93 (0.63, 1.37)	0.85 (0.56, 1.29)	0.451
BBQ'd/Grilled fish	239	264	1.28 (0.90, 1.82)	1.35 (0.93, 1.96)	0.118	0.93 (0.66, 1.32)	0.97 (0.66, 1.41)	0.863
Roasted/Baked vegetables	338	165	1.21 (0.84, 1.76)	1.29 (0.87, 1.93)	0.205	1.17 (0.81, 1.70)	1.27 (0.85, 1.91)	0.240
Fried vegetables	206	297	1.55 (1.08, 2.21)	1.64 (1.12, 2.39)	0.010	0.88 (0.62, 1.26)	0.95 (0.65, 1.38)	0.787
BBQ'd/Grilled vegetables	216	287	0.88 (0.62, 1.26)	0.92 (0.63, 1.35)	0.680	0.83 (0.58, 1.18)	0.88 (0.60, 1.29)	0.505
Roasted/Baked potatoes	444	59	0.76 (0.44, 1.31)	0.87 (0.48, 1.57)	0.635	1.03 (0.60, 1.78)	1.37 (0.74, 2.51)	0.312
Fried potatoes	219	284	1.16 (0.82, 1.66)	1.16 (0.79, 1.69)	0.445	0.74 (0.52, 1.05)	0.76 (0.52, 1.11)	0.150
BBQ'd/Grilled potatoes	67	436	1.19 (0.71, 2.00)	1.21 (0.70, 2.08)	0.494	1.19 (0.71, 2.00)	1.18 (0.68, 2.04)	0.560
Doneness of food (continuous variable scale 0 to 44)								
Doneness			1.00 (0.99-1.02)	1.00 (0.99-1.02)	0.952	0.99 (0.97-1.00)	0.99 (0.97-1.01)	0.931

* *P* values were for the adjusted models with adjusting for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, sleep duration, smoking status, alcohol consumption, and total energy intake

Table 4.7 Adherence to Mediterranean diet and its associations with reaction times

		Mediterranean diet			Total
		Low adherence	Moderate adherence	High adherence	
Number of Participants (%)		117 (23.2)	265 (52.7)	121 (24.1)	503 (100)
Simple reaction time					
	Fast group (N, %)	60 (23.8)	126 (50.0)	66 (26.2)	252 (100)
	Slow group (N, %)	57 (22.7)	139 (55.4)	55 (21.9)	251 (100)
Choice reaction time					
	Fast group (N, %)	54 (21.4)	138 (54.8)	60 (23.8)	252 (100)
	Slow group (N, %)	63 (25.1)	127 (50.6)	61 (24.3)	251 (100)
Odds Ratios of being in slow groups (95%CI)					***P* trend**[†]
Simple reaction time					
	Unadjusted	ref	1.16 (0.75, 1.79)	0.88 (0.53, 1.46)	0.944
	Adjusted[*]	ref	1.34 (0.83, 2.17)	0.94 (0.52, 1.70)	0.222
Choice reaction time					
	Unadjusted	ref	0.79 (0.51, 1.22)	0.87 (0.52, 1.45)	0.724
	Adjusted[*]	ref	0.83 (0.51, 1.35)	0.83 (0.45, 1.51)	0.739

[*] Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, sleep duration, smoking status, alcohol consumption, and total energy intake; [†] tests for linear trend of adherence to the Mediterranean diet in relation to reaction times.

Table 4.8 Distribution of eating patterns and its associations with reaction times

		Eating patterns			
		Meat/fish non-eaters	Fish eaters	Poultry eaters	Red-meat eaters
Number of Participants (%)		114 (22.7)	74 (14.7)	14 (2.8)	121 (59.8)
Simple reaction time					
	Fast group (N, %)	59 (23.4)	39 (15.5)	10 (4.0)	144 (57.1)
	Slow group (N, %)	55 (21.8)	35 (13.9)	4 (1.6)	157 (62.7)
Choice reaction time					
	Fast group (N, %)	51 (20.2)	40 (15.8)	9 (3.5)	152 (60.5)
	Slow group (N, %)	63 (25.1)	34 (13.5)	5 (2.0)	149 (59.4)
Odds Ratios of being in slow groups (95%CI)					
Simple reaction time					
	Unadjusted	ref	0.96 (0.54, 1.73)	0.43 (0.13, 1.45)	1.18 (0.76, 1.81)
	Adjusted*	ref	0.94 (0.51, 1.72)	0.29 (0.08, 1.14)	1.09 (0.69, 1.71)
Choice reaction time					
	Unadjusted	ref	0.69 (0.38, 1.24)	0.45 (0.14, 1.43)	0.79 (0.51, 1.22)
	Adjusted*	ref	0.68 (0.36, 1.26)	0.33 (0.09, 1.16)	0.78 (0.49, 1.24)

* Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, sleep duration, smoking status, alcohol consumption, and total energy intake.

Table 4.9 Factor-loading matrix of food groups characteristic to principal dietary components in the principal component analysis (n = 503)*

	PC1	**PC2**	**PC3**	**PC4**	**PC5**	**PC6**
Food groups	Western pattern	Prudent pattern	High-fat pattern	Whole dairy & fish	More-alcohol type	Egg and grain type
Wholegrain products & cereals	**-0.200**	**0.350**	-0.118	-0.011	-0.043	**0.371**
Refined grain products	0.191	0.100	**0.300**	**-0.313**	0.180	**-0.309**
Plain Potatoes	0.175	**0.252**	-0.024	**0.254**	-0.127	**-0.312**
Potatoes with added fat	**0.322**	-0.021	0.185	-0.097	**-0.219**	0.014
Low-fat dairy products	0.074	**0.215**	**-0.440**	**-0.453**	0.007	0.026
High-fat dairy products	0.144	-0.037	**0.304**	**0.381**	**-0.420**	0.139
Low-fat dressing, spread, sauce	0.081	**0.332**	0.154	-0.172	-0.097	**0.237**
High-fat dressing, spread, sauce	0.151	0.106	**0.378**	-0.115	**0.260**	0.088
Eggs & Egg dishes	**0.215**	**0.264**	0.149	-0.001	-0.026	**0.412**
Soybean products	**-0.241**	-0.008	**0.218**	0.139	0.139	-0.052
Pulses & Legumes	-0.119	**0.376**	0.138	0.014	-0.033	**-0.261**
Fish & fish dishes	**0.276**	**0.201**	**-0.225**	**0.324**	0.133	**0.213**
Red & processed meat, offal	**0.440**	0.008	-0.061	**0.222**	0.108	-0.063
Poultry	**0.402**	0.091	**-0.241**	0.169	0.123	-0.104
Vegetables	-0.126	**0.411**	0.061	0.187	**0.244**	**-0.304**
Fruits	**-0.232**	**0.364**	-0.097	0.115	-0.084	**-0.200**
Nuts & Seeds	-0.193	0.148	**0.335**	0.050	0.107	**0.266**
Refreshments & snacks	**0.218**	0.016	**0.251**	**-0.303**	**-0.258**	**-0.240**
Beverages	0.122	**0.200**	-0.096	**-0.299**	-0.109	0.108
Alcohol	0.124	-0.102	0.100	-0.024	**0.653**	0.112

*Foods or food groups that had absolute rotated factor loading scores ≥0.2 were in bold. *Abbr.*: PC, principal component.

Table 4.10 The first six principal dietary components and their associations with reaction times

Principal dietary components*		Simple Reaction Time		Choice Reaction Time	
		Odds Ratios of being in slow groups (95%CI)		Odds Ratios of being in slow groups (95%CI)	
		Unadjusted	Adjusted**	Unadjusted	Adjusted**
PC1	Western pattern	1.04 (0.93, 1.16)	1.08 (0.93, 1.26)	0.93 (0.84, 1.05)	1.05 (0.91, 1.23)
PC2	Prudent pattern	1.06 (0.94, 1.19)	1.16 (0.93, 1.44)	1.00 (0.89, 1.13)	1.16 (0.93, 1.44)
PC3	High-fat pattern	0.97 (0.85, 1.11)	1.03 (0.87, 1.21)	0.99 (0.86, 1.13)	1.11 (0.94, 1.31)
PC4	Whole dairy & fish	1.01 (0.87, 1.18)	0.93 (0.78, 1.10)	0.99 (0.86, 1.16)	0.89 (0.75, 1.05)
PC5	More-alcohol type	0.99 (0.84, 1.16)	0.98 (0.75, 1.28)	1.00 (0.86, 1.17)	0.98 (0.75, 1.28)
PC6	Egg and grain type	1.21 (1.02, 1.44)	1.18 (0.98, 1.42)	1.06 (0.89, 1.25)	1.00 (0.83, 1.20)

* All six components were regressed in one at a time

** Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, sleep duration, smoking status, alcohol consumption, and total energy intake.

4.3.6 Discussion of the reaction-time sub-study

The results indicate that consumption of meat, fish, and vegetables, and nutrient intakes in middle-aged women were not associated with reaction ability 10–15 years later. Compared with low adherence to the MeDi, moderate and high adherence did not influence the risk of being in the slow reaction-time groups. A similar observational analysis however, suggested that adherence to the MeDi assessed 22 years previously was positively associated with cognitive function in the Health Professionals Follow-up Study, a prospective cohort initiated in 1986 among 51,529 US men aged 40–75 years [265]. Although some evidence shows that there is a potentially protective effect of the MeDi against cognitive decline, most studies have focused on memory and attention which tend to be assessed by the mini-mental state examination (MMSE) [266,267]. Few studies have been done on the associations between the MeDi and reaction time ability so far. A cross-sectional study involving 93 participants in Australia showed that the MeDi score did not differ significantly between the faster reaction time group and the slower reaction time group [268], consistent with the results in this sub-study.

The findings show that consumption of fried vegetables was associated with a slower simple reaction time. This could be due to acrylamide produced in carbohydrate-rich food during frying, a high-temperature cooking process [72,269]. However, fried potatoes, a carbohydrate-rich food, did not show a similar negative association with reaction times; therefore, some caution should be exercised when interpreting these results. In addition, in this sub-study cooking methods of meat or fish did not show associations with reaction times in either unadjusted or adjusted models. Since both non-consumers and consumers of certain-method cooked fish or meat were likely mixed with those who may also have selected different cooking methods, confounding bias might have occurred with these associations. Oily fish is high in unsaturated fatty acids which could be reduced during the long-lasting and high-temperature cooking process like roasting/baking or frying. At the same time, unsaturated fatty acids such as n-3 fatty acids were found to be associated with better global cognition [117]. However, in this sub-study oily fish and non-oily fish were not investigated separately, which may potentially explain that consumption of fish cooked by certain methods was not related to odds of having slow reaction times. Potential mechanisms why only fried vegetables had

detrimental associations with simple reaction time remain unclear, and similar studies are limited; more evidence needs be provided from other populations including cooking methods, especially on different types of food consumption.

Strengths of this sub-study include its novelty to explore effects of cooking methods on cognitive function, the longitudinal design, and multivariate regression models. The exploration of frequencies of cooking methods is novel in relation to health-related outcomes, and has not been conducted in other studies to date. There is a possibility that these frequencies might be under- or over- reported. These potential measurement errors could reduce the power to detect real associations between dietary exposures and reaction ability; therefore, results should be interpreted with caution. Moreover, as an observational study causality cannot be established and potential confounding bias is always a possibility.

This sub-study is also limited in assessments of nutritional supplement use which were not included potentially resulting in underestimation of nutrient intakes. Other diet quality indices apart from the Mediterranean diet were not conducted in the analyses; it may be that combinations of nutrients and foods in dietary patterns are more comprehensive than individual nutrients in relation to reaction times. In addition, most studies on the prevalence of dementia focus on people aged over 65 years; for those aged 45–64 years in this study, the prevalence is relatively low at 98 per 100,000 [93]. The mean age of women who took part in the reaction time tests may be not old enough to show changes of reaction ability, and the number of participants was limited, which might have resulted in the non-significant associations. It should be acknowledged that the reaction time is just one of cognitive domains which could not reflect the whole picture of cognitive function; therefore, more cognitive tests were analysed in Chapter 5, where five cognitive functions were available with large sample sizes in the UK Biobank.

Overall, this sub-study indicates no associations were observed between reaction ability and consumption of total meat, fish, vegetables, energy-adjusted nutrient intakes, and dietary patterns such as Mediterranean diet. However, there was a suggestion that foods cooked by specific methods may be related to reaction ability. This needs further exploration in additional studies.

4.4 The dementia cases of death sub-study

4.4.1 Determination of dementia cases of death

The UK Women's Cohort Study (UKWCS) dataset contains information on diet, health, and lifestyle. This database was updated with mortality information from the UK Office of National Statistics (ONS) up to January 2018, which was subject to the National Health Service Act 2006 -s251- 'Control of patient information', and stored electronically in restricted access files. The causes of death data in the UKWCS were coded based on the International Classification of Disease (ICD) 9th and 10th editions. In this sub-study, ICD codes related to dementia as well as its main symptoms were used to extract corresponding cases using Structured Query Language (SQL, shown in the A-Table 4.2 of Appendix D). Related ICD 9th and ICD 10th codes and the number of cases of death for each code are summarized in Table 4.11. To investigate the risk of women dying of dementia, only primary causes of death were considered in this sub-study.

Table 4.11 Dementia related ICD 9th and ICD 10th codes for case extraction [61]

ICD-10	F01 Dementia in Alzheimer's disease (n=0)
	F02 Dementia in other diseases classified elsewhere (n=0)
	F03 Unspecified dementia (n=163)
	F04 Organic amnesic syndrome, not induced by alcohol and other psychoactive substances (n=0)
	F06.7 Mild cognitive disorder (n=0)
	G30 Alzheimer's disease (n=119)
	R41 Other symptoms and signs involving cognitive function and awareness (n=0)
ICD-9	290 Dementias (n=1)
	294 Persistent mental disorders due to conditions classified elsewhere (n=0)
	317 Mild intellectual disabilities (n=0)
	318 Other specified intellectual disabilities (n=0)
	319 Unspecified intellectual disabilities (n=0)
	331 Other cerebral degenerations (n=0)

Abbr.: ICD, the International Classification of Disease.

4.4.2 Regression models

Cox proportional-hazards regressions were fitted with the duration of follow-up in years as the timescale to examine associations between dietary factors and dementia mortality; hazard ratios (HR) as well as 95%CI were reported. The updating date of the linkage data was 31 January 2018 which was used as the censoring date in this study. The follow-up time of participants in person-years was calculated from the date of recruitment until date of death or censoring date. Unadjusted model and

adjusted model were conducted separately, where the adjustment set of potential confounding factors was detailed above.

4.4.3 Results from the dementia cases of death sub-study

4.4.3.1 Baseline characteristics between dementia death cases and controls

Among 35,372 women, there were 283 cases who died of dementia up to January 2018. Taking the rest of participants as controls, demographic characteristics are summarized in Table 4.12. The dementia cases of death were generally much older than controls (mean age: 66 vs 52 years old). The percentage of participants with no-educational qualifications was significantly higher in cases (47%) than in controls (24%), while the percentages of O-level, A-level and University degree were significantly lower in cases (14%, 20%, and 20%, respectively) than in controls (29%, 22%, and 25%, respectively). Also, the percentage of women who were single or widowed was significantly higher in cases (30%) than in controls (14%), while the percentage of women who were married or living as married was obviously lower in cases (62%) than in controls (76%). With regards to socio-economic status (SES), 64% women in the UKWCS were professional or managerial while there was no difference between cases and controls. Dementia cases of death had fewer mean hours of vigorous exercise than controls (0.22 h vs. 0.25 h per day, respectively). The mean BMI was 24.5 kg/m^2 (SD: 4.2 kg/m^2) for the whole sample, and no difference was observed between cases and controls. Most women in this cohort were non-smokers (89%) and without a stroke history (99%), which were similar between cases and controls.

4.4.3.2 Comparisons of main foods and nutrient intakes between women who died of dementia and controls

In Table 4.13, we can see that the daily energy intake was 2352 kcal (SD: 798 kcal/day) for the whole sample, and there was no significant difference between cases and controls. The daily protein intake among women was 90 g (SD: 32 g/day), and the daily fat intake was 85 g (SD: 36 g/day) including 29±14 g/day of saturated fat and 28±12 g/day of mono-unsaturated fat. Women in the case group consumed more fish per day than those in the control group (33 g/day vs. 28 g/day with 5 g/day (95%CI: 1, 8) of difference). However, women who died of dementia consumed less polyunsaturated fatty acids (P =0.011) even after energy adjustment

(P =0.006) compared with controls. Other main food consumption and energy-adjusted nutrient intakes were not significantly different between cases and controls (Table 4.13).

4.4.3.3 Associations of main foods and energy-adjusted nutrient intakes with risk of dementia mortality

The logistic regression results with or without adjustment for age, ethnicity, marital status, SES, physical activity, BMI, smoking status, alcohol consumption, sleep duration, and total energy intake, are summarized in Table 4.14. From the results we can see that consumption of total fish and PUFAs as well as vitamin D had significant associations with dementia cases of death in unadjusted models, consistent with descriptive analyses; however, these associations were no longer significant in adjusted models. In addition, higher intakes of protein, vitamin B12, and zinc have a tendency of being associated with reduced risk of dementia mortality; however, no associations were significant (Table 4.14).

4.4.3.4 Adherence to Mediterranean diet, eating patterns and their associations with risk of dementia mortality

As shown in Table 4.15, 24% of the 35,372 UKWCS participants were low adherent to the MeDi, while 53% were moderately adherent and 23% were highly adherent. Women who died of dementia were less adherent to the MeDi than the controls. Compared with low adherence to the MeDi, moderate adherence was associated with 10% reduced risk of dying of dementia without adjustment (unadjusted HR =0.90, 95%CI: 0.83, 0.97; P =0.006); however, the association was no longer significant with adjustment for confounding factors (adjusted OR =1.01, 95%CI: 0.94, 1.09; P =0.703) (Table 4.16).

With regards to eating patterns, 16% were meat/fish non-eaters, 13% were fish-eaters, 3% were poultry-eaters, and 68% were red-meat eaters in the whole sample. When stratified by case status, 75% cases were red-meat eaters and 11% were meat/fish non-eaters, while 68% controls were red-meat eaters and 16% were meat/fish non-eaters, but the differences were not statistically significant between the case group and the control group (P =0.083; Table 4.15). Compared with meat/fish non-eaters, the fish eaters, poultry eaters, or red-meat eaters were not related to risk of dementia mortality (Table 4.16).

4.4.3.5 Analyses of dietary patterns derived from the principal component analysis

In this sub-study, the principal components derived from the PCA that were more than 1 were retrieved as indicated in the scree plot of eigenvalues (Figure 4.7), and thereby the first six components were retained which explained 49.1% of the variation in food groups (Table 4.17).

The first principal component (PC) was characterized by high factor loadings in low-fat dairy products, vegetables, pulses & legumes, eggs, plain potatoes, fish dishes, and red & processed meat, offal, poultry, alongside consumption of snacks and beverages, which was labelled as the "Typical pattern" (13.4% variance). The second PC, defined as the "Western pattern" (10.7% variance), had high factor loadings in red & processed meat, offal, potatoes with added fat, poultry, and refreshments & snacks. The third PC featured high-fat foods such as high-fat spread, high-fat dairy, nuts & seeds, and therefore was labelled as the "High-fat type" (7.9% variance). The fourth PC was defined as the "Low-fat type" (6.5% variance) due to its main factor loading on low-fat dairy, low-fat dressing, spread, sauces, but also on refined grain products, snacks, and beverages, while the fifth PC was labelled as the "More-alcohol type" (5.5% variance) due to its main factor loading on the alcohol drinking. The sixth PC was characterized by high factor loadings in soybean products, potatoes with added fat, refined grain products, plain potatoes, pulses & legumes, and therefore was labelled as the "Plant-based type" (5.2% variance). The Cox regression results showed that none of these six dietary types were significantly associated with the risk of dementia mortality in adjusted models (Table 4.18).

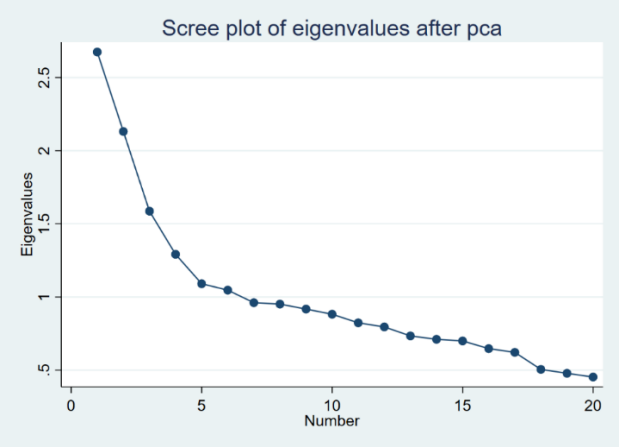


Figure 4.7 The scree plot of Principal Component Analysis on food groups in the dementia cases of death sub-study

Table 4.12 Baseline demographics in the dementia cases of death sub-study

		Cases (N=283)	Controls (N=35,089)	*P*	Total (N=35,372)
Age (years)	Mean±SD	66±6.2	52±9.2	<0.001	52±9.3
Ethnicity (%)	White	100	98.7	0.536	98.7
	Asian	0	0.5		0.5
	Black	0	0.2		0.2
	Other	0	0.6		0.6
Educational level (%)	None	47.0	24.1	<0.001	24.3
	O-level	13.8	28.5		28.4
	A-level	19.8	22.5		22.5
	University degree	19.4	24.9		24.8
Marital status (%)	Married or living as married	62.2	75.5	<0.001	75.4
	Separated or divorced	7.8	10.9		10.9
	Single or widowed	30.0	13.6		13.7
Socio-economic status (%)	Routine and manual	9.9	9.1	0.869	9.1
	Intermediate	26.1	26.9		26.9
	Professional and managerial	64.0	64.0		64.0
Vigorous exercise (hour/day)	Mean±SD	0.22±0.47	0.25±0.47	<0.001	0.25±0.47
Body mass index (Kg/m^2)	Mean±SD	24.6±3.8	24.5±4.2	0.595	24.5±4.2
Smoking status (%)	Yes	8.8	10.8	0.291	10.8
	No	91.2	89.2		89.2
Stroke history (%)	Yes	0.7	0.7	0.938	0.7
	No	99.3	99.3		99.3
Alcohol drinking (g/day)	Mean±SD	6±8	9±10	<0.001	9±10

Table 4.13 Profiles of main foods and nutrient intakes between women who died of dementia and controls

		Cases (N=283)	Controls (N=35,089)	Difference (95% CI)	*P*	Total (N=35,372)
Main food consumption: Mean (SD)						
Vegetables	(g/day)	298 (171)	317 (193)	-19 (-42, 4)	0.098	317 (193)
Fruits	(g/day)	341 (244)	316 (244)	25 (-3, 54)	0.083	316 (244)
Oily fish	(g/day)	9 (11)	9 (13)	0.3 (-1, 2)	0.712	9 (13)
Total fish	(g/day)	33 (48)	28 (29)	5 (1, 8)	0.006	28 (29)
Processed meat	(g/day)	15 (20)	13 (15)	2 (0, 4)	0.017	13 (15)
Unprocessed red meat	(g/day)	37 (42)	34 (43)	3 (-2, 8)	0.210	34 (43)
Unprocessed poultry	(g/day)	17 (20)	17 (21)	0 (-2, 2)	0.968	17 (21)
Total meat	(g/day)	71 (63)	66 (66)	6 (-2, 13)	0.159	66 (66)
Nutrient intakes: Mean (SD)						
Energy intake	(kcal/day)	2298 (743)	2353 (799)	-55 (-148, 39)	0.251	2352 (798)
	(MJ/day)	10 (3)	10 (3)	-0.2 (-0.6, 0.2)	0.251	10 (3)
Protein	(g/day)	89 (30)	90 (32)	-1 (-5, 3)	0.614	90 (32)
	(%energy)	16 (3)	15 (3)	0.1 (-0.2, 0.5)	0.373	15 (3)
Carbohydrate	(g/day)	308 (105)	313 (112)	-4 (-17, 9)	0.512	313 (112)
	(%energy)	54 (7)	53 (7)	0.5 (-0.4, 1.3)	0.254	53 (7)
Fat	(g/day)	83 (34)	85 (36)	-2 (-6, 2)	0.416	85 (36)
	(%energy)	32 (6)	32 (6)	0.3 (-0.4, 0.9)	0.456	32 (6)
SFAs	(g/day)	30 (14)	29 (14)	0 (-2, 2)	0.935	29 (14)
	(%energy)	11 (3)	11 (3)	0.3 (-0.0, 0.7)	0.068	11 (3)
PUFAs	(g/day)	15 (7)	16 (8)	-1 (-2, 0)	0.011	16 (8)
	(%energy)	6 (2)	6 (2)	-0.3 (-0.5, -0.1)	0.006	6 (2)
MUFAs	(g/day)	27 (12)	28 (12)	-1 (-2, 1)	0.448	28 (12)

	(%energy)	11 (3)	11 (2)	0.1 (-0.2, 0.3)	0.571	11 (2)
Vitamin C	(mg/k kcal)	78 (38)	75 (33)	3 (-1, 7)	0.127	76 (33)
Vitamin B1	(ug/k kcal)	1191 (813)	1324 (1025)	-133 (-252, 13)	0.030	1322 (1024)
Vitamin B2	(ug/k kcal)	1130 (281)	1103 (283)	27 (-6, 61)	0.105	1103 (283)
Vitamin B6	(ug/k kcal)	1222 (239)	1205 (244)	17 (-11, 46)	0.231	1205 (244)
Vitamin B12	(ug/k kcal)	3 (1)	2 (1)	0.1 (-0.0, 0.3)	0.061	2 (1)
Folate	(ug/k kcal)	178 (46)	175 (41)	3 (-2, 8)	0.201	175 (41)
Vitamin A	(ug/k kcal)	466 (216)	443 (229)	24 (-3, 51)	0.081	443 (229)
Vitamin D	(ug/k kcal)	1 (1)	1 (1)	0.1 (0.0, 0.2)	0.001	1 (1)
Vitamin E	(ug/k kcal)	4122 (1495)	4127 (1282)	-5 (-155, 145)	0.947	4127 (1284)
Calcium	(mg/k kcal)	502 (129)	497 (120)	5 (-9, 19)	0.512	497 (120)
Iron	(mg/k kcal)	8 (3)	8 (2)	0.1 (-0.2, 0.3)	0.661	8 (2)
Zinc	(mg/k kcal)	5 (1)	5 (1)	0.1 (-0.1, 0.2)	0.334	5 (1)

Abbr.: SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids.

Table 4.14 Associations of main foods and energy-adjusted nutrient intakes in relation to dementia cases of death

		Unadjusted models				Adjusted models*			
		HR	LCL	UCL	*P*	HR	LCL	UCL	*P*
Main foods (OR, 95%CI)									
Vegetables	per 10g/1000kcal	1.03	0.91	1.17	0.654	1.04	0.96	1.14	0.307
Fruits	per 10g/1000kcal	1.03	0.93	1.14	0.571	1.02	0.90	1.14	0.783
Oily fish	per 10g/1000kcal	1.01	0.99	1.03	0.254	1.01	0.99	1.03	0.525
Total fish	per 10g/1000kcal	1.01	1.01	1.02	0.001	1.01	0.94	1.09	0.703
Processed meat	per 10g/1000kcal	1.02	0.96	1.07	0.571	1.04	0.98	1.09	0.209
Unprocessed red meat	per 10g/1000kcal	1.08	1.00	1.18	0.059	1.04	0.97	1.12	0.263
Unprocessed poultry	per 10g/1000kcal	1.01	0.96	1.06	0.661	0.99	0.94	1.03	0.544
Total meat	per 10g/1000kcal	1.05	0.94	1.16	0.387	1.01	0.84	1.20	0.949
Nutrient consumption (OR, 95%CI)									
Energy intake	per 1000kcal	1.01	0.86	1.17	0.937	1.03	0.91	1.17	0.654
Protein	per %energy	0.84	0.74	0.97	0.014	0.97	0.85	1.10	0.610
Carbohydrate	per %energy	1.04	0.96	1.13	0.329	1.03	0.94	1.12	0.557
Fat	per %energy	1.06	0.95	1.18	0.274	1.07	0.95	1.20	0.287
SFAs	per %energy	1.07	0.93	1.23	0.360	1.02	0.88	1.17	0.830
PUFAs	per %energy	0.90	0.83	0.97	0.006	1.00	0.98	1.02	0.790
MUFAs	per %energy	0.97	0.88	1.07	0.518	0.98	0.90	1.08	0.731
Vitamin C	per 10mg/1000kcal	1.04	1.00	1.09	0.040	1.03	0.99	1.07	0.141
Vitamin B1	per 10μg/1000kcal	0.88	0.75	1.03	0.114	0.96	0.65	1.42	0.851
Vitamin B2	per 10μg/1000kcal	0.82	0.63	1.07	0.147	1.01	0.77	1.33	0.929
Vitamin B6	per 10μg/1000kcal	1.01	0.99	1.03	0.521	1.00	0.97	1.02	0.678
Vitamin B12	per μg/1000kcal	0.94	0.90	0.99	0.016	0.91	0.77	1.07	0.243
Folate	per 10μg/1000kcal	1.03	0.98	1.08	0.289	1.03	0.99	1.07	0.141
Vitamin A	per 10μg/1000kcal	1.01	0.99	1.03	0.456	1.01	0.99	1.03	0.541
Vitamin D	per μg/1000kcal	1.06	1.00	1.12	0.044	1.00	0.86	1.17	0.975
Vitamin E	per 10μg/1000kcal	1.01	1.00	1.01	0.147	0.99	0.99	1.00	0.147
Calcium	per 10mg/1000kcal	1.03	1.00	1.07	0.068	1.00	0.96	1.03	0.903
Iron	per mg/1000kcal	0.93	0.83	1.04	0.197	1.00	0.99	1.01	0.982
Zinc	per mg/1000kcal	0.97	0.95	0.99	0.019	0.99	0.93	1.05	0.303

* Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, smoking status, alcohol consumption, sleep duration, and total energy intake. *Abbr.*: SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids; HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

Table 4.15 Distribution of adherence to Mediterranean diet and eating patterns between women who died of dementia and controls

		Cases N (%)	**Controls** N (%)	***P***	**Total** N (%)
Mediterranean diet	Low adherence	85 (30.0)	8490 (24.2)	0.007	8575 (24.2)
	Moderate adherence	154 (54.4)	18727 (53.4)		18881 (53.4)
	High adherence	44 (15.6)	7872 (22.4)		7916 (22.4)
Eating patterns	Meat/fish non-eaters	31 (11.0)	5527 (15.8)	0.083	5558 (15.7)
	Fish eaters	33 (11.7)	4703 (13.4)		4736 (13.4)
	Poultry eaters	8 (2.8)	981 (2.8)		989 (2.8)
	Red-meat eaters	211 (74.6)	23878 (68.1)		24089 (68.1)

Table 4.16 Mediterranean diet and eating patterns in relation to dementia cases of death

		Unadjusted models				Adjusted models*			
		HR	LCL	UCL	*P*	HR	LCL	UCL	*P*
Mediterranean diet	Low adherence	ref	ref	ref	ref	ref	ref	ref	ref
	Moderate adherence	0.90	0.83	0.97	0.006	1.01	0.94	1.09	0.703
	High adherence	0.82	0.63	1.07	0.147	1.01	0.77	1.33	0.929
Eating patterns	Meat/fish non-eaters	ref	ref	ref	ref	ref	ref	ref	ref
	Fish eaters	0.93	0.86	1.01	0.090	1.00	0.89	1.12	0.963
	Poultry eaters	0.99	0.92	1.07	0.868	0.90	0.76	1.05	0.186
	Red-meat eaters	1.25	0.77	2.05	0.372	1.07	0.93	1.23	0.360

* Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, smoking status, alcohol consumption, sleep duration, and total energy intake. *Abbr.*: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

Table 4.17 Factor-loading matrix of food groups characteristic to the principal dietary components in the principal component analysis (n =35,372)*

	PC1	**PC2**	**PC3**	**PC4**	**PC5**	**PC6**
Food groups	Typical pattern	Western pattern	High-fat type	Low-fat type	More-alcohol type	Plant-based type
Wholegrain products & cereals	0.187	**-0.364**	0.006	0.151	-0.013	-0.174
Refined grain products	**0.200**	0.158	0.114	**0.232**	**0.284**	**0.285**
Plain Potatoes	**0.252**	-0.012	-0.027	0.064	**-0.266**	**0.236**
Potatoes with added fat	0.179	**0.303**	0.090	0.174	-0.145	**0.349**
Low-fat dairy products	0.093	-0.053	**-0.563**	**0.324**	0.191	-0.067
High-fat dairy products	0.123	0.182	**0.464**	-0.101	**-0.210**	**-0.399**
Low-fat dressing, spread, sauce	**0.305**	-0.034	0.043	**0.297**	0.120	-0.042
High-fat dressing, spread, sauce	0.184	0.124	**0.357**	0.021	**0.305**	**-0.206**

Eggs & Egg dishes	**0.310**	0.152	0.045	-0.043	0.072	-0.014
Soybean products	-0.021	**-0.212**	**0.249**	-0.042	**-0.255**	**0.474**
Pulses & Legumes	**0.323**	**-0.286**	0.066	0.002	0.040	**0.297**
Fish & fish dishes	**0.281**	0.027	-0.186	**-0.383**	-0.034	**-0.200**
Red & processed meat, offal	**0.258**	**0.397**	-0.136	**-0.226**	-0.119	0.059
Poultry	**0.222**	**0.266**	**-0.294**	**-0.299**	-0.151	0.036
Vegetables	**0.343**	**-0.334**	-0.010	**-0.215**	0.025	0.084
Fruits	**0.246**	**-0.331**	-0.085	-0.164	-0.158	-0.164
Nuts & Seeds	0.132	**-0.220**	**0.249**	-0.052	0.171	-0.117
Refreshments & snacks	**0.220**	**0.203**	0.125	**0.347**	-0.127	-0.102
Beverages	**0.201**	0.033	-0.147	**0.274**	0.106	-0.204
Alcohol	0.002	0.085	0.047	**-0.352**	**0.670**	**0.214**

*Foods or food groups that had absolute rotated factor loading scores ≥0.2 were in bold. *Abbr.*: PC, principal component.

Table 4.18 The first six principal dietary components and their associations with dementia cases of death

Principal dietary components*		Unadjusted models				Adjusted models**			
		HR	LCL	UCL	*P*	HR	LCL	UCL	*P*
PC1	Typical pattern	1.01	0.99	1.03	0.456	1.01	0.99	1.03	0.541
PC2	Western pattern	1.04	0.96	1.13	0.329	1.03	0.94	1.12	0.557
PC3	High-fat type	1.08	1.00	1.18	0.059	1.04	0.97	1.12	0.263
PC4	Low-fat type	0.97	0.88	1.07	0.518	0.98	0.90	1.08	0.731
PC5	More-alcohol type	1.01	0.96	1.06	0.661	0.99	0.94	1.03	0.544
PC6	Plant-based type	0.90	0.83	0.97	0.006	1.01	0.94	1.09	0.703

* All six components were regressed in one at a time. ** Adjusted for age, ethnicity, marital status, socioeconomic status, physical activity, body mass index, smoking status, alcohol consumption, sleep duration, and total energy intake. *Abbr.*: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

4.4.4 Discussion in the dementia cases of death sub-study

The prevalence of dementia in the general population aged 60 and over is 5–8% and this figure is expected to rise in coming decades [270]. There is an emerging awareness that women may disproportionately bear the burden of dementia almost globally compared with men [271]. Age is a strong risk factor for dementia and cognitive decline, and the average life expectancy worldwide is greater for women than men which makes dementia an important concern for women [272]. There are also sex-specific biological mechanisms that could possibly result in increased susceptibility of women to Alzheimer's dementia [270]. The present longitudinal observational analysis was conducted in a female-only cohort study; allowing exploration of dietary exposures and subsequent dementia cases of death in women for the first time.

The results show that high intakes of protein, vitamin B12, and zinc were potentially associated with reduced risk of dementia mortality in the UKWCS, but no significant associations were observed since a stringent significance level of 0.01 was used in this study. Protein intake is important for humans to keep a well-nourished nutritional status. Compared to dementia cases with good nutritional status, malnourished people with dementia had 3 to 4 times higher risk of having severe dementia and dying from dementia, and even those at risk of malnutrition had twice the risk [273]. A systematic review summarized the plasma nutrient status of patients with Alzheimer's disease and found that compared with controls AD patients had significantly lower plasma levels of vitamin B12 (P <0.001) but non-significantly lower levels of zinc (P =0.050) [274]; those findings suggest that evidence on nutrients in relation to dementia remains uncertain.

In addition, in this sub-study meat consumption and saturated fatty acids intake were unrelated to risk of dementia mortality. However, some studies have shown that high consumption of meat was associated with poor cognitive function and high risk of developing dementia [275,276]; so, these contradictory findings need to be investigated in other studies.

The results also show that fish consumption, and vitamin D intakes were potentially associated with increased risk of dementia mortality while intakes of polyunsaturated fatty acids with decreased risk in the UKWCS; however, these

associations were no longer significant in adjusted models. Among the adjustment set, age was the most influential confounding factor. A similar picture was observed in adherence to Mediterranean diet; where a significant association from moderate adherence was adjusted away when adjusting for confounding factors, especially age. In addition, this sub-study also suggests that fish eaters, poultry eaters, and red-meat eaters compared to meat/fish non-eaters, and all PCA-derived dietary patterns, did not show significant associations with risk of dementia mortality.

Currently there are few studies on the associations between risk of dementia mortality and food consumption, nutrient intakes, as well as dietary patterns. Most related studies are on the dementia incidence or prevalence. For example, a Dutch cohort where 5395 participants free of dementia were followed up for 9.6 years showed that total fish consumption was not associated with risk of dementia, no matter that was lean fish or fatty fish; dietary omega-3 PUFA intake was also unrelated to dementia risk in this cohort [277], which is consistent with present findings in the UKWCS. However, a cross-sectional study conducted in Chinese people with systematic literature reviews showed that people who consumed any amount of fish had reduced risk of dementia, and pooled dose-response analyses suggested that the higher consumption of fish the more reduced risk of dementia people had, particularly lower risk of Alzheimer's disease [278]. Comparing population characteristics between those cohorts, socioeconomic, cultural, and ethnic factors may explain the differences in associations between fish consumption and dementia risk. At the same time, types and cooking methods of fish consumed are also potential factors which need to be investigated.

To my knowledge, this sub-study was the first research to investigate associations between diet consumption and dementia cases of death with a longitudinal study design. The cases of death in this study were determined via the UK Office of National Statistics (ONS) which may make the ascertainment of dementia death cases more specific and robust. In addition, the association between dementia cases of death and diet was investigated in a relatively comprehensive way including food consumption, nutrient intakes, and dietary patterns.

However, several limitations in this sub-study should be noted. Firstly, although data linkages to the UK ONS were more reliable, the number of dementia cases of death was quite small which may have limited the ability to find significant

associations. Secondly, the dementia cases in this sub-study were women who died of dementia as a primary cause of death meaning that those were severe dementia cases. The dementia cases of death were generally older than controls; although age has been adjusted for, participants with much older age could be more fragile and consume less certain foods than controls, which may have resulted in potential selection bias and could influence the real relationship between diet and dementia risk. Therefore, studies on incident dementia cases in relation to diet should be conducted further.

Overall, the findings show that no significant associations were indicated between risk of dementia mortality and diet including food consumption, energy-adjusted nutrient intakes, and dietary patterns; however, research limitations should be noted and more related studies are needed.

CHAPTER V

5. The associations between food consumption and cognitive performance in the UK Biobank

5.1 Summary

5.1.1 Highlights

- Consumption of vegetables, fruits, and fish may be negatively associated with cognitive performance, while meat consumption may be related to good cognitive performance cross-sectionally; however, the effect sizes were generally small in comparison to the mean scores of cognitive tests.
- High intakes of fruit and fish may be associated with increased risk of deteriorating visual memory, while vegetable consumption may be linked with increased risk of declined prospective memory after a follow-up of 6–8 years.
- The results are not consistent with the dominant findings available in the literature; therefore, they need to be interpreted with caution and to be confirmed in other studies.

5.1.2 Abstract

Background: Cognitive decline is of increasing concern in aging societies worldwide and could highlight a key time window for prevention of developing dementia. Diet has been implicated in cognitive decline which needs to be confirmed.

Methods: The consumption frequencies of common foods including vegetables, fruits, total fish (oily fish and non-oily fish), and total meat (processed meat, unprocessed red meat, and unprocessed poultry) were assessed via a 47-item food frequency questionnaire in 502,493 UK Biobank participants (mean age: 56.5 years, SD: 8.1; female: 54%) at recruitment in 2006–2010. Prevalent dementia cases (n=564) were excluded before analyses. Cognitive decline from baseline to follow-up 6–8 years later was characterised in five separate cognitive functions: visual memory (n=51,295), numeric memory (n=3131), fluid intelligence (n=16,122),

reaction ability (n=52,929), and prospective memory (n=16,400). The cognitive change was estimated using a standardized multiple regression-based approach. Associations between food consumption and cognitive performance and cognitive changes were fitted in generalized linear models cross-sectionally and longitudinally.

Results: In this population-based cohort study, men had better cognitive performance than women. Cross-sectional analyses show that high consumption of vegetables, fruits, oily fish, and total fish individually were associated with poor cognitive performance in most cognitive tests, while consumption of unprocessed poultry was related to better cognitive performance in visual memory, reaction ability, and prospective memory. Consumption of processed meat, unprocessed red meat, or total meat had inconsistent associations with the five cognitive function tests. The longitudinal results show that high fruit consumption was associated with increased odds of deteriorating visual memory (OR=1.04, 95%CI: 1.01, 1.06; *P* =0.002), whereas high vegetable consumption was linked with increased odds of deteriorating prospective memory (OR=1.14, 95%CI: 1.07, 1.21; *P* <0.001). Consumption of oily fish was associated with deteriorating visual memory in the total sample (OR=1.08, 95%CI: 1.04, 1.12; *P* <0.001), but this was observed in women only (OR=1.11, 95%CI: 1.05, 1.17; *P* =0.001). Consumption of total fish was associated with a decline in visual memory in the total sample (OR=1.05, 95%CI: 1.02, 1.08; *P* <0.001) and in men (OR=1.05, 95%CI: 1.02, 1.09; *P* =0.003), and a decline in reaction ability only in women (OR=1.05, 95%CI: 1.01, 1.09; *P* =0.007). Meat consumption of any type was not related to cognitive decline in all five cognitive tests.

Conclusions: High consumption of vegetable, fruit and fish may be associated with increased risk of cognitive decline, which is not consistent with the hypothesis of this thesis. Underlying reasons for the findings are not understood; one possible explanation is high consumption of fruits and vegetables may be associated with lower protein intakes. Animal protein has been associated with better cognitive performance. These findings need to be interpreted with caution and confirmed in other studies.

5.2 Introduction

The global population aged 60 years and over is projected to reach 2 billion by 2050 which will be around 22% of the people in the world [279]. Brain aging is associated with a decline in some cognitive function including memory, attention, speed of processing, and executive function [48]; changes that may result in mild incapacity even prior to the onset of dementia [280]. Some studies have suggested that diet, a modifiable lifestyle factor, may play a key role in cognitive aging [112]; however, current evidence about associations between dietary factors and cognitive function is limited.

Several commonly consumed foods were investigated in this study including vegetables, fruits, meat, and fish. Consumption of vegetables and fruits has been related to the prevention of many chronic diseases [281]; however, as detailed in Chapter 2, evidence on their associations with cognitive performance in older adults remains few and inconsistent. Evidence regarding the associations between meat intakes and cognitive function has focussed on several types of meat, such as beef, pork, and lamb [5]. Studies that investigate processed versus unprocessed red meat are called for, as these meat subtypes may have a different health impact [169]. In contrast, although evidence concerning the associations between higher fish consumption and lower risk of dementia or Alzheimer's disease (AD) has been more consistent [278,282], the association with cognitive function is limited and inconclusive. There is an indication of the association between high fish consumption and better performance in cognitive tests [283]; however, associations may depend on fish types consumed [284].

This current study aimed to investigate associations between baseline consumption of main food groups, such as vegetables, fruits, meat as well as its subtypes, and fish especially oily fish, with cognitive function cross-sectionally and with cognitive changes longitudinally. In the present study, higher consumption of vegetables, fruits, and fish was hypothesized to be associated with better cognitive performance at baseline and lower risk of cognitive decline at follow-up; whereas consumption of meat, especially processed meat, was assumed to be linked with poor cognitive performance at baseline and cognitive deterioration at follow-up.

5.3 Methods

5.3.1 Study design

The UK Biobank is a large-scale population-based cohort study of half a million participants aged 40–69 years recruited from across the United Kingdom between 2006 and 2010 [285]. The Biobank recruited participants using National Health Service patient registers and conducted the baseline assessments across 22 assessment centres in England, Scotland, and Wales which included touchscreen questionnaires, verbal interviews, physical measures, and bio-sample collections. At recruitment, participants electronically signed consent forms and completed various touchscreen questionnaires and measurements. All available resources are listed on the UK Biobank website (http://www.ukbiobank.ac.uk/resources/). Ethical approval was granted for the UK Biobank by North West - Haydock Research Ethics Committee (REC reference: 16/NW/0274). The UK Biobank dataset for this project included 502,493 participants.

5.3.2 Baseline dietary assessments

At the recruitment assessment-centre visit, each participant was asked to complete a touchscreen brief food frequency questionnaire (FFQ) with 47 dietary items covering main foods, food groups, and drinking habits [286]. Food groups including meat, fish, vegetables, fruits, and alcohol drinking were analysed or adjusted for due to potential associations with cognitive function.

Meat

There were five questions on meat (fish not included) comprising processed meat (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets), poultry (processed poultry not counted), beef (processed beef not counted), lamb/mutton (processed lamb/mutton not counted), and pork (processed pork not counted). Participants were asked how often each item was consumed with eight options to select being: ‘never’, ‘less than once a week’, ‘once a week’, ‘2–4 times a week’, ‘5–6 times a week’, ‘once or more daily’, ‘do not know’, ‘prefer not to answer’. The responses on meat were converted into weekly-based consumption frequencies as follows: 0, 0.5, 1, 3, 5.5, and 7 times per week respectively, where responses like ‘do not know’, ‘prefer not to answer’ were converted into missing values. Unprocessed beef, unprocessed lamb/mutton, and unprocessed pork were

summed into one group titled ‘unprocessed red meat’, and then processed meat, unprocessed poultry, and unprocessed red meat were combined into one group titled ‘total meat’. Each meat type was used as a continuous variable in regression models.

Fish

There were two questions on fish including oily fish (such as sardines, salmon, mackerel, herring), and other types of fish (such as cod, tinned tuna, haddock) with eight options to select. The same approach used for meat-related items was used to deal with fish items. Oily fish and other types of fish were summed into ‘total fish’, and then took weekly-based consumption frequencies of oily fish and total fish as continuous variables in regression models.

Fruits and vegetables

Participants were asked to either directly input the specific daily numbers of consumed pieces of fresh fruit (one apple, one banana, 10 grapes etc as one piece), pieces of dried fruit (one prune, one dried apricot, 10 raisins etc as one piece), heaped tablespoons of cooked vegetables, and heaped tablespoons of salad/raw vegetables, or select ‘less than one’, ‘do not know’ or ‘prefer not to answer’ over four separate questions on fruits and vegetables. Response of ‘less than one’ was treated as 0.5, and responses like ‘do not know’ or ‘prefer not to answer’ were treated as missing. One piece of fresh fruit, two ‘pieces’ of dried fruit, two heaped tablespoons of cooked vegetables, and two heaped tablespoons of salad/raw vegetables were counted as one serving respectively. Servings of fresh fruit and dried fruit were summed into “total fruits”, and servings of cooked vegetables and salad/raw vegetables into “total vegetables”, which were taken as continuous variables in regression models.

Alcohol drinking

Participants were asked how often they drink alcohol with 7 options: daily or almost daily, 3–4 times a week, once or twice a week, 1–3 times a month, special occasions only, never, or prefer not to answer. Response of ‘prefer not to answer’ was treated as missing. All responses were grouped into four categories as follows: less than once a week, once or twice a week, three or four times a week, and daily or almost daily according to the distribution of data to get approximately equal-sized categories. The ‘alcohol drinking’ variable was then adjusted for as one of

covariates in regression models.

5.3.3 Cognitive function tests

At the assessment-centre visits, there were several touch-screen cognitive function tests performed on participants in the following order: prospective memory test (shapes-Part 1), pairs matching test, numeric memory, fluid intelligence test (reasoning), reaction time test (snap), prospective memory test (shapes-Part 2). Because some of the tests have an "abandon" option for participants to be able to skip that test as they want, the sample size varied across the five tests.

5.3.3.1 Prospective memory test

Before other cognitive tests are performed, an indication "*At the end four coloured shapes will show up with an instruction asking you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead*" appears as the Part 1. Then other cognitive tests follow, and after those tests the four coloured shapes appear, where participants are asked to touch the Blue Square (actually, the Orange Circle is the right answer) as the Part 2. In the present study, this test was scored dichotomously (yes=0/no=1) according to whether the initial answer was right or not.

5.3.3.2 Visual memory test (Pairs-matching)

In this test, participants are shown a set of picture cards and asked to remember as many of pictures as they can. Then the pictures are turned over, and participants are asked to identify each pair of pictures by touching the cards on the screen. This test includes two rounds, the round 1 has 3 pairs shown for 3 seconds and the round 2 has 6 pairs shown for 5 seconds to remember. The number of incorrect matches and the number of correct matches in each round were collected with time taken to complete each round. Since the first round was relatively simple which was not suitable to differentiate memory ability and could be treated as a training test, only the number of incorrect matches in round 2 was analyzed in this chapter. Since participants could quit at any time during this test, some incorrect matches could be present within incomplete tests which were excluded in analyses. A minus natural log-transformation '*-log(scores+1)*' on the raw data were applied due to very skewed distribution, where the higher the new score the better the cognitive performance.

5.3.3.3 Numeric memory test

In the numeric memory test, participants are shown a number starting with 2 digits to remember, where the display duration (milliseconds, ms) follows a formula of "*2000ms + (the number of digits * 500ms)*". During the memory test, the on-screen keyboard is inactive, and then the number disappears followed by a wait period of 3000ms. Then the participant is asked to enter the remembered number onto the activated screen. A new random number would become 1-digit longer each time they remember correctly up to 12 digits with a washout period where the keyboard deactivated for 600ms before either displaying the next number or ending the test. The maximal number of digits remembered correctly was taken as the final score in current study.

5.3.3.4 Fluid intelligence test (reasoning)

The fluid intelligence test is used to measure the capacity of participants to solve problems that require logic and reasoning ability, which is independent of acquired knowledge. In this test, participants are given a maximum of two minutes to answer as many of 13 questions as possible. Participants are prompted not to spend too long on any one question and can skip any question if they wish. Once the participant selects "start", a timer is started and the 13 questions are displayed in sequence until the 2 minutes have elapsed from the beginning. A correct answer was recorded as a 1 score for each question, while either a wrong answer or a skipped answer was recorded as a 0 score. The final summed score was analyzed in current study which ranged from 0 to 13 across participants in the cohort.

5.3.3.5 Reaction time test (Snap)

The Snap game is designed to test reaction ability by recording the time from two identical cards showing on the touchscreen until participants pressing a button. Participants are shown two cards at a time on the touch-screen and instructed to press the button on the button box as quickly as possible when the symbols on the cards match. This exercise involves 12 pairs of cards without an "abandon button". The first four pairs were treated as "training" which were not included when calculating the overall mean reaction time. Mean time taken to correctly identify matches were calculated and used in current study.

5.3.3.6 Determination of cognitive decline

After the baseline assessment-centre visit (2006–2010), there were three repeated assessment-centre visits (2012–2013, 2014–2018, 2018+ respectively) until May 2019 when the data was released to the project with results of cognitive function tests. To assess the maximal cognitive difference, the latest results of cognitive tests were compared with the baseline test results.

Several methods of determining cognitive changes have been reported including the standard deviation method, reliable change indices with correction for measurement error or practice effects or regression to the mean, and standardized regression-based methods using a simple regression equation or a multiple regression equation [287]. In present study, the standardized regression-based (SRB) method with a multiple regression equation was used following the previous study conducted in the UK Biobank [288]. Briefly, the SRB method is to derive a predicted follow-up score (predicted X2) based on the initial test performance (X1), where multiple regression was used in the analyses: 1) regressing post-test scores (X2) on pre-test scores (X1), as well as age, gender, ethnicity, educational level, socioeconomic status, and test-retest interval; 2) developing the regression model and predicting the "predicted X2" for each participant based on the model; 3) calculating the standardized change score (SCS) between the actual X2 and the predicted X2 based on the formula below to determine whether the magnitude of the observed test score change exceeds the expected amount of variability.

$$\text{Formula: } SCS = (X2 - \text{predicted } X2)/S.E.E.$$

where S.E.E. refers to the standard error of estimate in the regression equation.

Values ±1.645 of the SCS (beyond 95% of the population) were used as the cut-points to define a reliable improvement or deterioration in cognitive function. For cognitive tests where the higher the test score the better the cognitive performance is (numeric memory test and fluid intelligence test), "improved cognition" was defined if SCS was more than or equal to 1.645, "cognitive deterioration" if SCS was less than or equal to -1.645, and "unchanged cognition" if SCS ranged from -1.645 to 1.645. For cognitive tests where the higher the test score the worse the cognitive performance is (pairs-matching test and reaction time), "improved cognition" was defined if SCS was less than or equal to -1.645, "cognitive deterioration" if SCS was more than or equal to 1.645, and "unchanged cognition"

if SCS ranged from -1.645 to 1.645. However, when cognitive tests like the prospective memory were scored dichotomously as right or wrong, "improved cognition" was defined if the pre-test was wrong and post-test was right, "cognitive deterioration" if the pre-test was right and post-test was wrong, otherwise "unchanged cognition" if both pre-test and post-test were right or wrong.

5.3.3.7 Flowchart of the number of participants in each cognitive test

Dementia cases were ascertained via self-report at baseline or data linkages to hospital admission and death registers (details can be seen in Chapter 6). Participants with self-reported dementia at baseline were deemed as prevalent cases. Dementia cases with diagnostic date no later than recruitment date were also treated as prevalent cases. Prevalent dementia cases (n=564) were excluded from the analyses. Since there is an "abandon" option in some cognitive tests (visual memory test, numeric memory test, and prospective memory test), the dataset contains some unfinished responses which were excluded from analyses. The number of participants in each cognitive test before and after exclusions were summarized in a flowchart (Figure 5.1).

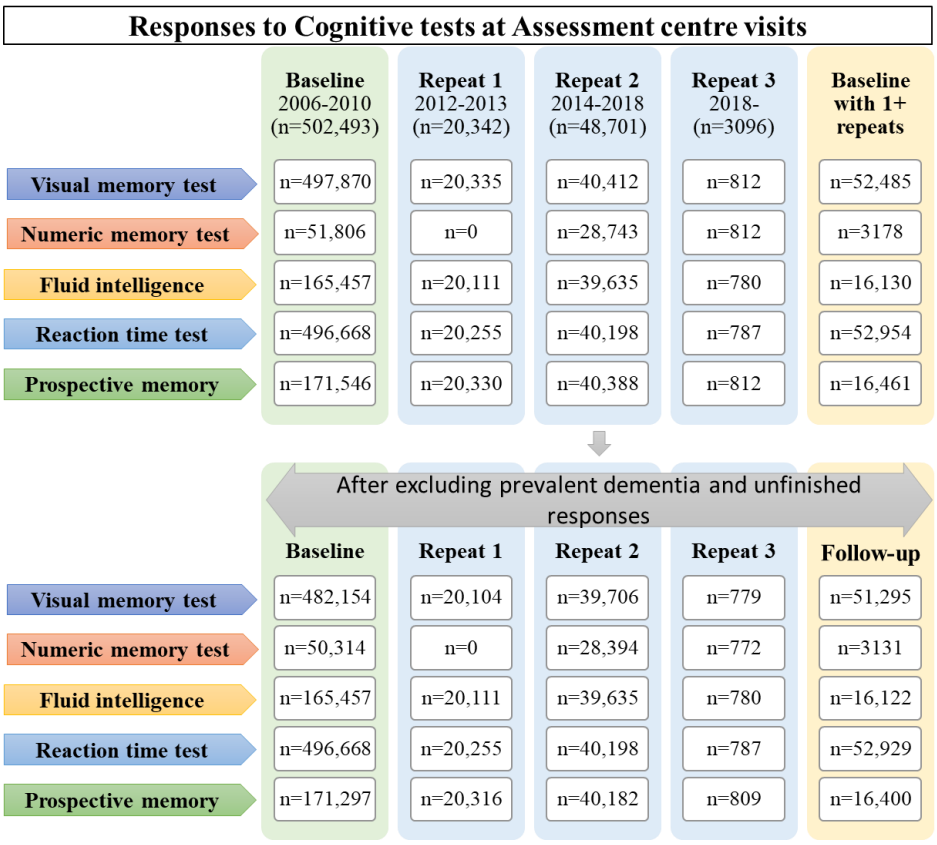


Figure 5.1 Flowchart of participants in each cognitive test in UK Biobank

5.3.4 Covariate assessments

For covariates where participants answered, ‘do not know’ or ‘prefer not to answer’, these responses were classified as missing.

Age at baseline

Age at baseline was calculated as year differences between birth dates and dates of assessment-centre visits and was treated as a continuous variable in adjustment sets.

Ethnicity

Participants were asked to select their ethnic group among ‘White’ (including British, Irish, any other White background), ‘Mixed’ (including White and Black Caribbean, White and Black African, White, and Asian, any other mixed background), ‘Asian or Asian British’ (including Indian, Pakistani, Bangladeshi, any other Asian background), ‘Black or Black British’ (including Caribbean, African, any other Black background), ‘Chinese’, ‘Other ethnic group’, ‘Do not know’ or ‘Prefer not to answer’. All responses were re-grouped into 5 categories as follows: White (White, British, Irish or any other white background); Asian or Asian British (Asian or Asian British, Chinese, Indian, Pakistani, Bangladeshi or any other Asian background); Black or Black British (Black or Black British, Caribbean, African or any other Black background); Mixed Race or others (any other ethnic groups or mixed ethnicity); and unknown (included participants who did not know or preferred not to answer)

Region

Participants were recruited via 22 assessment centres across UK. These centres were grouped into three regions as follows: England (St Bartholomew’s Hospital, Hounslow, Croydon, Stockport, Manchester, Liverpool, Bury, Newcastle, Middlesbrough, Leeds, Sheffield, Stoke, Birmingham, Nottingham, Oxford, Reading, Bristol); Wales (Swansea, Wrexham, Cardiff); Scotland (Glasgow, Edinburgh).

Townsend deprivation Index (TDI)

The Townsend deprivation index was calculated to reflect the socio-economic level of participants based on postcode-specific information on percentage of unemployment, percentage of overcrowded households, percentage of people with

no car ownership, and percentage of non-home owners [289]. The higher the score is the more deprived the participants are. The scores were then categorized into three equal-sized groups as follows: low deprivation, moderate deprivation, and high deprivation, based on the data distribution. Given the risk of over-adjustment in socioeconomic perspective, only TDI was included as a categorical variable in adjustment sets without extra adjustment for employment and home incomes.

Education

Participants were asked to select their acquired qualifications among 'College or University degree', 'A levels/AS levels or equivalent', 'O levels/GCSEs or equivalent', 'CSEs or equivalent', 'NVQ or HND or HNC or equivalent', 'Other professional qualifications e.g.: nursing, teaching', 'None of the above' and 'Prefer not to answer'. These qualifications were regrouped into 'with college/university degree' and 'without college/university degree' based on higher education criteria in the UK (https://www.nidirect.gov.uk/articles/what-higher-education).

Body Mass Index (BMI)

Standing height and weight were measured at baseline according to a standard protocol. BMI was calculated using the formula 'BMI (kg/m^2) = Weight (kg) / Height^2 (m^2)'. BMI was then categorized into three groups as follows: normal or underweight <25 kg/m^2, overweigh 25–29.9 kg/m^2, and obese ≥30 kg/m^2 according to the World Health Organisation (WHO) and National Institute for Health and Clinical Excellence (NICE) criteria [290].

Physical activity

Participants were asked a series of questions about their usual daily activities at baseline that were taken from the International Physical activity questionnaire (IPAQ) short form [291]. Physical activity was calculated and categorized into three levels: low, moderate, and high, according to the guideline for data processing and analysis of IPAQ Short Forms developed by an International Consensus Group [292] (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/ipaq_analysis.pdf).

Smoking status

Participants were asked about specific current and past smoking behaviours separately. These behaviours were grouped into 'Current' (meaning smoking in

current days no matter what situations of previous days were), ‘Past’ (meaning smoking or alcohol drinking in previous days only but not in current days), and ‘Never’ (mean no smoking or alcohol drinking in either current days or previous days).

Sleep duration

Participants were asked about their sleep duration using a question "how many hours sleep do you get in every 24 hours? (include naps)" with rejection of <1 hour or >23 hours, and requests to confirmation of <3 hour or >12 hours. The sleep duration was categorized into three levels: <7, 7–8, >8 hours/day, based on data distribution and used as a categorical variable in adjustment sets.

Stroke history

Participants were asked to report whether they have suffered from a range of conditions including heart disease, stroke, diabetes, Alzheimer’s disease, or dementia, etc. with multiple choices available, and responses to the stoke condition were used to ascertain a stroke history.

Family history of dementia

Participants were asked to report whether their family members (father, adopted father, mother, adopted mother, brothers/sisters, adopted brothers/sisters) have suffered from a range of conditions (including heart disease, stroke, diabetes etc. with multiple choices available). Participants who reported any biological family members with Alzheimer’s disease/dementia were recorded as having a family history of dementia.

5.3.5 Determination of the minimal adjustment set

A directed acyclic graph (DAG) was plotted via the online tool DAGitty (http://www.dagitty.net/) to determine the minimal adjustment set [293]. The DAG below shows the relationships among the exposure (Diet; represented by the green oval with the triangle), the outcome (cognition/dementia; represented by the blue oval pointed by the green arrow), and potentially related factors. Factors that are associated with the exposure as well as the outcome, were automatically labelled as pink ovals if they are not in the middle biological path of the exposure to the outcome; or were automatically labelled as blue ovals if they are in the middle

biological path of the exposure to the outcome. Factors labelled as pink ovals were included in the minimal adjustment set.

The directed acyclic graph (Figure 5.2) showed that age at baseline, gender, self-reported ethnicity, educational level, and socioeconomic status should be adjusted for in the minimally-adjusted model, whereas other potential confounding factors were additionally adjusted for in the fully-adjusted models including body mass index, physical activity level, smoking status, typical sleep duration, stroke history, family history of dementia, region, and alcohol drinking.

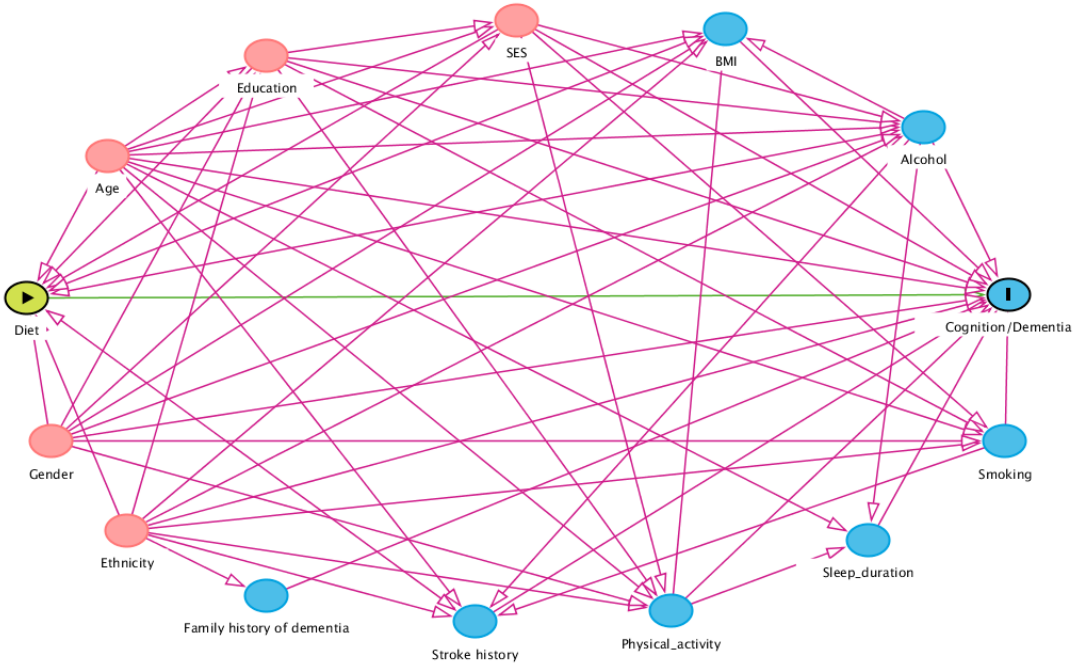


Figure 5.2 Directed acyclic graph to determine the minimal adjustment set

Variables represented as pink ovals are ancestors of the exposure and outcome while variables represented as blue ovals are ancestors only of the outcome. Pink lines are biasing paths and the green line between the exposure and outcome is the causal path of interest. SES, social economic status; BMI, body mass index.

5.3.6 Statistical analysis

Baseline sociodemographic, lifestyle factors, main dietary characteristics, and cognitive performance were summarized for the total sample and among female and male subgroups separately. Cognitive results from baseline assessments of visual memory (number of errors made in pairs-matching test, minus natural log-transformed), numeric memory (number of digits remembered correctly), fluid intelligence score (number of items answered correctly), and reaction time

(milliseconds) were analysed as continuous outcome variables. The prospective memory test at baseline was analysed as a binary outcome variable with the correct answer as the reference. The derived cognitive changes (cognitive deterioration, improved cognition, and unchanged cognition) were used as binary outcome variables with the unchanged cognition as the reference.

Each cognitive test was treated as a separate outcome. For continuous outcomes, the linear regression was used to fit associations with food consumption where beta coefficients (β) and 95% confidence intervals (CI) were reported. For binary outcomes, logistic regression was used to fit associations with food consumption where odds ratios (OR) and 95%CI were reported. Three models were applied in the analyses including unadjusted models, minimally-adjusted models, and fully-adjusted models detailed above. A significant level of P <0.01 was used due to the potential for multiple testing in cognitive tests. Statistical analyses were conducted using Stata/IC, version 16.1 (Stata Corp LP, College Station, TX).

5.4 Results

5.4.1 Baseline characteristics of participants stratified by gender in UK Biobank

Before analyses 564 prevalent dementia cases were excluded. These were determined by self-reports or linkages to hospital episode statistics and death registers. Baseline characteristics of participants are summarized in Table 5.1 stratified by gender. The participants had mean age of 56.5 (SD =8.1) years at baseline, most of them were of white ethnicity and from England, and around 32% had a college/university degree. Compared with women, men were more likely to be deprived (e.g., high deprivation: 34% vs. 33% for men and women respectively), past or current smokers (past smokers: 38% men vs. 31% women; current smokers: 13% men vs. 9% women), drink alcohol more frequently (3–4 times per week or more: 51% men vs. 36% women), overweight (49% men vs. 36% women), and have a stroke history (2% men vs. 1% women). In terms of main food intakes, women consumed more vegetables, fruits, total fish, but less total meat particularly processed meat than men. Regarding the five cognitive function tests, women and men had similar scores in the visual memory test. However, men had more correctly remembered digits, higher fluid intelligence scores, shorter reaction time, and lower proportion of incorrect answers in prospective memory compared with women

(Table 5.1).

Table 5.1 Baseline characteristics of participants for the total sample and among female and male subgroups in the UK Biobank cohort study[1]

	All participants (n = 501,929)	Females (n = 273,128)	Males (n = 228,801)	*P* for difference
Age at baseline (years)	56 (8)	56 (8)	57 (8)	<0.001
Gender		273,128 (54%)	228,801 (46%)	<0.001
Ethnicity				
White	472,690 (94%)	257,434 (94%)	215,256 (94%)	<0.001
Asian	11,413 (2%)	5555 (2%)	5858 (3%)	
Black	8034 (2%)	4636 (2%)	3398 (2%)	
Mixed	3028 (1%)	1894 (1%)	1134 (1%)	
Others/unknown	7328 (1%)	3859 (1%)	3469 (1%)	
Region				
England	445,845 (89%)	242,147 (89%)	203,698 (89%)	<0.001
Wales	20,807 (4%)	11,289 (4%)	9518 (4%)	
Scotland	35,841 (7%)	19,942 (7%)	15,899 (7%)	
Townsend deprivation index				
Low deprivation	167,376 (33%)	90,876 (33%)	76,500 (33%)	<0.001
Moderate deprivation	167,205 (33%)	92,144 (34%)	75,061 (33%)	
High deprivation	167,289 (33%)	90,031 (33%)	77,258 (34%)	
Missing	623 (0.1%)	327 (0.1%)	296 (0.1%)	
Educational level				
Without college/university degree	333,718 (66%)	184,880 (68%)	148,838 (65%)	<0.001
With college/university degree	162,562 (32%)	85,287 (31%)	77,275 (34%)	
Missing	6213 (1%)	3211 (1%)	3002 (1%)	
Smoking status				
Never	273,548 (54%)	162,068 (59%)	111,480 (49%)	<0.001
Past	173,133 (34%)	85,487 (31%)	87,646 (38%)	
Current	52,983 (11%)	24,368 (9%)	28,615 (13%)	
Missing	2829 (0.6%)	1455 (0.5%)	1374 (0.6%)	
Physical activity				
Low level	76,216 (15%)	39,389 (14%)	36,827 (16%)	<0.001
Moderate level	164,018 (33%)	90,518 (33%)	73,500 (32%)	
High level	162,138 (32%)	80,888 (30%)	81,250 (35%)	
Missing	100,121 (20%)	62,583 (23%)	37,538 (16%)	
Body mass index (BMI)				
Normal/underweight (<25 Kg/m^2)	165,068 (33%)	107,766 (39%)	57,302 (25%)	<0.001
Overweight (25-29.9 Kg/m^2)	212,147 (42%)	99,886 (36%)	112,261 (49%)	
Obese (≥30 Kg/m^2)	122,273 (24%)	64,316 (24%)	57,957 (25%)	
Missing	3005 (0.6%)	1410 (0.5%)	1595 (0.7%)	
Sleep duration				
<7 hours/day	123,311 (24%)	65,875 (24%)	57,436 (25%)	<0.001
7-8 hours/day	336,754 (67%)	183,428 (67%)	153,326 (67%)	
>8 hours/day	38,356 (8%)	21,606 (8%)	16,750 (7%)	
Missing	4072 (0.8%)	2469 (0.9%)	1603 (0.7%)	
With stroke history	7668 (2%)	3153 (1%)	4515 (2%)	<0.001
With family history of dementia	58,426 (12%)	33,382 (12%)	25,044 (11%)	<0.001
Alcohol drinking				
Less than once a week	154,500 (31%)	102,709 (38%)	51,791 (23%)	<0.001
Once or twice a week	129,289 (26%)	70,176 (26%)	59,113 (26%)	
Three or four times a week	115,435 (23%)	55,893 (20%)	59,542 (26%)	
Daily or almost daily	101,768 (20%)	43,861 (16%)	57,907 (25%)	
Missing	1501 (0.3%)	739 (0.3%)	762 (0.3%)	

Main food consumption				
Total vegetables (servings/day)	2.5 (1.7)	2.6 (1.6)	2.3 (1.7)	<0.001
Total fruits (servings/day)	2.7 (2.0)	2.9 (2.0)	2.4 (2.0)	<0.001
Total fish (times/week)	2.3 (1.6)	2.3 (1.6)	2.2 (1.6)	<0.001
Oily fish (times/week)	1.1 (1.0)	1.1 (1.0)	1.1 (1.1)	<0.001
Total meat (times/week)	5.5 (2.8)	5.0 (2.6)	6.1 (2.9)	<0.001
Processed meat (times/week)	1.5 (1.4)	1.1 (1.2)	1.9 (1.5)	<0.001
Unprocessed Poultry (times/week)	1.9 (1.3)	1.9 (1.3)	1.9 (1.2)	0.871
Unprocessed Red meat (times/week)	2.1 (1.5)	2 (1.4)	2.3 (1.5)	<0.001
Cognitive function tests				
Visual memory (number of incorrect matches) (N=482,154)	4.3 (3.4)	4.3 (3.3)	4.3 (3.5)	0.861
Numeric memory (Maximum digits) (N=50,314)	6.7 (1.3)	6.6 (1.3)	6.8 (1.4)	<0.001
Fluid intelligence (scores) (N=165,457)	6.0 (2.2)	5.9 (2.1)	6.1 (2.2)	<0.001
Reaction time (ms) (N=496,668)	560 (118)	567 (118)	550 (117)	<0.001
Prospective memory (N=171,297)				
Wrong answer	40,530 (24%)	22,436 (24%)	18,094 (23%)	<0.001
Right answer	130,767 (76%)	70,804 (76%)	59,963 (77%)	

[1]Continues variables are displayed as means (SD), and categorical variables are displayed as numbers (percentages).

5.4.2 Cross-sectional associations between main food consumption and cognitive performance among females and males respectively

The cross-sectional association between main food consumption and cognitive performance was fitted in general linear regression. Reported beta-coefficients indicated the degree of cognitive change as one portion increase of food consumption. In terms of visual memory, the incorrect matches were used as the score with a minus natural log-transformation due to very skewed distribution, so the positive beta-coefficient means better visual memory and vice versa. From Table 5.2, we can see that higher consumption of vegetables, fruits, oily fish, and total fish individually was associated with poorer visual memory, while higher consumption of processed meat, unprocessed poultry, unprocessed red meat, and total meat was related to better visual memory. These associations were consistent among all three models and in both men and women subgroups.

A similar picture can be seen in the numeric memory test and the fluid intelligence test. Higher consumption of vegetables and fruits was related to poorer numeric memory, but higher consumption of unprocessed red meat was related to better numeric memory, particularly in men (Table 5.3). Higher consumption of vegetables, fruits, oily fish, and total fish individually was linked with lower fluid

intelligence scores, while higher consumption of processed meat and total meat was related to higher fluid intelligence scores in both men and women (Table 5.4).

Regarding reaction ability, one portion increase per day of vegetable intakes was associated with 0.9 milliseconds shorter reaction time, particularly in women (1.27 milliseconds shorter), and one portion increase per week of unprocessed poultry intake was related to 1.26 milliseconds shorter reaction time in both men and women. However, higher consumption of fruits, oily fish, total fish, processed meat, unprocessed red meat, and total meat individually was associated with longer reaction time (Table 5.5).

In the prospective memory test, scores were dichotomously recorded (right/wrong initial answers) and then odds ratios were reported using logistic regression. From Table 5.6 we can see that higher consumption of vegetables, fruits, oily fish, total fish, and unprocessed red meat was associated with increased odds of wrong answers both in men and women, while higher consumption of processed meat, unprocessed poultry, and total meat was related to decreased odds of wrong answers.

Table 5.2 Associations between food consumption and visual memory for the total sample and among females and males respectively

	Unadjusted Models				Minimally-adjusted Models[1]				Fully-adjusted Models[2]			
	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*
Total												
Vegetables[3]	473,612	-0.017	-0.019, -0.015	<0.001	469,070	-0.013	-0.015, -0.010	<0.001	382,698	-0.012	-0.014, -0.009	<0.001
Fruits[3]	476,077	-0.010	-0.011, -0.009	<0.001	471,414	-0.009	-0.010, -0.008	<0.001	383,415	-0.008	-0.009, -0.007	<0.001
Oily fish[4]	479,579	-0.018	-0.020, -0.016	<0.001	474,766	-0.017	-0.019, -0.016	<0.001	384,672	-0.017	-0.019, -0.015	<0.001
Total fish[4]	478,170	-0.011	-0.012, -0.010	<0.001	473,428	-0.011	-0.012, -0.010	<0.001	384,047	-0.011	-0.012, -0.010	<0.001
Processed meat[4]	481,217	0.011	0.010, 0.012	<0.001	476,339	0.009	0.008, 0.011	<0.001	385,451	0.008	0.007, 0.010	<0.001
Unprocessed red meat[4]	477,160	0.005	0.004, 0.006	<0.001	472,490	0.006	0.004, 0.007	<0.001	383,588	0.004	0.003, 0.006	<0.001
Unprocessed poultry[4]	481,316	0.006	0.005, 0.008	<0.001	476,404	0.009	0.007, 0.010	<0.001	385,481	0.007	0.006, 0.009	<0.001
Total meat[4]	476,345	0.007	0.006, 0.007	<0.001	471,732	0.006	0.005, 0.007	<0.001	383,271	0.005	0.004, 0.006	<0.001
Females												
Vegetables[3]	259,296	-0.014	-0.017, -0.011	<0.001	256,847	-0.012	-0.015, -0.009	<0.001	201,476	-0.010	-0.014, -0.007	<0.001
Fruits[3]	259,816	-0.009	-0.011, -0.008	<0.001	257,345	-0.009	-0.010, -0.008	<0.001	201,481	-0.008	-0.009, -0.006	<0.001
Oily fish[4]	261,758	-0.018	-0.020, -0.015	<0.001	259,211	-0.017	-0.019, -0.015	<0.001	202,148	-0.017	-0.020, -0.014	<0.001
Total fish[4]	261,094	-0.011	-0.013, -0.010	<0.001	258,581	-0.011	-0.013, -0.010	<0.001	201,888	-0.011	-0.013, -0.009	<0.001
Processed meat[4]	262,441	0.009	0.007, 0.011	<0.001	259,878	0.009	0.007, 0.011	<0.001	202,454	0.007	0.005, 0.009	<0.001
Unprocessed red meat[4]	260,485	0.007	0.005, 0.009	<0.001	258,003	0.008	0.006, 0.009	<0.001	201,615	0.006	0.004, 0.008	<0.001
Unprocessed poultry[4]	262,556	0.005	0.003, 0.007	<0.001	259,975	0.008	0.006, 0.009	<0.001	202,500	0.006	0.004, 0.008	<0.001
Total meat[4]	260,067	0.006	0.005, 0.008	<0.001	257,621	0.007	0.006, 0.008	<0.001	201,458	0.006	0.004, 0.007	<0.001
Males												
Vegetables[3]	214,316	-0.018	-0.021, -0.015	<0.001	212,223	-0.013	-0.016, -0.010	<0.001	181,222	-0.013	-0.016, -0.009	<0.001
Fruits[3]	216,261	-0.009	-0.011, -0.008	<0.001	214,069	-0.009	-0.010, -0.007	<0.001	181,934	-0.008	-0.009, -0.006	<0.001
Oily fish[4]	217,821	-0.018	-0.021, -0.016	<0.001	215,555	-0.018	-0.020, -0.015	<0.001	182,524	-0.017	-0.020, -0.014	<0.001
Total fish[4]	217,076	-0.011	-0.013, -0.010	<0.001	214,847	-0.011	-0.013, -0.010	<0.001	182,159	-0.011	-0.013, -0.009	<0.001
Processed meat[4]	218,776	0.011	0.009, 0.012	<0.001	216,461	0.010	0.008, 0.011	<0.001	182,997	0.009	0.007, 0.011	<0.001
Unprocessed red meat[4]	216,675	0.002	0.000, 0.004	0.033	214,487	0.004	0.002, 0.006	<0.001	181,973	0.003	0.001, 0.005	0.005
Unprocessed poultry[4]	218,760	0.009	0.006, 0.011	<0.001	216,429	0.010	0.008, 0.012	<0.001	182,981	0.009	0.007, 0.012	<0.001
Total meat[4]	216,278	0.005	0.004, 0.006	<0.001	214,111	0.006	0.005, 0.007	<0.001	181,813	0.005	0.004, 0.006	<0.001

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: 95%CI, 95% confidence interval.

Table 5.3 Associations between food consumption and numeric memory for the total sample and among females and males respectively

	Unadjusted Models				Minimally-adjusted Models[1]				Fully-adjusted Models[2]			
	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*
Total												
Vegetables[3]	49,440	-0.071	-0.085, -0.057	<0.001	48,892	-0.059	-0.073, -0.045	<0.001	40,134	-0.055	-0.070, -0.040	<0.001
Fruits[3]	49,642	-0.020	-0.026, -0.014	<0.001	49,075	-0.017	-0.023, -0.011	<0.001	40,175	-0.015	-0.022, -0.008	<0.001
Oily fish[4]	50,037	0.008	-0.004, 0.019	0.180	49,455	-0.002	-0.013, 0.009	0.712	40,314	-0.005	-0.017, 0.007	0.413
Total fish[4]	49,908	0.006	-0.002, 0.013	0.121	49,332	0.001	-0.006, 0.009	0.746	40,254	0.002	-0.006, 0.010	0.613
Processed meat[4]	50,202	0.023	0.014, 0.031	<0.001	49,611	0.005	-0.003, 0.014	0.216	40,395	0.006	-0.003, 0.016	0.185
Unprocessed red meat[4]	49,835	-0.014	-0.022, -0.006	0.001	49,262	-0.022	-0.031, -0.014	<0.001	40,222	-0.019	-0.028, -0.010	<0.001
Unprocessed poultry[4]	50,231	-0.001	-0.010, 0.008	0.815	49,631	0.006	-0.003, 0.015	0.218	40,406	0.007	-0.003, 0.018	0.165
Total meat[4]	49,755	0.004	-0.001, 0.009	0.146	49,193	-0.007	-0.013, -0.002	0.008	40,197	-0.005	-0.011, 0.001	0.083
Females												
Vegetables[3]	27,109	-0.042	-0.061, -0.022	<0.001	26,812	-0.040	-0.060, -0.021	<0.001	21,167	-0.034	-0.055, -0.012	0.002
Fruits[3]	27,120	-0.002	-0.010, 0.006	0.680	26,829	-0.005	-0.013, 0.003	0.229	21,154	-0.005	-0.014, 0.005	0.334
Oily fish[4]	27,350	0.017	0.002, 0.032	0.029	27,042	0.005	-0.011, 0.020	0.563	21,223	-0.002	-0.019, 0.015	0.847
Total fish[4]	27,290	0.008	-0.002, 0.018	0.099	26,987	0.002	-0.008, 0.012	0.655	21,200	0.002	-0.010, 0.013	0.781
Processed meat[4]	27,415	-0.004	-0.018, 0.009	0.513	27,109	-0.001	-0.013, 0.013	0.959	21,255	0.006	-0.009, 0.021	0.438
Unprocessed red meat[4]	27,236	-0.020	-0.031, -0.008	0.001	26,936	-0.021	-0.032, -0.010	<0.001	21,177	-0.014	-0.027, -0.001	0.032
Unprocessed poultry[4]	27,433	-0.008	-0.021, 0.004	0.186	27,121	0.001	-0.012, 0.013	0.975	21,260	0.004	-0.010, 0.018	0.606
Total meat[4]	27,194	-0.010	-0.018, -0.002	0.011	26,901	-0.010	-0.017, -0.002	0.016	21,164	-0.005	-0.014, 0.004	0.309
Males												
Vegetables[3]	22,331	-0.083	-0.103, -0.063	<0.001	22,080	-0.076	-0.096, -0.056	<0.001	18,967	-0.075	-0.097, -0.054	<0.001
Fruits[3]	22,522	-0.026	-0.035, -0.016	<0.001	22,246	-0.030	-0.039, -0.021	<0.001	19,021	-0.026	-0.036, -0.016	<0.001
Oily fish[4]	22,687	0.001	-0.015, 0.018	0.874	22,413	-0.008	-0.025, 0.008	0.331	19,091	-0.008	--0.026, 0.010	0.371
Total fish[4]	22,618	0.006	-0.005, 0.017	0.288	22,345	0.001	-0.010, 0.012	0.864	19,054	0.004	-0.008, 0.015	0.555
Processed meat[4]	22,787	0.005	-0.006, 0.016	0.393	22,502	0.010	-0.001, 0.021	0.089	19,140	0.006	-0.006, 0.018	0.330
Unprocessed red meat[4]	22,599	-0.025	-0.037, -0.013	<0.001	22,326	-0.024	-0.035, -0.012	<0.001	19,045	-0.024	-0.037, -0.011	<0.001
Unprocessed poultry[4]	22,798	0.008	-0.006, 0.022	0.248	22,510	0.012	-0.002, 0.026	0.089	19,146	0.011	-0.004, 0.026	0.159
Total meat[4]	22,561	-0.007	-0.015, 0.000	0.055	22,292	-0.005	-0.012, 0.002	0.184	19,033	-0.006	-0.014, 0.002	0.136

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: 95%CI, 95% confidence interval.

Table 5.4 Associations between food consumption and fluid intelligence for the total sample and among females and males respectively

	Unadjusted Models				Minimally-adjusted Models[1]				Fully-adjusted Models[2]			
	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*
Total												
Vegetables[3]	162,531	-0.188	-0.200, -0.175	<0.001	162,531	-0.153	-0.164, -0.142	<0.001	132,307	-0.144	-0.156, -0.132	<0.001
Fruits[3]	163,233	-0.033	-0.039, -0.028	<0.001	163,233	-0.032	-0.037, -0.027	<0.001	132,513	-0.031	-0.037, -0.025	<0.001
Oily fish[4]	164,437	-0.035	-0.045, -0.025	<0.001	164,437	-0.051	-0.061, -0.042	<0.001	132,966	-0.048	-0.059, -0.038	<0.001
Total fish[4]	163,981	-0.025	-0.032, -0.019	<0.001	163,981	-0.036	-0.042, -0.030	<0.001	132,761	-0.034	-0.041, -0.027	<0.001
Processed meat[4]	164,947	0.059	0.052, 0.066	<0.001	164,947	0.035	0.028, 0.042	<0.001	133,207	0.041	0.034, 0.049	<0.001
Unprocessed red meat[4]	163,749	-0.009	-0.016, -0.001	0.022	163,749	-0.008	-0.015, -0.001	0.026	132,629	-0.008	-0.016, -0.001	0.029
Unprocessed poultry[4]	165,035	-0.021	-0.029, -0.012	<0.001	165,035	0.010	0.002, 0.018	0.011	133,239	0.005	-0.004, 0.013	0.269
Total meat[4]	163,489	0.021	0.017, 0.026	<0.001	163,489	0.011	0.007, 0.016	<0.001	132,529	0.013	0.008, 0.018	<0.001
Females												
Vegetables[3]	88,935	-0.160	-0.177, -0.144	<0.001	88,935	-0.143	-0.158, -0.128	<0.001	69,842	-0.136	-0.153, -0.119	<0.001
Fruits[3]	89,071	-0.029	-0.036, -0.022	<0.001	89,071	-0.032	-0.039, -0.025	<0.001	69,835	-0.035	-0.043, -0.028	<0.001
Oily fish[4]	89,726	-0.032	-0.045, -0.019	<0.001	89,726	-0.051	-0.063, -0.038	<0.001	70,080	-0.051	-0.065, -0.037	<0.001
Total fish[4]	89,520	-0.024	-0.033, -0.016	<0.001	89,520	-0.035	-0.043, -0.027	<0.001	69,995	-0.034	-0.043, -0.025	<0.001
Processed meat[4]	89,935	0.039	0.027, 0.050	<0.001	89,935	0.037	0.026, 0.048	<0.001	70,168	0.046	0.034, 0.058	<0.001
Unprocessed red meat[4]	89,344	0.001	-0.009, 0.011	0.889	89,344	0.009	0.000, 0.019	0.050	69,899	0.005	-0.006, 0.016	0.369
Unprocessed poultry[4]	89,995	-0.035	-0.046, -0.025	<0.001	89,995	0.004	-0.006, 0.014	0.473	70,193	0.002	-0.010, 0.013	0.759
Total meat[4]	89,208	0.015	0.008, 0.022	<0.001	89,208	0.018	0.012, 0.025	<0.001	69,849	0.019	0.012, 0.026	<0.001
Males												
Vegetables[3]	73,596	-0.200	-0.218, -0.182	<0.001	73,596	-0.162	-0.178, -0.145	<0.001	62,465	-0.149	-0.167, -0.131	<0.001
Fruits[3]	74,162	-0.024	-0.032, -0.016	<0.001	74,162	-0.033	-0.041, -0.026	<0.001	62,678	-0.026	-0.035, -0.018	<0.001
Oily fish[4]	74,711	-0.034	-0.049, -0.019	<0.001	74,711	-0.051	-0.065, -0.037	<0.001	62,886	-0.045	-0.060, -0.030	<0.001
Total fish[4]	74,461	-0.024	-0.034, -0.014	<0.001	74,461	-0.038	-0.047, -0.029	<0.001	62,766	-0.034	-0.044, -0.024	<0.001
Processed meat[4]	75,012	0.041	0.030, 0.051	<0.001	75,012	0.033	0.024, 0.043	<0.001	63,039	0.038	0.027, 0.048	<0.001
Unprocessed red meat[4]	74,405	-0.035	-0.046, -0.024	<0.001	74,405	-0.025	-0.035, -0.015	<0.001	62,730	-0.021	-0.031, -0.010	<0.001
Unprocessed poultry[4]	75,040	-0.003	-0.016, 0.010	0.640	75,040	0.016	0.004, 0.028	0.008	63,046	0.007	-0.006, 0.019	0.310
Total meat[4]	74,281	0.004	-0.003, 0.011	0.234	74,281	0.005	-0.002, 0.011	0.151	62,680	0.008	0.001, 0.015	0.023

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: 95%CI, 95% confidence interval.

Table 5.5 Associations between food consumption and reaction ability for the total sample and among females and males respectively

	Unadjusted Models				Minimally-adjusted Models[1]				Fully-adjusted Models[2]			
	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*	Num.	β	95%CI	*P*
Total												
Vegetables[3]	486,567	0.48	0.10, 0.86	0.014	481,551	-1.39	-1.77, -1.02	<0.001	388,834	-0.90	-1.31, -0.49	<0.001
Fruits[3]	489,269	1.05	0.88, 1.21	<0.001	484,117	0.26	0.10, 0.43	0.002	389,621	0.42	0.23, 0.60	<0.001
Oily fish[4]	493,133	1.09	0.78, 1.39	<0.001	487,772	0.71	0.41, 1.01	<0.001	390,935	1.06	0.73, 1.39	<0.001
Total fish[4]	491,563	0.77	0.57, 0.97	<0.001	486,293	0.62	0.43, 0.82	<0.001	390,269	0.88	0.67, 1.10	<0.001
Processed meat[4]	494,930	-0.58	-0.81, -0.35	<0.001	489,478	1.47	1.24, 1.70	<0.001	391,754	1.35	1.10, 1.61	<0.001
Unprocessed red meat[4]	490,428	-0.10	-0.32, 0.12	0.368	485,244	0.28	0.06, 0.50	0.011	389,762	0.26	0.02, 0.50	0.036
Unprocessed poultry[4]	495,037	-1.26	-1.51, -1.01	<0.001	489,552	-1.61	-1.86, -1.36	<0.001	391,797	-1.26	-1.54, -0.99	<0.001
Total meat[4]	489,496	-0.32	-0.47, -0.18	<0.001	484,375	0.65	0.50, 0.79	<0.001	389,417	0.63	0.47, 0.79	<0.001
Females												
Vegetables[3]	266,061	-0.76	-1.34, -0.19	0.009	263,362	-1.78	-2.34, -1.21	<0.001	204,452	-1.27	-1.89, -0.66	<0.001
Fruits[3]	266,649	0.43	0.19, 0.67	<0.001	263,936	0.13	-0.11, 0.36	0.288	204,473	0.24	-0.03, 0.50	0.082
Oily fish[4]	268,793	0.95	0.49, 1.40	<0.001	265,969	0.72	0.28, 1.16	0.001	205,172	1.15	0.65, 1.64	<0.001
Total fish[4]	268,054	0.64	0.35, 0.94	<0.001	265,275	0.61	0.33, 0.90	<0.001	204,896	0.94	0.62, 1.26	<0.001
Processed meat[4]	269,516	1.55	1.18, 1.92	<0.001	266,657	1.79	1.43, 2.16	<0.001	205,486	1.57	1.16, 1.98	<0.001
Unprocessed red meat[4]	267,338	-0.08	-0.43, 0.26	0.630	264,595	-0.14	-0.47, 0.19	0.400	204,587	-0.10	-0.47, 0.27	0.590
Unprocessed poultry[4]	269,645	-1.04	-1.40, -0.68	<0.001	266,777	-1.38	-1.73, -1.03	<0.001	205,544	-1.06	-1.45, -0.67	<0.001
Total meat[4]	266,865	0.43	0.21, 0.66	<0.001	264,160	0.50	0.28, 0.73	<0.001	204,416	0.48	0.23, 0.73	<0.001
Males												
Vegetables[3]	220,506	0.43	-0.11, 0.98	0.118	218,189	-0.96	-1.50, -0.42	0.001	184,382	-0.49	-1.07, 0.09	0.099
Fruits[3]	222,620	0.43	0.19, 0.67	0.001	220,181	0.33	0.09, 0.57	0.007	185,148	0.52	0.26, 0.78	<0.001
Oily fish[4]	224,340	0.89	0.45, 1.34	<0.001	221,803	0.61	0.18, 1.05	0.006	185,763	0.91	0.44, 1.38	<0.001
Total fish[4]	223,509	0.65	0.36, 0.94	<0.001	221,018	0.57	0.28, 0.86	<0.001	185,373	0.78	0.47, 1.09	<0.001
Processed meat[4]	225,414	0.97	0.66, 1.27	<0.001	222,821	1.18	0.87, 1.48	<0.001	186,268	1.17	0.84, 1.50	<0.001
Unprocessed red meat[4]	223,090	1.14	0.83, 1.45	<0.001	220,649	0.64	0.33, 0.94	<0.001	185,175	0.54	0.21, 0.87	0.001
Unprocessed poultry[4]	225,392	-1.62	-1.99, -1.24	<0.001	222,775	-1.91	-2.28, -1.53	<0.001	186,253	-1.50	-1.90, -1.10	<0.001
Total meat[4]	222,631	0.83	0.63, 1.03	<0.001	220,215	0.72	0.52, 0.92	<0.001	185,001	0.71	0.50, 0.92	<0.001

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: 95%CI, 95% confidence interval.

Table 5.6 Associations between food consumption and prospective memory for the total sample and among females and males respectively

	Unadjusted Models				Minimally-adjusted Models[1]				Fully-adjusted Models[2]			
	Num.	OR	95%CI	*P*	Num.	OR	95%CI	*P*	Num.	OR	95%CI	*P*
Total												
Vegetables[3]	167,901	1.13	1.12, 1.14	<0.001	166,022	1.08	1.07, 1.10	<0.001	135,548	1.08	1.07, 1.10	<0.001
Fruits[3]	168,723	1.05	1.05, 1.06	<0.001	166,797	1.04	1.03, 1.04	<0.001	135,769	1.04	1.03, 1.05	<0.001
Oily fish[4]	170,169	1.05	1.04, 1.06	<0.001	168,149	1.05	1.04, 1.06	<0.001	136,268	1.06	1.05, 1.08	<0.001
Total fish[4]	169,604	1.03	1.02, 1.04	<0.001	167,619	1.04	1.03, 1.04	<0.001	136,026	1.04	1.03, 1.05	<0.001
Processed meat[4]	170,761	0.95	0.94, 0.96	<0.001	168,708	0.97	0.97, 0.98	<0.001	136,545	0.97	0.96, 0.98	<0.001
Unprocessed red meat[4]	169,280	1.01	1.00, 1.02	0.084	167,334	1.01	1.00, 1.02	0.023	135,872	1.01	1.00, 1.02	0.010
Unprocessed poultry[4]	170,885	0.99	0.98, 1.00	0.006	168,809	0.98	0.97, 0.99	<0.001	136,586	0.98	0.97, 0.99	<0.001
Total meat[4]	168,950	0.98	0.98, 0.99	<0.001	167,034	0.99	0.99, 1.00	0.022	135,752	0.99	0.99, 1.00	0.048
Females												
Vegetables[3]	91,803	1.11	1.09, 1.13	<0.001	90,793	1.08	1.06, 1.09	<0.001	71,481	1.07	1.05, 1.09	<0.001
Fruits[3]	91,965	1.06	1.05, 1.07	<0.001	90,947	1.04	1.04, 1.05	<0.001	71,467	1.05	1.04, 1.06	<0.001
Oily fish[4]	92,748	1.06	1.04, 1.07	<0.001	91,675	1.06	1.04, 1.07	<0.001	71,733	1.07	1.05, 1.09	<0.001
Total fish[4]	92,489	1.03	1.02, 1.04	<0.001	91,435	1.04	1.03, 1.05	<0.001	71,630	1.05	1.03, 1.06	<0.001
Processed meat[4]	92,986	0.96	0.94, 0.97	<0.001	91,910	0.97	0.96, 0.99	<0.001	71,834	0.97	0.96, 0.99	<0.001
Unprocessed red meat[4]	92,257	0.99	0.98, 1.00	0.092	91,222	0.99	0.98, 1.00	0.270	71,522	1.00	0.98, 1.01	0.532
Unprocessed poultry[4]	93,063	0.99	0.98, 1.00	0.268	91,977	0.98	0.97, 0.99	0.002	71,865	0.98	0.97, 1.00	0.017
Total meat[4]	92,090	0.98	0.97, 0.99	<0.001	91,076	0.99	0.98, 1.00	0.002	71,463	0.99	0.98, 1.00	0.008
Males												
Vegetables[3]	76,098	1.14	1.12, 1.16	<0.001	75,229	1.09	1.07, 1.11	<0.001	64,067	1.09	1.07, 1.11	<0.001
Fruits[3]	76,758	1.05	1.04, 1.05	<0.001	75,850	1.03	1.02, 1.04	<0.001	64,302	1.03	1.02, 1.04	<0.001
Oily fish[4]	77,421	1.05	1.03, 1.07	<0.001	76,474	1.05	1.03, 1.06	<0.001	64,535	1.06	1.04, 1.08	<0.001
Total fish[4]	77,115	1.03	1.02, 1.04	<0.001	76,184	1.03	1.02, 1.04	<0.001	64,396	1.04	1.02, 1.05	<0.001
Processed meat[4]	77,775	0.95	0.94, 0.96	<0.001	76,798	0.97	0.96, 0.99	<0.001	64,711	0.97	0.96, 0.98	<0.001
Unprocessed red meat[4]	77,023	1.03	1.02, 1.04	<0.001	76,112	1.02	1.01, 1.04	<0.001	64,350	1.03	1.01, 1.04	<0.001
Unprocessed poultry[4]	77,822	0.98	0.97, 0.99	0.004	76,832	0.97	0.96,0.98	<0.001	64,721	0.97	0.96, 0.99	0.001
Total meat[4]	76,860	0.99	0.98, 1.00	0.004	75,958	1.00	0.99, 1.01	0.791	64,289	1.00	0.99, 1.01	0.691

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; 95%CI, 95% confidence interval.

5.4.3 Cognitive change: associations between food consumption and cognitive deterioration among females and males respectively

In present study, the standardized regression-based method (SRB) with multiple regression equation was used to determine cognitive changes including cognitive deterioration and improved cognition. The number of participants, cognitive test scores at baseline and at follow-up, and the follow-up intervals among those with cognitive deterioration, those with improved cognition as well as those with unchanged cognition, are summarized in Table 5.7 for each cognitive test. Although the sample size in each cognitive test varied considerably, we can see that cognitive performance became worse in the cognitive deterioration groups and got better in the improved groups for all cognitive tests indicating the SRB method with multiple regression was effective to differentiate participants in current study.

The associations between food consumption and cognitive deterioration were examined for all cognitive tests for the total sample and additionally stratified by gender. In Table 5.8, higher consumption of fruits, oily fish, and total fish was associated with increased risk of deteriorating visual memory. Those associations were consistent among three adjustment models. Consumption of vegetables and all types of meat were not associated with risk of deteriorating visual memory.

In terms of numeric memory, none of the main food groups investigated was associated with a risk of cognitive deterioration in the whole population, and in either women or men subgroups (Table 5.9). The fluid intelligence test has a similar picture, all associations were not significant (Table 5.10).

Regarding reaction ability (Table 5.11), all associations were not significant except that consumption of total fish was linked with increased risk of deteriorating reaction ability only in women (full-adjusted OR=1.05, 95%CI: 1.01, 1.09; P =0.007). In the prospective memory test (Table 5.12), one portion increase per day consumption of vegetables increased the risk of deteriorating prospective memory by 14% (full-adjusted OR=1.14, 95%CI: 1.07, 1.21; P <0.001) in the whole population; the same as in both women and men subgroups. However, consumption of oily fish and total fish individually was related to increased risk of deteriorating prospective memory in unadjusted models in the whole population only, not in either women or men, whereas these associations were adjusted away in the fully-adjusted models.

Table 5.7 The number of participants and classification of cognitive changes in each cognitive test.

	The number of participants	Cognitive deterioration	Improved cognition	Unchanged cognition
Visual memory (Pairs-matching)	51,295	3162 (6%)	206 (0.4%)	47,844 (93%)
Incorrect matches at baseline (Mean±SD)		4.66 ± 3.65	11.9 ± 5.20	3.80 ± 2.94
Incorrect matches at follow-up (Mean±SD)		11.5 ± 3.31	0.35 ± 0.70	3.24 ± 2.07
Follow-up interval (years, Mean±SD)		7.68 ± 2.47	7.51 ± 2.48	7.67 ± 2.45
Numeric memory	3131	168 (5%)	134 (4%)	2820 (90%)
Remembered digits correctly at baseline (Mean±SD)		6.80 ± 1.25	6.72 ± 1.67	6.99 ± 1.21
Remembered digits correctly at follow-up (Mean±SD)		4.43 ± 0.93	8.88 ± 0.97	6.85 ± 1.06
Follow-up interval (years, Mean±SD)		8.89 ± 0.74	8.93 ± 0.77	8.87 ± 0.75
Fluid intelligence (reasoning)	16,122	794 (5%)	795 (5%)	14,499 (90%)
Number of right answers at baseline (Mean±SD)		7.15 ± 1.93	6.72 ± 2.05	6.74 ± 2.03
Number of right answers at follow-up (Mean±SD)		3.81 ± 1.38	9.97 ± 1.38	6.74 ± 1.86
Follow-up interval (years, Mean±SD)		6.91 ± 2.30	6.97 ± 2.03	6.88 ± 2.26
Reaction ability (snap)	52,929	2971 (6%)	901 (2%)	48,969 (93%)
Reaction time at baseline (ms, Mean±SD)		579 ± 111	736 ± 182	536 ± 95
Reaction time at follow-up (ms, Mean±SD)		857 ± 129	499 ± 74	573 ± 87
Follow-up interval (years, Mean±SD)		7.85 ± 2.40	7.80 ± 2.53	7.68 ± 2.46
Prospective memory	16,400	1320 (8%)	1429 (9%)	13,651 (83%)
Wrong answers at baseline N (%)		0 (0%)	1429 (66%)	744 (34%)
Wrong answers at follow-up N (%)		1320 (64%)	0 (0%)	744 (36%)
Follow-up interval (years, Mean±SD)		7.60 ± 2.01	6.68 ± 2.29	6.83 ± 2.25

Table 5.8 Associations between food consumption and **cognitive deterioration** in visual memory in the UK Biobank

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	50,822	1.08	1.04	1.13	<0.001	50,822	1.07	1.03	1.12	0.001	43,710	1.05	1.00	1.10	0.032
Fruits[3]	50,898	1.04	1.02	1.06	<0.001	50,898	1.04	1.02	1.06	<0.001	43,726	1.04	1.01	1.06	0.002
Oily fish[4]	51,118	1.10	1.07	1.14	<0.001	51,118	1.08	1.05	1.12	<0.001	43,832	1.08	1.04	1.12	<0.001
Total fish[4]	51,059	1.07	1.04	1.09	<0.001	51,059	1.06	1.03	1.08	<0.001	43,809	1.05	1.02	1.08	<0.001
Processed meat[4]	51,177	1.00	0.98	1.03	0.954	51,177	0.99	0.96	1.01	0.339	43,871	0.98	0.95	1.01	0.255
Unprocessed red meat[4]	50,999	0.99	0.97	1.02	0.607	50,999	0.98	0.95	1.01	0.118	43,780	0.98	0.95	1.01	0.150
Unprocessed poultry[4]	51,178	0.98	0.95	1.01	0.124	51,178	0.98	0.95	1.01	0.265	43,875	0.99	0.96	1.03	0.725
Total meat[4]	50,966	0.99	0.98	1.01	0.406	50,966	0.99	0.97	1.00	0.089	43,762	0.99	0.98	1.01	0.171
Females															
Vegetables[3]	26,344	1.06	1.00	1.14	0.068	26,344	1.05	0.98	1.12	0.184	21,844	1.04	0.97	1.12	0.255
Fruits[3]	26,350	1.05	1.02	1.08	<0.001	26,350	1.04	1.01	1.07	0.012	21,832	1.04	1.01	1.08	0.029
Oily fish[4]	26,456	1.12	1.07	1.18	<0.001	26,456	1.10	1.05	1.16	<0.001	21,877	1.11	1.05	1.17	0.001
Total fish[4]	26,427	1.07	1.03	1.10	<0.001	26,427	1.06	1.02	1.09	0.001	21,866	1.05	1.01	1.09	0.021
Processed meat[4]	26,476	0.99	0.95	1.04	0.735	26,476	1.00	0.96	1.05	0.984	21,891	0.99	0.94	1.04	0.671
Unprocessed red meat[4]	26,409	0.99	0.95	1.03	0.522	26,409	0.98	0.94	1.02	0.255	21,853	0.97	0.92	1.01	0.141
Unprocessed poultry[4]	26,484	0.98	0.93	1.02	0.238	26,484	0.98	0.94	1.02	0.305	21,894	0.98	0.94	1.03	0.435
Total meat[4]	26,391	0.99	0.97	1.01	0.323	26,391	0.99	0.97	1.01	0.297	21,843	0.99	0.96	1.01	0.221
Males															
Vegetables[3]	24,478	1.11	1.06	1.17	<0.001	24,478	1.09	1.04	1.15	0.001	21,866	1.06	1.00	1.13	0.069
Fruits[3]	24,548	1.05	1.02	1.07	<0.001	24,548	1.04	1.01	1.07	0.004	21,894	1.03	1.00	1.06	0.028
Oily fish[4]	24,662	1.09	1.04	1.14	<0.001	24,662	1.07	1.02	1.12	0.006	21,955	1.07	1.01	1.12	0.011
Total fish[4]	24,632	1.07	1.04	1.10	<0.001	24,632	1.06	1.02	1.09	<0.001	21,943	1.05	1.02	1.09	0.003
Processed meat[4]	24,701	0.97	0.94	1.01	0.105	24,701	0.98	0.95	1.02	0.250	21,980	0.98	0.94	1.02	0.297
Unprocessed red meat[4]	24,590	0.98	0.95	1.02	0.398	24,590	0.98	0.94	1.02	0.257	21,927	0.99	0.95	1.03	0.506
Unprocessed poultry[4]	24,694	0.98	0.94	1.02	0.238	24,694	0.99	0.95	1.03	0.541	21,981	1.00	0.96	1.05	0.873
Total meat[4]	24,575	0.98	0.97	1.00	0.080	24,575	0.99	0.97	1.01	0.160	21,919	0.99	0.97	1.01	0.433

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

Table 5.9 Associations between food consumption and **cognitive deterioration** in numeric memory in the UK Biobank

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	3098	0.97	0.79	1.19	0.745	3098	0.98	0.80	1.20	0.858	2694	0.94	0.73	1.21	0.611
Fruits[3]	3105	1.04	0.95	1.13	0.434	3105	1.04	0.95	1.13	0.412	2693	1.01	0.91	1.11	0.902
Oily fish[4]	3114	0.96	0.82	1.13	0.604	3114	0.95	0.81	1.12	0.545	2697	0.94	0.79	1.13	0.516
Total fish[4]	3111	0.97	0.87	1.07	0.531	3111	0.97	0.87	1.08	0.559	2696	0.97	0.86	1.09	0.557
Processed meat[4]	3120	1.06	0.95	1.18	0.337	3120	1.04	0.93	1.18	0.496	2702	1.00	0.87	1.14	0.965
Unprocessed red meat[4]	3113	1.01	0.90	1.13	0.887	3113	1.00	0.89	1.13	0.989	2699	0.98	0.86	1.12	0.796
Unprocessed poultry[4]	3122	1.16	1.02	1.33	0.021	3122	1.16	1.02	1.33	0.025	2703	1.14	0.99	1.32	0.073
Total meat[4]	3112	1.05	0.99	1.11	0.093	3112	1.05	0.98	1.11	0.151	2698	1.02	0.96	1.10	0.495
Females															
Vegetables[3]	1588	1.04	0.83	1.30	0.729	1588	1.06	0.86	1.31	0.591	1336	—	—	—	—
Fruits[3]	1587	1.07	0.95	1.20	0.295	1587	1.06	0.93	1.19	0.409	1334	1.01	0.87	1.17	0.891
Oily fish[4]	1589	0.96	0.72	1.29	0.804	1589	0.97	0.72	1.30	0.816	1334	1.02	0.75	1.33	0.881
Total fish[4]	1586	0.98	0.82	1.16	0.789	1586	0.98	0.82	1.18	0.854	1333	1.02	0.84	1.23	0.875
Processed meat[4]	1593	1.13	0.92	1.39	0.258	1593	1.16	0.94	1.43	0.180	1336	1.14	0.90	1.45	0.269
Unprocessed red meat[4]	1589	0.91	0.74	1.10	0.318	1589	0.89	0.72	1.10	0.264	1335	0.86	0.68	1.08	0.193
Unprocessed poultry[4]	1594	1.14	0.94	1.39	0.188	1594	1.13	0.93	1.37	0.217	1337	1.09	0.89	1.35	0.409
Total meat[4]	1588	1.04	0.94	1.15	0.493	1588	1.03	0.93	1.15	0.533	1334	1.01	0.90	1.14	0.818
Males															
Vegetables[3]	1510	0.93	0.66	1.30	0.661	1510	0.92	0.64	1.30	0.624	1358	0.83	0.52	1.34	0.454
Fruits[3]	1518	1.02	0.91	1.16	0.723	1518	1.02	0.90	1.15	0.736	1359	1.01	0.88	1.15	0.939
Oily fish[4]	1525	0.95	0.79	1.14	0.587	1525	0.94	0.78	1.14	0.535	1363	0.88	0.71	1.09	0.241
Total fish[4]	1525	0.96	0.84	1.09	0.514	1525	0.96	0.84	1.09	0.524	1363	0.92	0.79	1.08	0.304
Processed meat[4]	1527	0.99	0.86	1.14	0.889	1527	1.00	0.87	1.14	0.944	1366	0.94	0.80	1.11	0.441
Unprocessed red meat[4]	1524	1.08	0.94	1.24	0.285	1524	1.09	0.95	1.26	0.234	1364	1.09	0.94	1.28	0.259
Unprocessed poultry[4]	1528	1.19	1.00	1.41	0.053	1528	1.19	1.00	1.41	0.052	1366	1.16	0.96	1.41	0.128
Total meat[4]	1524	1.05	0.98	1.13	0.178	1524	1.06	0.98	1.13	0.146	1364	1.03	0.95	1.12	0.443

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

Table 5.10 Associations between food consumption and **cognitive deterioration** in fluid intelligence in the UK Biobank

	Unadjusted Models					**Minimally-adjusted Models[1]**					**Fully-adjusted Models[2]**				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	15,987	1.00	0.91	1.08	0.902	15,987	1.01	0.92	1.10	0.884	13,855	1.01	0.92	1.11	0.789
Fruits[3]	16,009	1.03	0.99	1.07	0.183	16,009	1.03	0.99	1.07	0.161	13,863	1.03	0.99	1.08	0.178
Oily fish[4]	16,054	1.03	0.96	1.11	0.353	16,054	1.04	0.97	1.11	0.327	13,886	1.02	0.95	1.10	0.606
Total fish[4]	16,039	1.02	0.97	1.07	0.517	16,039	1.02	0.97	1.07	0.476	13,880	1.00	0.95	1.06	0.923
Processed meat[4]	16,083	1.02	0.97	1.08	0.383	16,083	1.01	0.96	1.06	0.782	13,905	1.00	0.95	1.06	0.879
Unprocessed red meat[4]	16,047	1.04	0.99	1.09	0.139	16,047	1.04	0.99	1.10	0.119	13,889	1.04	0.98	1.09	0.220
Unprocessed poultry[4]	16,080	1.04	0.98	1.10	0.234	16,080	1.05	0.99	1.11	0.106	13,904	1.05	0.99	1.12	0.140
Total meat[4]	16,043	1.02	1.00	1.05	0.095	16,043	1.02	1.00	1.05	0.102	13,886	1.02	0.99	1.05	0.181
Females															
Vegetables[3]	8111	0.92	0.79	1.06	0.224	8111	0.93	0.81	1.07	0.307	6758	0.92	0.79	1.08	0.311
Fruits[3]	8109	1.01	0.95	1.07	0.845	8109	1.01	0.95	1.08	0.734	6754	1.01	0.93	1.09	0.823
Oily fish[4]	8136	1.02	0.92	1.14	0.678	8136	1.03	0.93	1.15	0.550	6767	0.98	0.87	1.10	0.720
Total fish[4]	8128	1.00	0.93	1.08	0.991	8128	1.01	0.94	1.08	0.855	6764	0.97	0.89	1.05	0.395
Processed meat[4]	8148	1.08	0.99	1.18	0.106	8148	1.08	0.99	1.18	0.088	6774	1.09	1.00	1.20	0.062
Unprocessed red meat[4]	8133	1.00	0.92	1.08	0.903	8133	1.01	0.94	1.09	0.762	6767	1.00	0.92	1.09	0.999
Unprocessed poultry[4]	8147	1.09	1.00	1.18	0.046	8147	1.12	1.03	1.22	0.010	6773	1.11	1.01	1.22	0.030
Total meat[4]	8130	1.03	0.99	1.08	0.122	8130	1.04	1.00	1.09	0.039	6764	1.04	1.00	1.09	0.067
Males															
Vegetables[3]	7876	1.07	0.97	1.19	0.177	7876	1.07	0.96	1.19	0.215	7097	1.08	0.96	1.20	0.202
Fruits[3]	7900	1.05	1.00	1.11	0.052	7900	1.05	1.00	1.11	0.077	7109	1.05	0.99	1.12	0.087
Oily fish[4]	7918	1.04	0.95	1.14	0.404	7918	1.04	0.95	1.14	0.429	7119	1.05	0.95	1.16	0.347
Total fish[4]	7911	1.03	0.97	1.09	0.405	7911	1.03	0.96	1.10	0.406	7116	1.03	0.97	1.10	0.364
Processed meat[4]	7935	0.97	0.91	1.03	0.294	7935	0.97	0.91	1.04	0.382	7131	0.97	0.90	1.03	0.321
Unprocessed red meat[4]	7914	1.06	1.00	1.14	0.071	7914	1.07	1.00	1.14	0.057	7122	1.07	0.99	1.14	0.079
Unprocessed poultry[4]	7933	0.99	0.91	1.07	0.752	7933	1.00	0.92	1.09	0.994	7131	1.01	0.93	1.10	0.831
Total meat[4]	7913	1.00	0.97	1.04	0.821	7913	1.01	0.97	1.05	0.608	7122	1.01	0.97	1.05	0.673

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

Table 5.11 Associations between food consumption and **cognitive deterioration** in reaction ability in the UK Biobank

	Unadjusted Models					**Minimally-adjusted Models[1]**					**Fully-adjusted Models[2]**				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	52,423	1.04	0.99	1.09	0.119	52,423	1.02	0.97	1.07	0.465	44,359	1.03	0.98	1.09	0.211
Fruits[3]	52,508	1.02	1.00	1.04	0.082	52,508	1.01	0.99	1.03	0.575	44,385	1.01	0.99	1.03	0.552
Oily fish[4]	52,738	1.03	0.99	1.07	0.137	52,738	1.00	0.97	1.04	0.866	44,492	1.02	0.98	1.06	0.420
Total fish[4]	52,676	1.02	1.00	1.05	0.073	52,676	1.01	0.99	1.03	0.445	44,468	1.02	0.99	1.04	0.251
Processed meat[4]	52,802	0.98	0.96	1.01	0.240	52,802	0.99	0.97	1.02	0.632	44,533	1.00	0.97	1.03	0.857
Unprocessed red meat[4]	52,627	1.01	0.98	1.03	0.724	52,627	1.00	0.97	1.02	0.758	44,439	0.99	0.96	1.02	0.343
Unprocessed poultry[4]	52,804	0.96	0.93	0.98	0.002	52,804	0.96	0.93	0.99	0.009	44,537	0.96	0.93	1.00	0.031
Total meat[4]	52,589	0.99	0.98	1.00	0.078	52,589	0.99	0.98	1.00	0.120	44,420	0.99	0.97	1.00	0.114
Females															
Vegetables[3]	27,134	1.05	0.98	1.13	0.147	27,134	1.03	0.96	1.11	0.372	22,128	1.04	0.96	1.12	0.314
Fruits[3]	27,141	1.03	1.00	1.05	0.055	27,141	1.01	0.98	1.04	0.534	22,119	1.02	0.99	1.05	0.305
Oily fish[4]	27,254	1.05	1.00	1.11	0.050	27,254	1.02	0.97	1.08	0.394	22,168	1.07	1.00	1.13	0.039
Total fish[4]	27,225	1.05	1.01	1.08	0.006	27,225	1.03	1.00	1.07	0.047	22,157	1.05	1.01	1.09	0.007
Processed meat[4]	27,277	0.98	0.94	1.03	0.386	27,277	0.99	0.94	1.03	0.585	22,182	1.01	0.96	1.06	0.737
Unprocessed red meat[4]	27,210	1.02	0.98	1.06	0.398	27,210	1.00	0.97	1.04	0.865	22,144	1.00	0.96	1.04	0.874
Unprocessed poultry[4]	27,285	0.97	0.93	1.01	0.146	27,285	0.97	0.93	1.02	0.214	22,185	0.98	0.93	1.02	0.325
Total meat[4]	27,190	0.99	0.97	1.01	0.532	27,190	0.99	0.97	1.01	0.469	22,134	1.00	0.97	1.02	0.695
Males															
Vegetables[3]	25,289	1.02	0.96	1.09	0.507	25,289	1.00	0.94	1.08	0.902	22,231	1.02	0.96	1.10	0.502
Fruits[3]	25,367	1.01	0.98	1.04	0.678	25,367	1.00	0.97	1.03	0.889	22,266	1.00	0.97	1.03	0.889
Oily fish[4]	25,484	1.00	0.95	1.06	0.899	25,484	0.98	0.94	1.04	0.528	22,324	0.97	0.92	1.03	0.352
Total fish[4]	25,451	0.99	0.96	1.03	0.744	25,451	0.98	0.95	1.02	0.366	22,311	0.98	0.94	1.02	0.281
Processed meat[4]	25,525	0.99	0.96	1.03	0.599	25,525	1.00	0.96	1.03	0.841	22,351	0.99	0.95	1.03	0.694
Unprocessed red meat[4]	25,417	1.00	0.96	1.03	0.827	25,417	0.99	0.95	1.03	0.531	22,295	0.98	0.94	1.02	0.277
Unprocessed poultry[4]	25,519	0.94	0.90	0.98	0.005	25,519	0.95	0.90	0.99	0.013	22,352	0.95	0.91	1.00	0.039
Total meat[4]	25,399	0.98	0.97	1.00	0.104	25,399	0.99	0.97	1.01	0.136	22,286	0.98	0.96	1.00	0.083

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

Table 5.12 Associations between food consumption and **cognitive deterioration** in prospective memory in the UK Biobank

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	16,291	1.17	1.11	1.24	<0.001	16,254	1.15	1.08	1.22	<0.001	14,062	1.14	1.07	1.21	<0.001
Fruits[3]	16,314	1.04	1.01	1.07	0.013	16,276	1.03	1.00	1.06	0.057	14,071	1.03	1.00	1.07	0.075
Oily fish[4]	16,363	1.10	1.04	1.16	0.001	16,327	1.07	1.01	1.13	0.026	14,095	1.03	0.97	1.10	0.306
Total fish[4]	16,347	1.05	1.01	1.09	0.008	16,311	1.04	1.00	1.08	0.057	14,089	1.01	0.97	1.06	0.495
Processed meat[4]	16,395	1.01	0.97	1.05	0.736	16,357	1.01	0.97	1.06	0.560	14,115	1.01	0.97	1.06	0.662
Unprocessed red meat[4]	16,355	1.03	0.99	1.07	0.166	16,319	1.01	0.97	1.06	0.533	14,098	1.01	0.97	1.06	0.564
Unprocessed poultry[4]	16,393	0.99	0.95	1.04	0.669	16,355	0.99	0.95	1.04	0.718	14,114	0.98	0.93	1.04	0.516
Total meat[4]	16,351	1.01	0.99	1.03	0.544	16,315	1.01	0.98	1.03	0.691	14,095	1.00	0.98	1.03	0.847
Females															
Vegetables[3]	8267	1.15	1.06	1.24	0.001	8247	1.12	1.04	1.22	0.004	6863	1.14	1.04	1.24	0.003
Fruits[3]	8264	1.05	1.01	1.10	0.023	8243	1.04	0.99	1.09	0.099	6858	1.03	0.98	1.09	0.233
Oily fish[4]	8296	1.11	1.03	1.20	0.008	8275	1.09	1.00	1.18	0.043	6873	1.05	0.96	1.15	0.255
Total fish[4]	8288	1.06	1.01	1.12	0.025	8267	1.05	1.00	1.11	0.077	6870	1.02	0.96	1.08	0.528
Processed meat[4]	8309	1.04	0.97	1.11	0.308	8288	1.04	0.97	1.12	0.255	6880	1.05	0.97	1.14	0.225
Unprocessed red meat[4]	8293	1.01	0.95	1.07	0.860	8273	0.99	0.93	1.05	0.721	6873	0.99	0.93	1.06	0.838
Unprocessed poultry[4]	8308	0.98	0.91	1.04	0.470	8287	0.97	0.90	1.03	0.308	6879	0.96	0.89	1.03	0.246
Total meat[4]	8290	1.00	0.97	1.04	0.850	8270	1.00	0.96	1.03	0.866	6870	1.00	0.96	1.04	0.909
Males															
Vegetables[3]	8024	1.20	1.11	1.31	<0.001	8007	1.18	1.08	1.29	<0.001	7199	1.14	1.05	1.25	0.003
Fruits[3]	8050	1.03	0.99	1.07	0.155	8033	1.02	0.98	1.07	0.261	7213	1.03	0.99	1.08	0.185
Oily fish[4]	8067	1.08	1.00	1.17	0.042	8052	1.05	0.97	1.13	0.226	7222	1.02	0.94	1.11	0.668
Total fish[4]	8059	1.04	0.99	1.10	0.124	8044	1.03	0.98	1.08	0.316	7219	1.01	0.96	1.07	0.686
Processed meat[4]	8086	0.98	0.93	1.03	0.457	8069	1.00	0.95	1.05	0.926	7235	0.99	0.94	1.05	0.760
Unprocessed red meat[4]	8062	1.05	0.99	1.11	0.098	8046	1.04	0.98	1.10	0.216	7225	1.03	0.97	1.10	0.342
Unprocessed poultry[4]	8085	1.00	0.94	1.07	0.913	8068	1.02	0.95	1.09	0.599	7235	1.01	0.94	1.08	0.769
Total meat[4]	8061	1.01	0.98	1.04	0.693	8045	1.01	0.98	1.04	0.458	7225	1.01	0.97	1.04	0.690

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

5.4.4 Cognitive change: associations between food consumption and improved cognition among females and males respectively

When taking the improved cognition as the outcome, an odds ratio of more than 1 means potentially protective effects and vice versa. In the A-Table 5.1 of Appendix E, consumption of the investigated foods was not associated with the improved visual memory in the fully-adjusted models. A same picture was seen in the numeric memory (the A-Table 5.2 of Appendix E), all associations were not significant.

In terms of the fluid intelligence (the A-Table 5.3 of Appendix E), one portion increase per day consumption of vegetables reduced the odds of improved fluid intelligence by 17% (fully-adjusted OR=0.83, 95%CI: 0.74, 0.93; *P* =0.002) in the whole population; the trend was consistent among the three adjustment models.

In the A-Table 5.4 of Appendix E, no significant association of food consumption was observed in relation to improved cognition in reaction ability. Regarding the prospective memory (the A-Table 5.5 of Appendix E), consumption of total fish was related to increased odds of improved prospective memory in the fully-adjusted models among the whole population (fully-adjusted OR=1.05, 95%CI: 1.01, 1.09; *P* =0.008) and the women subgroup (fully-adjusted OR=1.08, 95%CI: 1.02, 1.14; *P* =0.006).

5.5 Discussion

In this population-based cohort study, results show that men had better cognitive performance than women in numeric memory, fluid intelligence, reaction ability, and prospective memory. High consumption of vegetables, fruits, oily fish, and total fish individually were associated with poor cognitive performance in most cognitive tests, while consumption of unprocessed poultry was related to better cognitive performance in visual memory, reaction ability, and prospective memory. Consumption of processed meat, unprocessed red meat, or total meat had inconsistent associations with the five cognitive function tests. Generally, these cross-sectional associations between food consumption and cognitive performance in UK Biobank did not support the initial hypotheses of this present study.

Higher consumption of vegetables and fruits has been shown to be associated with better cognitive performance in some epidemiological studies. A community survey

study (45 to 102 years old, n=193) in Germany showed that healthy dwellers of any age consuming high amounts of fruits and vegetables had better cognitive performance than those of any age with low daily intakes of fruits and vegetables; where the association may be potentially explained by with higher levels of antioxidants and lower levels of oxidative stress biomarkers in blood related to higher daily intakes of fruits and vegetables [294]. A cross-sectional study conducted in 22,635 older adults from 11 European countries showed that fruit and vegetable consumption correlated positively with short-term memory and long-term memory, but the correlations were small and there were substantial cross-national differences [295]. The effect sizes of food consumption on cognition in present study were small in comparison to the mean values of cognitive tests. For example, each one portion per day increase of vegetable consumption was associated with decreased numeric memory by 0.055 scores, only accounting for 0.8% of the mean value (a score of 6.7) in the numeric memory test. Each one portion per day increase of fruit consumption was associated with 0.42 ms longer in reaction ability test, accounting for 0.07% of the mean reaction time (560 ms). Therefore, the cross-sectional associations could be a chance finding due to large sample sizes. However, the direction of effect is not always consistent between the cognitive tests in the literature. Intakes of fruit and vegetable were positively associated with verbal memory scores, but negatively associated with executive functioning scores in 2533 French adults [296]. In addition, higher intakes of vegetables were related to lower information processing speed ($P = 0.02$) and worse cognitive flexibility ($P = 0.03$) cross-sectionally in the Doetinchem Cohort Study [297]; findings that are in line with current results.

Generally, in the literature the association between fish consumption and cognitive performance is inconsistent [219] or non-significant [283]. Although higher consumption of oily fish has been associated with better verbal memory, statistically non-significant associations have been found with other fish types [284]. The evidence concerning meat consumption and cognitive performance is weak and limited. A study on cognitively healthy individuals in Sweden showed that low consumption of meat and meat products was associated with better cognitive performance in clinical dementia screening tests [174]. However, vegan or vegetarian diets were found not to be associated with cognitive impairment in a

systematic review which has retrieved one cross-sectional study and one prospective study from 1249 publications up to July 2018 [298]. One previous review on meat consumption found there were non-significant associations with cognitive performance in most studies [5]. Those studies as well as the findings in this analysis suggested that the cross-sectional associations between food consumption and cognitive performance were unstable, and longitudinal studies are needed.

The longitudinal results of present study show that high fruit consumption was associated with increased risk of deteriorating visual memory, while high vegetable consumption was related to increased risk of deteriorating prospective memory. Higher intakes of oily fish and total fish were associated with higher risks of cognitive decline in visual memory, and reaction ability. Meat consumption of any types was not related to cognitive decline in all five cognitive tests. Although these associations were against the initial hypotheses of this study, the effect direction is consistent with the cross-sectional findings above.

Regular consumption of vegetables has been linked with a reduced risk of cognitive decline in previous studies. The Nurses' Health Study including 121,700 female nurses suggested that consumption of vegetables, especially cruciferous vegetables and most green leafy vegetables, was significantly associated with a lower risk of cognitive decline [299]. A dose-response analysis showed that compared with participants who consumed vegetables in the lowest quintile, cognitive function in participants of the fourth quintile declined at a slower rate by 0.019 standardized units per year, and in participants of the fifth quintile declined at a slower rate by 0.018 standardized units per year [300]. The findings in present study were not consistent with these previous studies. The underlying reasons for the positive associations in this project between fruit and vegetable consumption and risk of cognitive decline are not understood. One explanation for current results may be a lower protein intake with high consumption of vegetables and fruits, since adequate protein intakes, especially animal-source protein such as from total meat and eggs, has been cross-sectionally associated with a better performance on certain cognitive tests [129] and linked to a reduced risk of mild cognitive impairment in the elderly [301]. On the other hand, dietary information on specific vegetable and fruit types was not available in this study since this was not collected, and in addition, the

dietary assessments may be not accurate and prone to measurement errors which may have biased current findings. In addition, the potentially protective effect of vegetable and fruit intakes may have a plateau whereby if one certain amount is reached, no further health benefits could be found. There is also a possibility of publication bias that non-significant results or contradictory results against the dominant findings are not published. Overall, further studies are needed to determine the optimal amount and specific types of food in relation to cognitive performance.

Several limitations of this study should be noted. Firstly, the baseline touchscreen brief FFQ was designed to collect basic dietary information on some commonly consumed foods or food groups; thus, it was recognised that this questionnaire was not suitable to assess total energy or nutrient intakes. Secondly, only linear trends of food consumption were analysed in relation to cognitive performance, while exploration of categorical or non-linear models potentially explaining the inconsistent findings in the study was not conducted. Thirdly, although the effect sizes were significant, they are relatively small; particularly the beta-coefficients were small compared with the mean values of cognitive tests. In addition, there were multiple tests in the analyses which might have resulted in increased type I errors due to multiple comparisons, even though a more stringent significant level (P <0.01) was used in present study. Therefore, there is a possibility that the statistical significance in present study may have occurred by chance.

Fourthly, the follow-up duration is relatively limited (6 to 8 years) which may have reduced the ability to distinguish cognitive decline observed in the Whitehall II cohort study with over 20 years follow-up [302]. Fifthly, the repeated scores of cognitive tests were only available in part of the total sample (6%–11%); many non-completers of cognitive tests either did not respond to the whole repeat assessment or quitted from some cognitive tests, which might have led to a potential selection bias. For example, participants who quitted from a certain cognitive test might not be able to complete the test and prone to deteriorating cognition. In addition, the cognitive change itself is complex, and the potential learning experience was not considered that may have improved the follow-up cognitive tests; therefore, methods of cognition assessment should be developed further.

In conclusion, the findings of present study suggest that higher intakes of vegetables,

fruits, and fish may be associated with poorer cognitive performance cross-sectionally and longitudinally, while meat consumption may be related to better cognitive performance cross-sectionally. These findings need to be confirmed in other studies since so far similar findings are few.

CHAPTER VI

6. The associations of food consumption with prevalent and incident dementia in the UK Biobank

6.1 Summary

6.1.1 Highlights

- High consumption of meat, especially processed meat, was associated with increased risk of prevalent and incident dementia in generalized linear models.
- A non-linear association between incident dementia and meat consumption was indicated, which was independent of the *APOE* ε4 allele.
- High consumption of vegetables, fruits, and fish was associated with increased risk of incident dementia but not prevalent dementia.

6.1.2 Abstract

Background: Worldwide, the prevalence of dementia is increasing but a potential role of food consumption in the development of dementia remains poorly understood. Meat consumption has been linked with dementia, but specific amounts and types have not been adequately explored. Consumption of several common foods, including vegetables, fruits, fish, and meat, were investigated in relation to risk of prevalent and incident dementia in the UK Biobank cohort.

Methods: Food consumption was estimated using a 47-item food frequency questionnaire completed at recruitment or repeated 24-h dietary assessments. All-cause dementia including Alzheimer's disease (AD) and vascular dementia (VD) was identified via self-report or electronic linkage to hospital admission and mortality records. Food intakes were analysed in generalized linear models and non-linear models in relation to dementia. Interactions between food consumption and the *APOE* ε4 allele were additionally explored.

Findings: Among 502,493 participants, 564 prevalent cases at baseline and 3096 incident cases of dementia (mean follow-up of 8 years (SD=1.1)) were identified. The results show that each additional portion per week consumption of meat,

especially processed meat (fully-adjusted OR=1.14, 95%CI: 1.07, 1.22, *P* <0.001 with prevalent dementia; HR=1.09, 95%CI: 1.06, 1.13 *P* <0.001 with incident dementia), may be positively associated with risk of prevalent and incident dementia in generalized linear models. Associations between incident dementia and total meat consumption were non-linear when using restricted cubic spline methods with reduced risk at low-frequency intakes and increased risk at higher-frequency intakes, observed for all-cause dementia and VD, but not AD. Compared with non-meat eaters, low-frequency consumption of processed meat was associated with a lower risk of all-cause dementia (fully-adjusted HR=0.77, 95%CI: 0.65, 0.91 for less than weekly; HR=0.84, 95%CI: 0.71, 0.99 for weekly), and high-frequency consumption with a higher risk (HR=1.31, 95%CI: 1.04, 1.66 for ≥5 times/week) in categorical models. Presence of the *APOE* ε4 allele increased risk of dementia by 2- to 9-fold but did not modify the non-linear associations with diet significantly. In addition, high consumption of vegetables, fruits, oily fish, and total fish individually were associated with increased risks of incident dementia, especially among *APOE* ε4 carriers; but these associations were not observed with prevalent dementia.

Conclusions: The findings highlight that consumption of meat, especially processed meat, may be non-linearly associated with risk of incident dementia, independent of the *APOE* ε4 carriage. Further research is needed to confirm these findings.

6.2 Introduction

Dementia is a worldwide “silent epidemic” with around 50 million cases globally and an incidence of nearly 10 million new cases per annum [303,304]. It comprises Alzheimer’s disease (AD, contributing to 50–70% of dementia cases), vascular dementia (VD, around 25%), and other forms of dementia [74,304]. Its development and progression are associated with both genetic and environmental factors, including diet and lifestyle [305,306]. Lifestyle-related and dietary factors associated with dementia development may be potentially modifiable and thus represent targets for primary prevention [307].

No consensus has been reached yet concerning associations between risk of dementia and commonly consumed food groups, including vegetables, fruits, fish, and meat consumption. As detailed in Chapter 2, consumption of vegetables, fruits,

and fish are traditionally considered beneficial to our health in relation to cardiovascular health and may also protect from other chronic diseases [308] and is also indicated in Mediterranean diet [309]; however, the benefits to brain function remain debatable and findings regarding dementia risk remain inconsistent.

Meat consumption in relation to health has gained increasing interest, for example, high consumption of processed meat and probably red meat was found to be consistently associated with an increased risk of colorectal cancer [164]. In recent decades meat consumption has doubled or even tripled globally, especially in developing countries [310]. This dietary transition has been associated with increasing AD prevalence in Japan, Peru, Cuba and other low- and middle-income countries in both ecological and cross-sectional studies [171,206]. As described in Chapter 3, the evidence of associations between risk of dementia and specific types or amounts of meat consumption is currently limited [311].

A consistent association has been established between carriage of the apolipoprotein E (*APOE*) ε4 allele and elevated risk of dementia or AD [312]. In *APOE* ε4 non-carriers, unfavourable lifestyle factors (e.g., less healthy dietary pattern, less physical activity, smoking, and social isolation) were associated with higher risk of dementia, but these associations were not detected in *APOE* ε4 carriers [313], suggesting that *APOE* genotypes may modify or mask associations between lifestyle factors and dementia risks.

Evidence about a role of diet in dementia and the potential for gene-diet interactions has been increasing. However, a few studies have investigated the interaction between the *APOE* gene and food consumption in relation to cognition or dementia, and the underlying mechanisms remain unclear. Compared with the ε2 and ε3 isoforms, the ε4 isoform has more compact and unstable structures which may attenuate its ability to bind lipids [314], increase lipid oxidation [315], and associate with earlier defects in cerebral glucose metabolism [316]. Animal models ε4 mice fed a high-fat diet showed decreased glucose uptake compared with either ε4 mice on a control diet or ε3 mice on high-fat diet [317]. Both ε4 carriers and AD cases showed impaired glucose uptake and utilization, and diet-related insulin resistance could have an additive effect on the connection between ε4 isoform and dementia development [314].

In the present chapter, the associations of consumption of meat, fish, vegetables, and fruits, as well as their potential interactions with *APOE* ε4 carriage, were investigated in relation to the prevalence and incidence of dementia in the UK Biobank cohort study.

6.3 Methods

6.3.1 Study participants

As described in Chapter 5, the UK Biobank is a large-scale cohort study with more than half a million participants recruited from across the United Kingdom between 2006 and 2010 [285]. At recruitment, participants electronically signed consent forms and completed various touchscreen questionnaires and measurements. Ethical approval was granted for the UK Biobank by North West - Haydock Research Ethics Committee (REC reference: 16/NW/0274). The UK Biobank dataset for this project included data from 502,493 participants collected at recruitment. The prevalent dementia cases (n=564) were subsequently excluded when analysing incident dementia during follow-up. Participants who did not provide biological samples or failed the genotyping quality control were also excluded in gene-related subgroup analyses (Figure 6.1). Details are shown in the following sections.

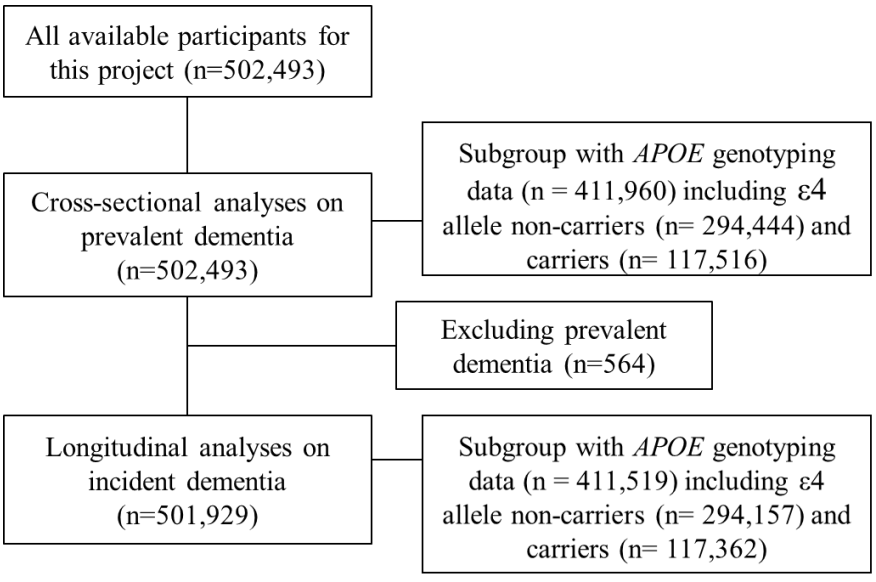


Figure 6.1 Flowchart of participants in dementia analyses of UK Biobank

6.3.2 Diet assessment

The baseline diet information was described in detail previously in Chapter 5, assessed by a 47-item food frequency questionnaire (FFQ) covering main foods, food groups, and drinking habits [286]. Briefly, meat and fish related items in the baseline FFQ were assessed under six frequency categories, which were assigned values as follows: never eaten =0, eaten less than once per week =0.5, once per week =1, 2–4 times per week =3, 5–6 times per week =5.5, and once or more daily =7. Meat related items included processed meat, unprocessed poultry, unprocessed beef, unprocessed lamb, and unprocessed pork, where the last three items were summed to provide "unprocessed red meat", and all items were combined for estimates of "total meat". Fish-related items included oily fish and non-oily fish, and were summed to estimate "total fish". The number of portions of vegetables and fruits consumed per day were input as an integer directly by participants. So, portions per week were used for consumption of meat (processed meat, unprocessed red meat, unprocessed poultry, and total meat) and fish (oily fish and total fish), and portions per day were used for consumption of vegetables and fruits. These food groups were treated as continuous variables in analyses.

The consumption of processed meat, unprocessed red meat, and unprocessed poultry were also analysed as categorical variables comprising five intake-frequency categories: never, less than once per week, once per week, 2–4 times per week, 5 times or more a week.

As an enhancement to the baseline FFQ, the Oxford WebQ dietary questionnaire [318] which provides more detailed dietary information over the previous 24 hours was added to assessment centres from April 2009 to September 2010. The Oxford WebQ questionnaire (available online at https://www.ukbiobank.ac.uk/wp-content/uploads/2019/08/Diet-questionnaire-for-website_copyright.pdf) covers 206 food items and has been validated in other studies [319]. The timeline of assessment scenarios is shown in Figure 6.2 (adapted from Bradbury *et al.* [320]). After the first administration at assessment centres in 2009–2010, the 24-h dietary assessment was subsequently administered online once every 3–4 months and repeated for a total of 4 rounds over a 16-month period from February 2011 to June 2012.

The Oxford WebQ asked participants to select the number of portions for each item

they consumed over the previous 24-h period with instructions specifying one standard portion size. For meat-related items, the portion size was specified as a 'serving', where two British sausages, or two rashers of bacon, or one slice of ham was assigned as one serving. Similar foods were then combined into four meat groups (processed meat, unprocessed red meat, unprocessed poultry, and total meat) to match these from the baseline FFQ. A large sub-group of participants (n = 211,006, 42% of total sample) completed at least one 24-h dietary assessment; multiple assessments were averaged to provide number of servings per day of food intakes. The dates when participants completed their last Oxford WebQ were treated as the start of follow-up analysis for the 24h dietary questionnaire. Consumption of total meat (servings/day) was used as a continuous variable in sensitivity analyses. For the three subtypes of meat intakes, servings per day were grouped into non-eaters (=0 servings/day), less than once a week (< 1/7 servings/day), once a week (≥ 1/7 servings/day & < 2/7 servings/day), 2–4 times per week (≥ 2/7 servings/day & < 5/7 servings/day), and 5 times or more per week (≥ 5/7 servings/day), and then were used as categorical variables in sensitivity analyses.

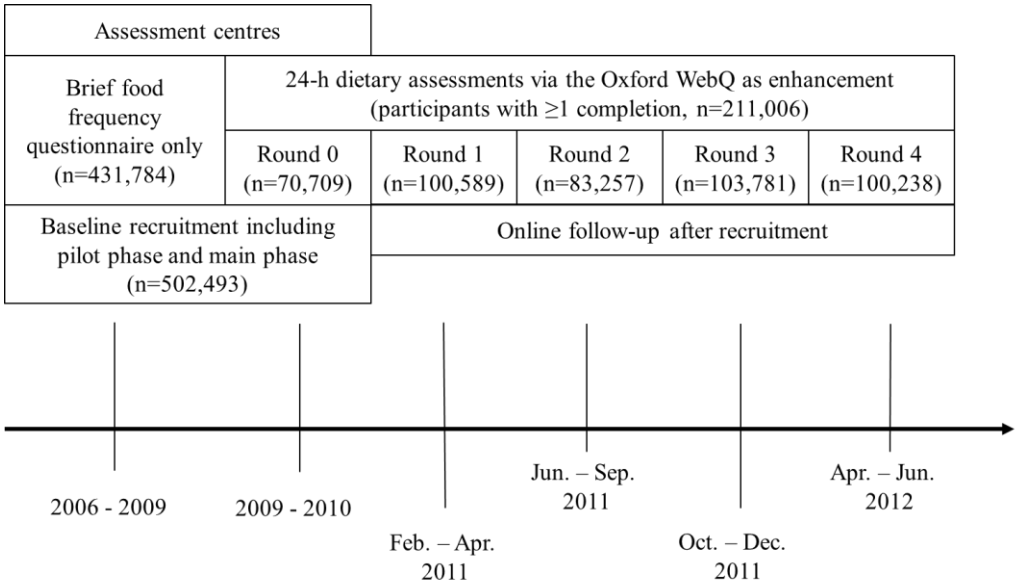


Figure 6.2 The timeline of diet assessments in UK Biobank [320]

6.3.3 Ascertainment of dementia

Prevalent and incident dementia cases within the UK Biobank cohort were ascertained through data linkage to hospital inpatient admissions and death

registries. Self-reported dementia cases at recruitment were additionally classified as prevalent cases. The electronic linkage to hospital inpatient data and death registry records includes primary and secondary events across healthcare systems in England, Scotland, and Wales. Date of diagnosis was set as the earliest date of dementia codes recorded regardless of source used. According to the International Classification of Diseases (ICD) [91], AD was defined as code 331.0 in edition 9 and codes F00 and G30 in edition 10; VD was defined as codes 290.4 in edition 9 and codes F01 and I67.3 in edition 10; all-cause dementia was defined as all the above codes plus ICD-9 codes 290, 291.2, 294.1, 331.0–331.2, and 331.5, and ICD-10 codes A81.0, F02, F05.1, F10.6, G31.0, G31.1, and G31.8. The updating date of the linkage data was 31 March 2017 in England, 31 October 2016 in Scotland, and 29 February 2016 in Wales in this study. The follow-up time of participants in person-years was calculated from the date of dietary assessment until date of dementia diagnosis, date of loss to follow-up, date of death, or updating date of the linkage data.

6.3.4 Covariates

As detailed in Chapter 5, covariate variables such as age at baseline, gender (females, males), ethnicity (White, Asian, Black, Mixed, Other/Unknown), socioeconomic status (Townsend deprivation index, TDI), educational level (with university/college degree, or not), living region (England, Wales, Scotland), body mass index (BMI, Kg/m^2), physical activity level (low, moderate, and high), alcohol status (never, past, and current), smoking status (never, past, and current), typical sleep duration (hours/day), stroke history (yes/no), and family history of dementia (yes/no), were collected either via a self-administered touchscreen questionnaire or via calculation from physical measurement for BMI. For covariates where participants answered, ‘do not know’ or ‘prefer not to answer’, these responses were classified as missing values.

Three models were applied in the analyses: unadjusted model, minimally-adjusted model, and fully-adjusted model. The minimally-adjusted model was adjusted for age at baseline, gender, self-reported ethnicity, socioeconomic status, educational level, determined by a directed acyclic graph [293] (detailed in Chapter 5). The fully-adjusted model was additionally adjusted for region, BMI, physical activity level, alcohol status, smoking status, typical sleep duration, stroke history, and

family history of dementia. More details on covariates can be seen in Chapter 5.

6.3.5 *APOE* genotyping

Genotypes of nearly half a million participants in UK Biobank were assayed using two very similar genotyping arrays manufactured by Affymetrix: the BiLEVE Axiom array for ~50,000 participants and the UK Biobank Axiom array for the remaining ~450,000 participants; genotyping quality control was performed by UK Biobank centrally [321]. In the dataset of this project, *APOE* genotypes were available on 413,111 UK Biobank participants. Data from UK Biobank participants with disagreement between reported sex and genetic sex (n=372), and those with unusually high heterozygosity and missingness (>5%) in genotyping (n=963) were excluded in *APOE* allele related analyses [322]. In addition, this study used genetic kinship to other participants (Biobank field ID 22021) as a covariate in the fully-adjusted model in *APOE* allele related analyses to limit confounding from population relatedness [323]. The *APOE* haplotypes (ε2/ε3/ε4) were directly genotyped and determined by two genetic variants rs429358 and rs7412. Participants with one or two ε4 alleles were defined as *APOE* ε4 carriers, otherwise as *APOE* ε4 non-carriers.

6.3.6 Generalized linear models

Logistic regressions were used to examine associations between food consumption and prevalent dementia; odds ratios (OR) and 95% confidence intervals (95%CI) were reported. Cox proportional-hazards regressions were fitted with the duration of follow-up in years as the timescale to examine associations between food consumption and incident dementia; hazard ratios (HR) as well as 95%CI were reported. The proportional hazards assumptions were verified by Schoenfeld's residuals tests. All consumption frequencies of food groups (portions per week for meat and fish, portions per day for vegetable and fruit) were treated as continuous variables in regression models; thus, the OR or HR indicates ratio change by 1 portion increase of food item intakes. In addition, to investigate potential modifying effects of the *APOE* ε4 allele on risk of dementia from food consumption, stratified analysis by *APOE* ε4 carriage was conducted in the above regression models.

6.3.7 Exploration of non-linear associations with meat consumption

Meat consumption was taken as an example to further explore the potential for non-

linear associations between amounts of food intake and risk of specific dementia outcomes. Participants with prevalent dementia (n=564), and those with incomplete data on meat-related variables (n=7964) were excluded before analyses (Figure 6.3). Given the possibility that underlying dementia may cause changes in dietary behaviours in advance of diagnosis, incident dementia cases that occurred during the first year of follow-up were further excluded (n=77) to limit the possibility of reverse causality [324]. The flowchart of numbers of participants in the exploration of non-linear associations can be seen in Figure 6.3. Socio-demographic and other lifestyle characteristics across the five categories of each meat type were summarized. In the exploration of non-linear associations, all-cause dementia, AD, and VD were analysed as separate outcomes.

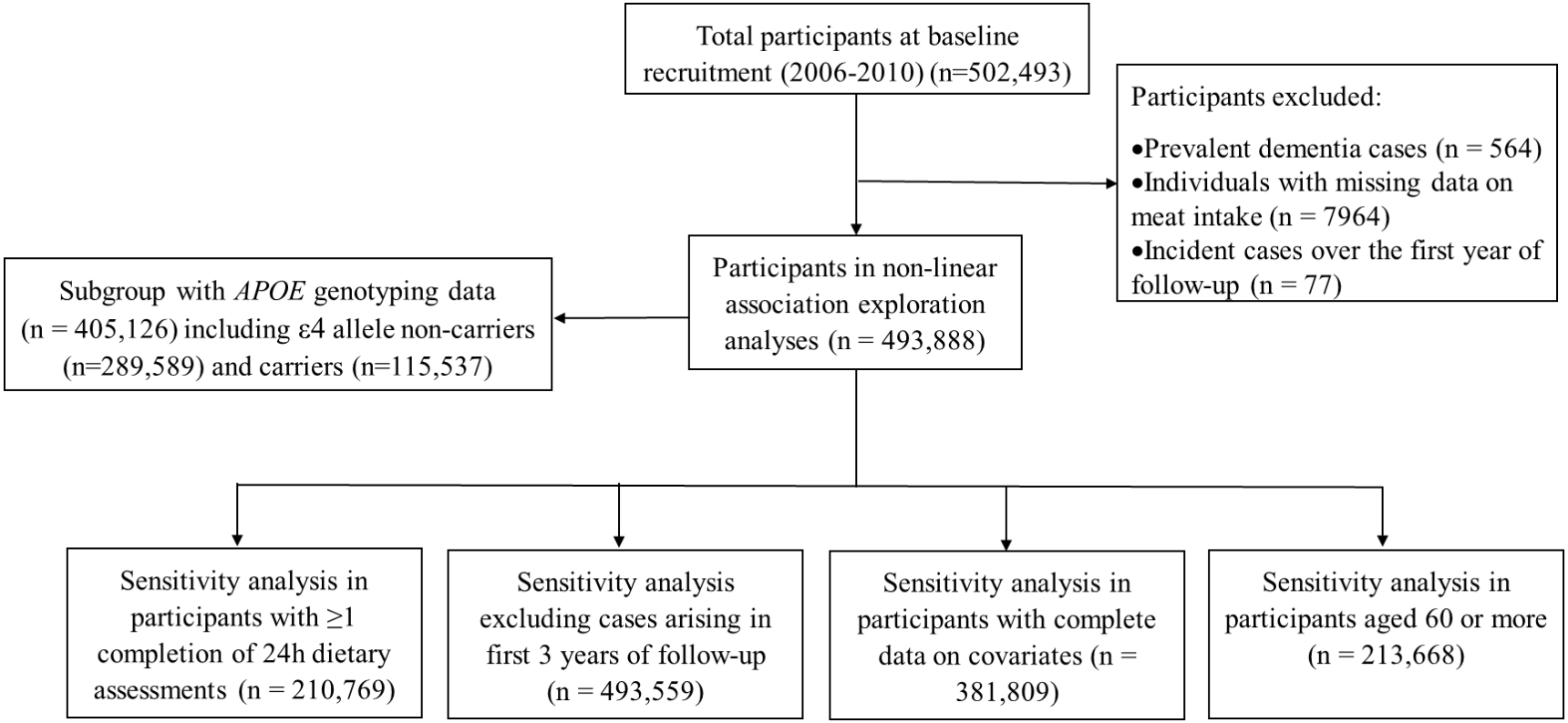


Figure 6.3 Flowchart of participants in examination of non-linear associations between meat consumption and incident dementia in UK Biobank

6.3.7.1 Restricted cubic spline models for consumption of total meat

Shapes of association between each incident dementia outcome and total meat consumption were plotted using restricted cubic spline (RCS) models with three knots at the 10th, 50th and 90th percentiles, where total meat intake was used as a continuous variable with the non-consumers (0 times/week) as the reference. Since the RCS model [325] has restricted the association to be linear at each end, any potential upturn compared with the non-consumers could be missed; thus, one knot placed in the middle and the others nearer each end are more efficient for modelling with three knots. The knot selection in the present project was based on the theory from Harrell *et al.* who did simulations on the most efficient knot positions, and found with the minimal three knots, positions should be at the 10th, 50th and 90th percentiles [326].

6.3.7.2 Categorical models for consumption of three meat subtypes

Unlike data for total meat consumption, the data for processed meat, unprocessed red meat, and unprocessed poultry have limited values which restricted their application in the RCS model. Therefore, consumption of meat subtypes was analysed as categorical variables, where the non-consumers (the lowest consumption category) were treated as the reference. *P* values for trend were additionally calculated for each meat type in all adjustment models.

6.3.7.3 Repeated RCS and categorical models in different conditions as sensitivity analyses

To examine whether the results were robust, a series of sensitivity analyses were conducted (Figure 6.3). First, since the baseline FFQ only had 47 items and assessed past long-term diet behaviour, potential recall bias and information bias might have occurred; therefore, analyses on the non-linear associations from the baseline FFQ were conducted using repeat 24-h dietary assessments, where total meat consumption (servings/day) was used as a continuous variable in the RCS model and intakes of meat subtypes (processed meat, unprocessed red meat, unprocessed poultry) were grouped into five categories (non-eaters, <1 times/week, once a week, 2–4 times/week, and 5+ times/week) were analysed in categorical models. Second, since there were missing values in covariate variables, sample sizes varied across the three adjustment models based on participants with complete data on

corresponding covariates; the effect of varying sample sizes was assessed by excluding participants with incomplete data on all covariates as a sensitivity analysis. Third, since reverse causality might occur beyond the first year of follow-up, a more stringent cut-off was applied excluding incident dementia cases (n=406) that occurred during the first 3 years of follow-up as a sensitivity analysis. As another sensitivity analysis, the main analyses were additionally repeated among participants aged 60 or more at baseline since individuals over 60 years might disproportionally have a higher risk of incident dementia [327].

6.3.7.4 Evaluation of interaction between meat consumption and *APOE* ε4 allele

To examine whether there is diet-gene interaction on dementia risk, *APOE* ε4 carrying status was considered (Figure 6.3). For total meat consumption, the RCS models were conducted amongst *APOE* ε4 carriers and non-carriers separately. For the three meat subtypes, an interaction term between the specific meat type and *APOE* ε4 carriage was included in the categorical models, and the non-consumers of each meat type in *APOE* ε4 non-carriers were treated as the reference.

6.3.8 Statistical analysis

Baseline sociodemographic and lifestyle factors, and main dietary characteristics were summarized and stratified by dementia status comprising prevalent dementia, incident dementia and no dementia. A stringent level of P <0.01 was used as the significance level due to the potential for multiple testing in regression models [259]. Statistical analyses were conducted using Stata/IC, version 16.1 (Stata Corp LP, College Station, TX).

6.4 Results

6.4.1 Descriptive characteristics

Among the 502,493 participants, there were 564 prevalent dementia cases at recruitment and 3096 incident dementia cases during follow-up period. As shown in Table 6.1, dementia cases, especially incident dementia cases, were much older, more likely to be male and a smoker, less likely to have a university/college degree, more likely to have a family history of dementia and be a *APOE* ε4 carrier compared with non-dementia participants. Both prevalent and incident dementia cases were more deprived, more likely to be an alcohol drinker, have a stroke history and a low level of physical activity compared with non-dementia participants. Regarding food

consumption, the percentages of non-consumers (0 times/week) of vegetables, fruits, fish, and meat were all less than 10% at baseline among prevalent dementia, incident dementia, and non-dementia participants. In addition, incident dementia cases had higher mean consumption frequencies of vegetables, fruits, and total fish than non-dementia participants.

Table 6.1 Baseline characteristics of participants stratified by dementia status in the UK Biobank cohort study [a]

	Incident Dementia (n = 3096)	**Prevalent Dementia** (n=564)	**Non-Dementia participants** (n = 498,833)
Age at baseline (years)			
Mean (SD)	64 (6)	59 (7)	56.5 (8)
Median (IQR)	65 (61, 68)	61 (54, 65)	58 (50, 63)
Duration of follow-up (years)			
Mean (SD)	5.7 (2.2)	—	8.0 (1.1)
Median (IQR)	6.1 (4.3, 7.4)	—	8.1 (7.4, 8.7)
Gender			
Men	1750 (56%)	314 (56%)	227,058 (46%)
Women	1346 (44%)	250 (44%)	271,788 (54%)
Ethnicity			
White	2934 (95%)	534 (95%)	469,235 (94%)
Asian	48 (2%)	10 (2%)	11,355 (2%)
Black	59 (2%)	2 (0%)	7973 (2%)
Mixed	14 (0%)	4 (1%)	3010 (1%)
Others/unknown	32 (1%)	10 (2%)	6394 (1%)
Missing	9 (0%)	4 (0%)	879 (0%)
Townsend deprivation index at recruitment			
Mean (SD)	-0.7 (3.5)	-0.1 (3.6)	-1.3 (3.1)
Median (IQR)	-1.6 (-3.4, 1.8)	-0.7 (-3, 2.9)	-2.1 (-3.6, 0.5)
Missing	2 (0%)	0 (0%)	621 (0%)
With college/university degree	605 (20%)	134 (24%)	161,826 (32%)
Missing	95 (3%)	12 (2%)	6106 (1%)
Alcohol status			
Never	214 (7%)	41 (7%)	22,132 (4%)
Previous	253 (8%)	73 (13%)	17,781 (4%)
Current	2602 (84%)	441 (78%)	457,349 (92%)
Missing	27 (1%)	9 (2%)	1584 (0%)
Smoking status			
Never	1354 (44%)	255 (45%)	271,944 (55%)
Previous	1305 (42%)	214 (38%)	171,621 (34%)
Current	403 (13%)	84 (15%)	52,497 (10%)
Missing	34 (1%)	11 (2%)	2784 (1%)
Physical activity			
Low level	523 (17%)	125 (22%)	75,572 (15%)
Moderate level	928 (30%)	166 (29%)	162,925 (33%)
High level	804 (26%)	136 (24%)	161,202 (32%)
Missing	841 (27%)	137 (24%)	99,147 (20%)
Body mass index (Kg/m^2)			
Mean (SD)	27.7 (5.1)	27.8 (5.3)	27.4 (4.8)
Missing	58 (2%)	22 (4%)	2926 (1%)
Sleep duration (hours/day)	7.3 (1.5)	7.5 (1.6)	7.2 (1.1)

Median (IQR)	7 (6, 8)	7 (6, 8)	7 (7, 8)
Missing	66 (2%)	17 (3%)	3989 (1%)
Stroke history	203 (7%)	62 (11%)	7403 (2%)
Family history of dementia	586 (19%)	82 (14%)	57,760 (12%)
APOE [b] ε4 carrying status			
Non-carriers	1278 (41%)	288 (51%)	293,699 (59%)
Carriers	1249 (40%)	154 (27%)	116,455 (23%)
Missing	569 (18%)	122 (22%)	88,692 (18%)
Dietary consumption			
Vegetables: Non-consumers	82 (3%)	22 (4%)	6426 (1%)
Consumers (servings/d) Mean (SD)	2.7 (2.1)	2.5 (1.7)	2.5 (1.7)
Median (IQR)	2.5 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)
Missing	147 (5%)	38 (7%)	10,767 (2%)
Fruits: Non-consumers	205 (7%)	43 (8%)	26276 (5%)
Consumers (servings/d) Mean (SD)	3.2 (2.8)	3.0 (2.6)	2.8 (1.9)
Median (IQR)	2.5 (2.0, 4.0)	2.5 (1.5, 4.0)	2.5 (1.5, 3.5)
Missing	95 (3%)	19 (3%)	7960 (2%)
Total meat: Non-consumers	96 (3%)	26 (5%)	20,380 (4%)
Consumers (times/week) Mean (SD)	5.9 (2.8)	6.2 (3.3)	5.8 (2.6)
Median (IQR)	5.5 (4.0, 7.5)	5.5 (4.0, 7.5)	5.5 (4.0, 7.5)
Missing	123 (4%)	28 (5%)	7841 (2%)
Total fish: Non-consumers	135 (4%)	27 (5%)	18,800 (4%)
Consumers (times/week) Mean (SD)	2.7 (1.8)	2.5 (1.8)	2.4 (1.6)
Median (IQR)	2.0 (1.5, 4.0)	2.0 (1.5, 3.5)	2.0 (1.5, 3.5)
Missing	83 (3%)	19 (3%)	5647 (1%)

[a] Continues variables were displayed as Mean (standard deviation, SD) and Median (interquartile range, IQR), and categorical variables were displayed as number (percentage%); [b] *APOE*, Apolipoprotein E

6.4.2 Prevalent dementia in relation to consumption of food groups at baseline

6.4.2.1 Associations in the whole population and sub-groups by gender

There were 564 prevalent dementia cases (mean age =59.3 years, SD =7.5). As shown in Table 6.2, increased odds of prevalent dementia were linked with processed meat by 14% (fully-adjusted OR =1.14, 95% CI: 1.07 to 1.22, *P* <0.001) for each additional portion of meat/week, but not significantly with consumption of total meat (fully-adjusted OR =1.05, 95% CI: 1.01 to 1.10, *P* =0.015), unprocessed red meat (fully-adjusted OR =1.09, 95% CI: 1.02 to 1.16, *P* =0.017), or unprocessed poultry (fully-adjusted OR =0.94, 95% CI: 0.87 to 1.03, *P* =0.195). Sex-specific associations between dementia prevalence and consumption of unprocessed red meat or total meat were pronounced in men (fully-adjusted OR =1.11, 95%CI: 1.04 to 1.19, *P* =0.002 for unprocessed red meat; fully-adjusted OR =1.07, 95% CI: 1.03 to 1.12, *P* =0.002 for total meat), but not in women (fully-adjusted OR =1.02, 95% CI: 0.86 to 1.21, *P* =0.783 for unprocessed red meat; fully-adjusted OR =1.02, 95% CI: 0.93 to 1.12, *P* =0.730 for total meat).

In terms of other food intakes, the results show that there was no significant

association between prevalent dementia and consumption of vegetables, fruits, oily fish, and total fish in all adjustment models, regardless of the gender (Table 6.2).

6.4.2.2 Associations in participants with the *APOE* ε4 allele

Among 413,111 UK Biobank participants with *APOE* genotypes available, 411,960 participants (mean age =56.5 years, SD =8.1) were eligible through genotype inclusion criteria to be included in this study. Of them, there were 441 prevalent dementia cases (mean age =59.3 years, SD =7.6). As shown in Table 6.3, the results in participants with *APOE* genotypes show that increased odds of prevalent dementia were observed for one portion/week increase in consumption of processed meat (fully-adjusted OR =1.14, 95%CI: 1.06 to 1.23, *P* =0.001) and unprocessed red meat (fully-adjusted OR =1.11, 95%CI: 1.02 to 1.20, *P* =0.010), but not unprocessed poultry (fully-adjusted OR =0.94, 95%CI: 0.85 to 1.04, *P* =0.203) or total meat (fully-adjusted OR =1.06, 95%CI: 1.01 to 1.12, *P* =0.030). In addition, associations between prevalent dementia and consumption of processed meat or total meat were pronounced in *APOE* ε4 carriers (fully-adjusted OR =1.33, 95%CI: 1.19 to 1.50, *P* <0.001 for processed meat; fully-adjusted OR =1.12, 95% CI: 1.03 to 1.22, *P* =0.007 for total meat), but not in *APOE* ε4 non-carriers (fully-adjusted OR =1.04, 95% CI: 0.94 to 1.15, *P* =0.486 for processed meat; fully-adjusted OR =1.02, 95% CI: 0.96 to 1.09, *P* =0.449 for total meat). In addition, the *P* values for interaction between food consumption and *APOE* ε4 allele on prevalent dementia in logistic regression models were 0.028 for processed meat and 0.272 for total meat (Table 6.5).

Regarding other food intakes, associations between prevalent dementia and consumption of vegetables, fruits, oily fish, and total fish were not significant in all adjustment models, regardless of the *APOE* ε4 carriage (Table 6.3). The *P* values for interaction between consumption of these foods and the *APOE* ε4 allele on prevalent dementia in logistic regression models were not significant (Table 6.5).

6.4.3 Incident dementia in relation to consumption of food groups

Participants with prevalent dementia were excluded before analyses on incident dementia. Consumption frequencies of foods were used as continuous variables in Cox proportional-hazard regression models. There were 2521 incident dementia cases (mean age =63.6 years, SD =5.6) during 8 years follow-up among 411,519

participants with *APOE* genotypes available.

As shown in Table 6.4, one portion/week increase in consumption of total meat was associated with increased risk of incident dementia (fully-adjusted OR =1.03, 95%CI: 1.01 to 1.04, *P* =0.008). Each additional portion of processed meat per week consumption was related to increased risk of incident dementia in the whole population (fully-adjusted OR =1.09, 95%CI: 1.06 to 1.13, *P* <0.001), and in both *APOE* ε4 carriers (fully-adjusted OR =1.08, 95%CI: 1.03 to 1.13, *P* =0.001) and non-carriers (fully-adjusted OR =1.10, 95%CI: 1.05 to 1.15, *P* <0.001). The *P* values for interaction between food consumption and *APOE* ε4 allele on incident dementia in Cox regression models was 0.113. Consumption of unprocessed red meat or unprocessed poultry was not associated with dementia risk, which was consistent across all adjustment models.

In terms of other food intakes, consumption of vegetables, fruits, and total fish individually were associated with increased risks of incident dementia with hazard ratios ranging from 1.05 to 1.10 in all adjustment models; these associations were also observed among *APOE* ε4 carriers but not among non-carriers (Table 6.4).

In addition, the *P* values for interaction between food consumption and *APOE* ε4 allele on incident dementia in Cox regression models were all not significant, such as 0.028 for oily fish and 0.021 for total fish (Table 6.5).

Table 6.2 Associations between food consumption and prevalent dementia among females and males respectively

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	491,542	0.91	0.79	1.05	0.194	486,282	0.89	0.79	1.01	0.068	386,418	0.93	0.82	1.06	0.279
Fruits[3]	494,419	1.01	0.96	1.06	0.708	489,011	1.03	0.98	1.07	0.222	387,240	1.03	0.98	1.08	0.285
Oily fish[4]	498,413	0.99	0.91	1.08	0.842	492,770	1.00	0.92	1.09	0.984	388,515	1.03	0.94	1.13	0.550
Total fish[4]	496,744	1.01	0.96	1.07	0.687	491,205	1.01	0.96	1.07	0.630	387,897	1.04	0.98	1.10	0.188
Processed meat[4]	500,263	1.18	1.12	1.24	<0.001	494,524	1.14	1.08	1.20	<0.001	389,321	1.14	1.07	1.22	<0.001
Unprocessed red meat[4]	495,494	1.08	1.01	1.15	0.017	490,049	1.07	1.01	1.13	0.033	387,399	1.09	1.02	1.16	0.017
Unprocessed poultry[4]	500,420	0.92	0.86	1.00	0.039	494,638	0.94	0.87	1.01	0.100	389,339	0.94	0.87	1.03	0.195
Total meat[4]	494,501	1.06	1.02	1.10	0.002	489,132	1.05	1.01	1.08	0.013	387,074	1.05	1.01	1.10	0.015
Females															
Vegetables[3]	268,676	0.95	0.75	1.19	0.628	265,846	0.89	0.72	1.09	0.256	202,783	0.88	0.69	1.12	0.297
Fruits[3]	269,329	1.02	0.94	1.11	0.583	266,480	1.03	0.96	1.11	0.377	202,829	1.04	0.95	1.13	0.390
Oily fish[4]	271,523	0.99	0.86	1.13	0.843	268,556	0.99	0.87	1.13	0.928	203,506	1.05	0.90	1.21	0.547
Total fish[4]	270,743	1.03	0.94	1.12	0.532	267,823	1.03	0.95	1.11	0.535	203,247	1.08	0.99	1.18	0.091
Processed meat[4]	272,269	1.17	1.06	1.29	0.002	269,266	1.16	1.05	1.28	0.003	203,824	1.16	1.03	1.31	0.016
Unprocessed red meat[4]	269,972	0.98	0.85	1.12	0.752	267,092	0.99	0.87	1.13	0.885	202,957	1.02	0.86	1.21	0.783
Unprocessed poultry[4]	272,423	0.88	0.78	0.99	0.037	269,407	0.89	0.79	1.00	0.053	203,864	0.89	0.77	1.03	0.126
Total meat[4]	269,468	1.00	0.94	1.08	0.893	266,633	1.01	0.94	1.08	0.797	202,799	1.02	0.93	1.12	0.730
Males															
Vegetables[3]	222,866	0.91	0.78	1.07	0.243	220,436	0.89	0.76	1.04	0.148	183,635	0.97	0.84	1.12	0.643
Fruits[3]	225,090	1.02	0.96	1.08	0.469	222,531	1.03	0.97	1.08	0.380	184,411	1.02	0.96	1.08	0.536
Oily fish[4]	226,890	1.00	0.89	1.12	0.982	224,214	1.00	0.90	1.12	0.970	185,009	1.02	0.90	1.15	0.807
Total fish[4]	226,001	1.00	0.93	1.08	0.912	223,382	1.00	0.93	1.08	0.931	184,650	1.01	0.94	1.09	0.790
Processed meat[4]	227,994	1.15	1.08	1.22	<0.001	225,258	1.13	1.06	1.20	<0.001	185,497	1.13	1.05	1.22	0.001
Unprocessed red meat[4]	225,522	1.12	1.05	1.19	<0.001	222,957	1.11	1.04	1.17	0.001	184,442	1.11	1.04	1.19	0.002
Unprocessed poultry[4]	227,997	0.97	0.88	1.06	0.476	225,231	0.98	0.90	1.08	0.737	185,475	0.99	0.89	1.09	0.777
Total meat[4]	225,033	1.08	1.03	1.12	<0.001	222,499	1.07	1.03	1.11	0.001	184,275	1.07	1.03	1.12	0.002

[1]Minimally-adjusted models: adjusted for age, gender, ethnicity, education, socioeconomic status. [2]Fully-adjusted models: adjusted for additionally region, body mass index, physical activity, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); *APOE*, Apolipoprotein E.

Table 6.3 Associations between food consumption and prevalent dementia by *APOE* ε4 carrying status

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	403,201	0.94	0.81	1.09	0.415	398,885	0.90	0.78	1.04	0.144	318,943	0.97	0.84	1.11	0.618
Fruits[3]	405,504	1.01	0.95	1.07	0.771	401,077	1.02	0.97	1.08	0.384	319,574	1.03	0.97	1.09	0.295
Oily fish[4]	408,854	1.04	0.94	1.14	0.448	404,216	1.04	0.95	1.14	0.392	320,656	1.08	0.97	1.19	0.153
Total fish[4]	407,484	1.03	0.97	1.10	0.348	402,923	1.03	0.97	1.09	0.364	320,138	1.05	0.99	1.12	0.127
Processed meat[4]	410,365	1.17	1.11	1.25	<0.001	405,638	1.14	1.07	1.21	<0.001	321,293	1.14	1.06	1.23	0.001
Unprocessed red meat[4]	406,423	1.10	1.02	1.17	0.008	401,940	1.09	1.02	1.17	0.010	319,688	1.11	1.02	1.20	0.010
Unprocessed poultry[4]	410,500	0.92	0.84	1.00	0.045	405,735	0.93	0.86	1.01	0.106	321,315	0.94	0.85	1.04	0.203
Total meat[4]	405,605	1.06	1.02	1.11	0.006	401,179	1.05	1.01	1.10	0.017	319,424	1.06	1.01	1.12	0.030
***APOE* ε4 carriers**															
Vegetables[3]	115,046	1.03	0.87	1.22	0.735	113,844	1.03	0.86	1.22	0.765	90,366	1.08	0.94	1.25	0.282
Fruits[3]	115,683	1.00	0.92	1.08	0.999	114,449	1.01	0.94	1.09	0.804	90,564	0.96	0.87	1.07	0.475
Oily fish[4]	116,631	1.02	0.88	1.18	0.772	115,327	1.04	0.91	1.20	0.552	90,832	1.07	0.91	1.25	0.397
Total fish[4]	116,267	1.01	0.92	1.12	0.776	114,989	1.03	0.94	1.13	0.537	90,706	1.07	0.96	1.18	0.212
Processed meat[4]	117,069	1.29	1.17	1.42	<0.001	115,738	1.30	1.17	1.44	<0.001	91,011	1.33	1.19	1.50	<0.001
Unprocessed red meat[4]	115,953	1.11	0.97	1.26	0.130	114,692	1.12	0.98	1.28	0.085	90,585	1.15	0.99	1.33	0.063
Unprocessed poultry[4]	117,115	0.99	0.86	1.14	0.860	115,775	1.01	0.88	1.17	0.875	91,013	0.95	0.80	1.12	0.530
Total meat[4]	115,709	1.11	1.03	1.19	0.004	114,459	1.12	1.04	1.20	0.003	90,513	1.12	1.03	1.22	0.007
***APOE* ε4 non-carriers**															
Vegetables[3]	288,155	0.88	0.70	1.11	0.269	281,186	0.82	0.68	1.00	0.052	228,577	0.88	0.72	1.08	0.227
Fruits[3]	289,821	1.01	0.93	1.10	0.772	282,728	1.03	0.96	1.11	0.401	229,010	1.06	1.00	1.13	0.071
Oily fish[4]	292,223	1.04	0.92	1.18	0.508	284,870	1.04	0.92	1.17	0.540	229,824	1.08	0.95	1.24	0.239
Total fish[4]	291,217	1.04	0.95	1.13	0.384	283,987	1.03	0.95	1.11	0.510	229,432	1.05	0.96	1.14	0.307
Processed meat[4]	293,296	1.11	1.03	1.19	0.008	285,865	1.05	0.97	1.14	0.217	230,282	1.04	0.94	1.15	0.486
Unprocessed red meat[4]	290,470	1.09	1.01	1.17	0.022	283,356	1.07	1.00	1.15	0.054	229,103	1.08	1.00	1.18	0.060
Unprocessed poultry[4]	293,385	0.88	0.79	0.98	0.015	285,885	0.89	0.80	0.99	0.029	230,302	0.93	0.83	1.06	0.274
Total meat[4]	289,896	1.03	0.98	1.09	0.184	282,862	1.02	0.97	1.07	0.499	228,911	1.02	0.96	1.09	0.449

[1]Minimally-adjusted models: adjusted for age, gender, ethnicity, education, socioeconomic status. [2]Fully-adjusted models: adjusted for additionally region, body mass index, physical activity, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); *APOE*, Apolipoprotein E.

Table 6.4 Associations between food consumption and incident dementia under different *APOE* ε4 carrying status

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	HR	LCI	UCI	*P*	Number	HR	LCI	UCI	*P*	Number	HR	LCI	UCI	*P*
Total															
Vegetables[3]	402,787	1.08	1.04	1.13	<0.001	398,478	1.07	1.03	1.11	0.001	323,674	1.10	1.06	1.14	<0.001
Fruits[3]	405,077	1.04	1.02	1.06	<0.001	400,658	1.05	1.03	1.06	<0.001	324,320	1.05	1.04	1.07	<0.001
Oily fish[4]	408,425	1.04	1.00	1.08	0.032	403,795	1.05	1.01	1.09	0.018	325,458	1.06	1.01	1.10	0.012
Total fish[4]	407,058	1.05	1.03	1.08	<0.001	402,505	1.05	1.03	1.08	<0.001	324,872	1.07	1.03	1.10	<0.001
Processed meat[4]	409,933	1.13	1.10	1.16	<0.001	405,214	1.09	1.06	1.12	<0.001	326,121	1.09	1.06	1.13	<0.001
Unprocessed red meat[4]	406,003	1.01	0.98	1.04	0.555	401,527	1.00	0.97	1.03	0.891	324,378	1.01	0.98	1.05	0.562
Unprocessed poultry[4]	410,065	0.99	0.96	1.03	0.776	405,308	0.99	0.96	1.02	0.512	326,176	1.00	0.96	1.04	0.912
Total meat[4]	405,189	1.03	1.02	1.05	<0.001	400,770	1.02	1.00	1.04	0.013	324,082	1.03	1.01	1.04	0.008
***APOE* ε4 carriers**															
Vegetables[3]	114,897	1.09	1.03	1.14	0.001	113,698	1.07	1.02	1.13	0.004	92,280	1.11	1.06	1.17	<0.001
Fruits[3]	115,531	1.06	1.03	1.08	<0.001	114,300	1.06	1.04	1.08	<0.001	92,489	1.06	1.04	1.08	<0.001
Oily fish[4]	116,478	1.07	1.02	1.13	0.010	115,177	1.08	1.03	1.14	0.004	92,781	1.09	1.03	1.15	0.005
Total fish[4]	116,114	1.08	1.04	1.12	<0.001	114,839	1.08	1.04	1.12	<0.001	92,619	1.09	1.05	1.13	<0.001
Processed meat[4]	116,916	1.09	1.05	1.14	<0.001	115,588	1.08	1.03	1.12	<0.001	92,974	1.08	1.03	1.13	0.001
Unprocessed red meat[4]	115,803	0.97	0.93	1.02	0.218	114,545	0.96	0.92	1.01	0.093	92,480	0.99	0.94	1.05	0.752
Unprocessed poultry[4]	116,962	0.99	0.95	1.04	0.787	115,625	0.99	0.94	1.04	0.577	92,988	0.99	0.94	1.05	0.825
Total meat[4]	115,560	1.01	0.99	1.04	0.241	114,313	1.00	0.98	1.03	0.728	92,392	1.02	0.99	1.05	0.255
***APOE* ε4 non-carriers**															
Vegetables[3]	287,890	1.07	1.00	1.15	0.048	284,780	1.06	0.99	1.13	0.082	231,394	1.08	1.01	1.15	0.021
Fruits[3]	289,546	1.01	0.98	1.05	0.523	286,358	1.03	1.00	1.06	0.042	231,831	1.04	1.01	1.07	0.016
Oily fish[4]	291,947	1.00	0.94	1.06	0.919	288,618	1.01	0.95	1.07	0.735	232,677	1.02	0.96	1.09	0.498
Total fish[4]	290,944	1.02	0.98	1.06	0.436	287,666	1.02	0.99	1.06	0.199	232,253	1.04	0.99	1.08	0.094
Processed meat[4]	293,017	1.16	1.12	1.20	<0.001	289,626	1.11	1.06	1.15	<0.001	233,147	1.10	1.05	1.15	<0.001
Unprocessed red meat[4]	290,200	1.05	1.00	1.09	0.035	286,982	1.03	0.99	1.07	0.158	231,898	1.03	0.98	1.07	0.261
Unprocessed poultry[4]	293,103	0.99	0.94	1.04	0.753	289,683	0.99	0.94	1.04	0.674	233,188	1.00	0.95	1.06	0.960
Total meat[4]	289,629	1.05	1.03	1.08	<0.001	286,457	1.03	1.01	1.06	0.002	231,690	1.03	1.01	1.06	0.011

[1]Minimally-adjusted models: adjusted for age, gender, ethnicity, education, socioeconomic status. [2]Fully-adjusted models: adjusted for additionally region, body mass index, physical activity, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); *APOE*, Apolipoprotein E.

Table 6.5 *P* values for interaction between food intakes and *APOE* ε4 allele

	Prevalent dementia	**Incident dementia**
Vegetables	*P* =0.043	*P* =0.229
Fruits	*P* =0.404	*P* =0.055
Oily fish	*P* =0.838	*P* =0.028
Total fish	*P* =0.581	*P* =0.021
Processed meat	*P* =0.028	*P* =0.113
Unprocessed red meat	*P* =0.731	*P* =0.236
Unprocessed poultry	*P* =0.931	*P* =0.689
Total meat	*P* =0.272	*P* =0.116

6.4.4 Exploration of non-linear association with meat consumption

In the previous two sections, consumption of food groups was treated as continuous variables in logistic or Cox regression analyses to see the association by one unit increment of consumption. In this section, potential non-linear associations were explored taking meat consumption in relation to incident dementia as the example.

6.4.4.1 Characteristics stratified by consumption categories for meat subtypes

According to data distribution, consumption frequencies were grouped into five categories to provide similar-sized groups. Characteristics across five categories of consumption frequency of processed meat, unprocessed red meat, and unprocessed poultry were summarized. From Table 6.6, we can see that compared with non-eaters of processed meat, those who consumed processed meat less than once a week had a lower incident rate of dementia, the same as those who consumed once a week, but those who consumed 2–4 times a week and 5 times or more a week did have a higher incident rate of dementia. However, there was no obvious difference in incident rate of dementia across five frequency categories in consumption of unprocessed red meat (Table 6.7) and unprocessed poultry (Table 6.8). Interestingly, the proportions of female and participants with college/university degree decreased as meat consumption frequency increased, while mean BMI, the proportion of participants with low levels of physical activity and stroke history increased as meat consumption frequency increased, indicating meat consumption differed by gender and education levels, and potentially had a role in BMI and stroke events. Compared to meat eaters, meat non-eaters of those types had distinct high percentages of alcohol non-drinker, non-smoker, high level of physical activity, indicating meat non-eaters may be inclined to a healthier lifestyle.

Table 6.6 Baseline characteristics of participants stratified by processed meat categories in the UK Biobank cohort study

	Processed meat (n=493,976)				
	Non-eaters (n=46,366)	Less than once a week (n=150,777)	Once a week (n=144,098)	2–4 times a week (n=133,397)	5 times or more a week (n=19,338)
Age at baseline (years)					
Mean (SD)	56 (8)	57 (8)	57 (8)	56 (8)	56 (8)
Median (IQR)	57 (49, 62)	58 (51, 63)	58 (50, 63)	57 (49, 63)	56 (48, 63)
Incident dementia cases	297 (0.6%)	741 (0.5%)	818 (0.6%)	942 (0.7%)	175 (0.9%)
Gender					
Men	12,271 (26%)	48,186 (32%)	66,910 (46%)	82,888 (62%)	14,490 (75%)
Women	34,095 (74%)	102,591 (68%)	77,188 (54%)	50,509 (38%)	4848 (25%)
Ethnicity					
White	40,438 (87%)	141,474 (94%)	138,188 (96%)	128,464 (96%)	18,357 (95%)
Asian	3281 (7%)	3362 (2%)	2060 (1%)	1682 (1%)	353 (2%)
Black	1160 (3%)	2901 (2%)	1710 (1%)	1414 (1%)	270 (1%)
Mixed	392 (1%)	1012 (1%)	778 (1%)	668 (1%)	101 (1%)
Others/unknown	1095 (2%)	2028 (1%)	1362 (1%)	1169 (1%)	257 (1%)
Townsend deprivation index at recruitment					
Mean (SD)	-0.8 (3.2)	-1.4 (3.0)	-1.5 (3.0)	-1.3 (3.1)	-0.8 (3.3)
Median (IQR)	-1.6 (-3.4, 1.3)	-2.3 (-3.7, 0.3)	-2.3 (-3.7, 0.2)	-2.1 (-3.6, 0.6)	-1.7 (-3.4, 1.4)
Missing	58 (0%)	186 (0%)	187 (0%)	153 (0%)	26 (0%)
With college/university degree	19,560 (42%)	51,343 (34%)	44,857 (31%)	39,768 (30%)	5984 (31%)
Missing	629 (1%)	1332 (1%)	1380 (1%)	1223 (1%)	192 (1%)
Alcohol status					
Never	4738 (10%)	6456 (4%)	5219 (4%)	4241 (3%)	763 (4%)
Past	3266 (7%)	5182 (3%)	4330 (3%)	4045 (3%)	769 (4%)
Current	38,291 (83%)	139,013 (92%)	134,421 (93%)	125,010 (94%)	17,774 (92%)
Missing	71 (0%)	126 (0%)	128 (0%)	101 (0%)	32 (0%)
Smoking status					
Never	27,329 (59%)	85,455 (57%)	78,813 (55%)	68,776 (52%)	9257 (48%)
Past	15,130 (33%)	51,778 (34%)	50,204 (35%)	47,255 (35%)	6616 (34%)
Current	3712 (8%)	13,101 (9%)	14,550 (10%)	16,976 (13%)	3409 (18%)
Missing	195 (0%)	443 (0%)	531 (0%)	390 (0%)	56 (0%)
Physical activity					

Low level	5965 (13%)	22023 (15%)	22332 (16%)	21642 (16%)	3398 (18%)
Moderate level	14712 (32%)	49894 (33%)	48107 (33%)	43822 (33%)	6078 (31%)
High level	17236 (37%)	49610 (33%)	45669 (32%)	42162 (32%)	6123 (32%)
Missing	8453 (18%)	29250 (19%)	27990 (19%)	25771 (19%)	3739 (19%)
Body mass index (Kg/m^2)					
Mean (SD)	25.9 (4.6)	27.1 (4.7)	27.6 (4.7)	28.1 (4.9)	28.1 (5.0)
Median (IQR)	25.2 (22.7, 28.3)	26.3 (23.8, 29.5)	26.9 (24.3, 30.0)	27.4 (24.8, 30.6)	27.4 (24.7, 30.6)
Missing	385 (1%)	665 (0%)	607 (0%)	691 (1%)	127 (1%)
Sleep duration (hours/day)					
Mean (SD)	7.1 (1.2)	7.2 (1.1)	7.2 (1.1)	7.1 (1.1)	7.1 (1.2)
Median (IQR)	7 (6, 8)	7 (7, 8)	7 (7, 8)	7 (7, 8)	7 (6, 8)
Missing	303 (1%)	748 (1%)	658 (0%)	660 (0%)	117 (1%)
With stroke history	622 (1%)	1995 (1%)	2185 (2%)	2220 (2%)	386 (2%)
With family history of dementia	5388 (12%)	18,139 (12%)	16,640 (12%)	15,313 (12%)	2260 (12%)
APOE4 carrying status					
Non-carriers	27,501 (59%)	88,956 (59%)	84,899 (59%)	77,789 (58%)	11,287 (58%)
Carriers	11,265 (24%)	35,672 (24%)	33,633 (23%)	30,974 (23%)	4354 (22%)
Missing	7600 (16%)	26,149 (17%)	25,566 (18%)	24,634 (18%)	3697 (19%)
Dietary consumption					
Vegetable: Non-consumers	540 (1%)	1358 (1%)	1447 (1%)	2133 (2%)	741 (4%)
Consumers (servings/d) Mean (SD)	3.1 (2.2)	2.6 (1.6)	2.4 (1.5)	2.3 (1.5)	2.3 (1.7)
Median (IQR)	2.5 (2.0, 3.5)	2.5 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.3, 3.0)
Missing	780 (2%)	2260 (2%)	2262 (2%)	2488 (2%)	441 (2%)
Fruit: Non-consumers	1413 (3%)	5343 (4%)	7037 (5%)	9577 (7%)	2460 (13%)
Consumers (servings/d) Mean (SD)	3.5 (2.4)	3.0 (1.9)	2.7 (1.8)	2.5 (1.7)	2.4 (1.9)
Median (IQR)	3.0 (2.0, 4.5)	3.0 (2.0, 4.0)	2.3 (1.5, 3.5)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
Missing	586 (1%)	1736 (1%)	1605 (1%)	1638 (1%)	268 (1%)
Total meat: Non-consumers	20,476 (44%)	0	0	0	0
Consumers (times/week) Mean (SD)	3.3 (2.0)	4.4 (1.8)	5.3 (1.8)	7.5 (2.0)	10.9 (2.8)
Median (IQR)	3.0 (2.0, 4.5)	4.5 (3.0, 5.5)	5.5 (4.0, 6.0)	7.5 (6.0, 8.5)	10.5 (9.0, 12.5)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total fish: Non-consumers	9855 (21%)	2472 (2%)	2459 (2%)	3052 (2%)	836 (4%)
Consumers (times/week) Mean (SD)	3.0 (2.0)	2.4 (1.6)	2.3 (1.5)	2.3 (1.5)	2.1 (1.5)
Median (IQR)	2.0 (1.5, 4.0)	2.0 (1.5, 3.5)	2.0 (1.5, 3.5)	2.0 (1.5, 3.5)	1.5 (1.0, 2.0)
Missing	301 (1%)	884 (1%)	884 (1%)	889 (1%)	202 (1%)

Table 6.7 Baseline characteristics of participants stratified by unprocessed red meat categories in the UK Biobank cohort study

	Unprocessed red meat (n=493,976)				
	Non-eaters (n=33,575)	Less than once a week (n=16,603)	Once a week (n=194,665)	2-4 times a week (n=223,574)	5 times or more a week (n=25,559)
Age at baseline (years)					
Mean (SD)	55 (8)	55 (8)	56 (8)	57 (8)	57 (8)
Median (IQR)	55 (48, 61)	56 (48, 62)	57 (50, 63)	58 (51, 64)	59 (51, 64)
Incident dementia cases	207 (0.6%)	106 (0.6%)	1108 (0.6%)	1326 (0.6%)	226 (0.9%)
Gender					
Men	10,362 (31%)	5953 (36%)	84,790 (44%)	108,802 (49%)	14,838 (58%)
Women	23,213 (69%)	10,650 (64%)	109,875 (56%)	114,772 (51%)	10,721 (42%)
Ethnicity					
White	29,750 (89%)	14,871 (90%)	185,329 (95%)	213,816 (96%)	23,155 (91%)
Asian	2547 (8%)	997 (6%)	3436 (2%)	3073 (1%)	685 (3%)
Black	501 (1%)	322 (2%)	2730 (1%)	2948 (1%)	954 (4%)
Mixed	266 (1%)	124 (1%)	1085 (1%)	1275 (1%)	201 (1%)
Others/unknown	511 (1%)	289 (2%)	2085 (1%)	2462 (1%)	564 (2%)
Townsend deprivation index at recruitment					
Mean (SD)	-0.7 (3.2)	-0.8 (3.2)	-1.3 (3.0)	-1.5 (3.0)	-0.9 (3.4)
Median (IQR)	-1.4 (-3.2, 1.4)	-1.6 (-3.3, 1.3)	-2.2 (-3.6, 0.4)	-2.3 (-3.7, 0.2)	-1.8 (-3.5, 1.3)
Missing	47 (0%)	27 (0%)	240 (0%)	259 (0%)	37 (0%)
With college/university degree	15,055 (45%)	4928 (30%)	63,458 (33%)	70,338 (32%)	7733 (30%)
Missing	410 (1%)	192 (1%)	1705 (1%)	2088 (1%)	361 (1%)
Drinking status					
Never	3168 (9%)	1507 (9%)	7980 (4%)	7591 (3%)	1171 (5%)
Previous	2499 (7%)	995 (6%)	6619 (3%)	6570 (3%)	909 (4%)
Current	27,853 (83%)	14,085 (85%)	179,895 (92%)	209,238 (94%)	23,438 (92%)
Missing	55 (0%)	16 (0%)	171 (0%)	175 (0%)	41 (0%)
Smoking status					
Never	19,811 (59%)	9801 (59%)	107,687 (55%)	119,923 (54%)	12,408 (49%)
Previous	10,910 (33%)	5111 (31%)	67,090 (35%)	78,761 (35%)	9111 (36%)
Current	2723 (8%)	1629 (10%)	19,293 (10%)	24,180 (11%)	3923 (15%)
Missing	131 (0%)	62 (0%)	595 (0%)	710 (0%)	117 (0%)
Physical activity					

	Low level	4306 (13%)	2427 (15%)	29723 (15%)	34981 (16%)	3923 (15%)
	Moderate level	10888 (32%)	5032 (30%)	64537 (33%)	74408 (33%)	7748 (30%)
	High level	12367 (37%)	5617 (34%)	62784 (32%)	71375 (32%)	8657 (34%)
	Missing	6014 (18%)	3527 (21%)	37621 (19%)	42810 (19%)	5231 (21%)
Body mass index (Kg/m^2)						
	Mean (SD)	25.8 (4.7)	26.9 (4.9)	27.3 (4.7)	27.7 (4.8)	28.4 (5.1)
	Median (IQR)	25.1 (22.6, 28.1)	26.1 (23.6, 29.3)	26.6 (24.0, 29.7)	27.0 (24.5, 30.2)	27.7 (25.0, 31.0)
	Missing	279 (1%)	132 (1%)	856 (0%)	1038 (0%)	170 (1%)
Sleep duration (hours/day)		7.1 (1.1)	7.1 (1.2)	7.1 (1.1)	7.2 (1.1)	7.2 (1.2)
	Median (IQR)	7 (6, 8)	7 (6, 8)	7 (6, 8)	7 (7, 8)	7 (6, 8)
	Missing	226 (1%)	123 (1%)	972 (0%)	1001 (0%)	164 (1%)
Stroke history		385 (1%)	259 (2%)	2769 (1%)	3466 (2%)	529 (2%)
Family history of dementia		3771 (11%)	1773 (11%)	22,709 (12%)	26,408 (12%)	3079 (12%)
APOE4 carrying status						
	Non-carriers	19,981 (60%)	9671 (58%)	114,271 (59%)	131,624 (59%)	14,885 (58%)
	Carriers	8199 (24%)	3933 (24%)	46,183 (24%)	51,768 (23%)	5815 (23%)
	Missing	5395 (16%)	2999 (18%)	34,211 (18%)	40,182 (18%)	4859 (19%)
Dietary consumption						
Vegetable: Non-consumers		647 (2%)	480 (3%)	2724 (1%)	1970 (1%)	398 (2%)
Consumers (servings/d)	Mean (SD)	3.0 (2.2)	2.6 (1.9)	2.4 (1.6)	2.4 (1.6)	2.6 (1.8)
	Median (IQR)	2.5 (2.0, 3.5)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)
	Missing	643 (2%)	345 (2%)	3350 (2%)	3335 (2%)	558 (2%)
Fruit: Non-consumers		1313 (4%)	1025 (6%)	9549 (5%)	11,943 (5%)	2000 (8%)
Consumers (servings/d)	Mean (SD)	3.4 (2.3)	3.1 (2.1)	2.8 (1.9)	2.7 (1.8)	2.7 (2.1)
	Median (IQR)	3.0 (2.0, 4.5)	3.0 (1.5, 4.0)	2.5 (1.5, 3.5)	2.3 (1.3, 3.5)	2.0 (1.0, 3.5)
	Missing	434 (1%)	185 (1%)	2233 (1%)	2552 (1%)	429 (2%)
Total meat: Non-consumers		20,476 (61%)	0	0	0	0
Consumers (times/week)	Mean (SD)	2.4 (1.9)	3.5 (1.9)	4.7 (1.9)	6.4 (2.1)	10.7 (3.0)
	Median (IQR)	2.0 (1.0, 3.5)	3.5 (2.0, 4.5)	5.0 (3.0, 5.5)	6.0 (5.0, 8.0)	10.5 (9.0, 12.5)
	Missing	0	0	0	0	0
Total fish: Non-consumers		9789 (29%)	680 (4%)	3382 (2%)	4012 (2%)	811 (3%)
Consumers (times/week)	Mean (SD)	3.1 (2.1)	2.5 (1.8)	2.4 (1.6)	2.3 (1.4)	2.4 (1.7)
	Median (IQR)	2.0 (1.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.5, 3.5)	2.0 (1.5, 3.5)	2.0 (1.5, 3.5)
	Missing	198 (1%)	172 (1%)	1190 (1%)	1323 (1%)	277 (1%)

Table 6.8 Baseline characteristics of participants stratified by unprocessed poultry categories in the UK Biobank cohort study

	Unprocessed poultry (n=493,976)				
	Non-eaters (n=25,475)	Less than once a week (n=53,016)	Once a week (n=177,107)	2-4 times a week (n=227,235)	5 times or more a week (n=11,143)
Age at baseline (years)					
Mean (SD)	55 (8)	58 (8)	57 (8)	56 (8)	54 (8)
Median (IQR)	55 (48, 61)	60 (52, 64)	59 (52, 64)	57 (49, 63)	53 (46, 61)
Incident dementia cases	156 (0.6%)	438 (0.8%)	1092 (0.6%)	1221 (0.5%)	66 (0.6%)
Gender					
Men	8781 (35%)	25,432 (48%)	83,146 (47%)	102,331 (45%)	5055 (45%)
Women	16,694 (65%)	27,584 (52%)	93,961 (53%)	124,904 (55%)	6088 (55%)
Ethnicity					
White	22511 (88%)	50316 (95%)	169738 (96%)	214966 (95%)	9390 (84%)
Asian	2048 (8%)	1161 (2%)	2896 (2%)	4132 (2%)	501 (5%)
Black	303 (1%)	577 (1%)	1809 (1%)	3974 (2%)	792 (7%)
Mixed	218 (1%)	300 (1%)	876 (0%)	1444 (1%)	113 (1%)
Others/unknown	395 (2%)	662 (1%)	1788 (1%)	2719 (1%)	347 (3%)
Townsend deprivation index at recruitment					
Mean (SD)	-0.7 (3.2)	-0.9 (3.2)	-1.4 (3.0)	-1.5 (3.0)	-0.5 (3.5)
Median (IQR)	-1.3 (-3.2, 1.4)	-1.7 (-3.4, 1.2)	-2.2 (-3.7, 0.3)	-2.3 (-3.7, 0.2)	-1.4 (-3.3, 1.9)
Missing	35 (0%)	53 (0%)	180 (0%)	322 (0%)	20 (0%)
With college/university degree	11,999 (47%)	19,183 (36%)	56,706 (32%)	70,290 (31%)	3334 (30%)
Missing	297 (1%)	565 (1%)	1750 (1%)	2012 (1%)	132 (1%)
Alcohol status					
Never	2383 (9%)	2481 (5%)	6844 (4%)	8822 (4%)	887 (8%)
Previous	1942 (8%)	2404 (4%)	5603 (3%)	7028 (3%)	615 (6%)
Current	21,106 (83%)	48,066 (91%)	164,495 (93%)	211,217 (93%)	9625 (86%)
Missing	44 (0%)	65 (0%)	165 (0%)	168 (0%)	16 (0%)
Smoking status					
Never	14,526 (57%)	26,981 (51%)	95,496 (54%)	126,336 (56%)	6291 (56%)
Previous	8458 (33%)	18,854 (36%)	61,653 (35%)	78,512 (35%)	3506 (32%)
Current	2383 (9%)	6987 (13%)	19,347 (11%)	21,722 (10%)	1309 (12%)
Missing	108 (0%)	194 (0%)	611 (0%)	665 (0%)	37 (0%)
Physical activity					

Low level	3407 (13%)	8247 (16%)	27362 (15%)	34574 (15%)	1770 (16%)
Moderate level	8316 (33%)	17201 (32%)	59440 (34%)	74439 (33%)	3217 (29%)
High level	9173 (36%)	16536 (31%)	55839 (32%)	75349 (33%)	3903 (35%)
Missing	4579 (18%)	11032 (21%)	34466 (19%)	42873 (19%)	2253 (20%)
Body mass index (Kg/m^2)					
Mean (SD)	25.9 (4.7)	26.9 (4.8)	27.2 (4.6)	27.8 (4.9)	28.6 (5.4)
Median (IQR)	25.1 (22.6, 28.2)	26.2 (23.6, 29.4)	26.6 (24.1, 29.6)	27.1 (24.5, 30.3)	27.8 (25.0, 31.3)
Missing	221 (1%)	314 (1%)	888 (1%)	987 (0%)	65 (1%)
Sleep duration (hours/day)	7.1 (1.1)	7.2 (1.2)	7.2 (1.1)	7.1 (1.1)	7.1 (1.3)
Median (IQR)	7 (6, 8)	7 (6, 8)	7 (7, 8)	7 (7, 8)	7 (6, 8)
Missing	179 (1%)	401 (1%)	852 (0%)	968 (0%)	86 (1%)
Stroke history	301 (1%)	952 (2%)	2734 (2%)	3234 (1%)	187 (2%)
Family history of dementia	2834 (11%)	6553 (12%)	21,154 (12%)	26,097 (12%)	1102 (10%)
APOE4 carrying status					
Non-carriers	15,157 (60%)	31,166 (59%)	104,239 (59%)	133,490 (59%)	6380 (57%)
Carriers	6145 (24%)	12,303 (23%)	41,225 (23%)	53,462 (23%)	2763 (25%)
Missing	4173 (16%)	9547 (18%)	31,643 (18%)	40,283 (18%)	2000 (18%)
Dietary consumption					
Vegetable: Non-consumers	508 (2%)	1510 (3%)	2104 (1%)	1866 (1%)	231 (2%)
Consumers (servings/d) Mean (SD)	3.1 (2.2)	2.4 (1.8)	2.4 (1.5)	2.5 (1.6)	2.8 (2.2)
Median (IQR)	2.5 (2.0, 3.5)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	2.5 (1.5, 3.5)
Missing	473 (2%)	1351 (2%)	3136 (2%)	3021 (1%)	250 (2%)
Fruit: Non-consumers	1109 (4%)	3787 (7%)	9321 (5%)	10828 (5%)	785 (7%)
Consumers (servings/d) Mean (SD)	3.3 (2.3)	2.8 (2.0)	2.7 (1.8)	2.8 (1.9)	3.0 (2.4)
Median (IQR)	3.0 (2.0, 4.3)	2.5 (1.5, 3.5)	2.3 (1.5, 3.5)	2.5 (1.5, 3.5)	2.5 (1.5, 4.0)
Missing	312 (1%)	729 (1%)	2111 (1%)	2486 (1%)	195 (2%)
Total meat: Non-consumers	20,476 (80%)	0	0	0	0
Consumers (times/week) Mean (SD)	3.6 (2.8)	3.7 (2.1)	4.7 (2.0)	6.9 (2.2)	10.0 (3.4)
Median (IQR)	3.0 (1.5, 5.0)	3.0 (2.5, 5.0)	4.0 (3.5, 6.0)	6.5 (5.5, 8.0)	9.0 (7.5, 11.5)
Missing	0	0	0	0	0
Total fish: Non-consumers	9798 (38%)	1422 (3%)	2772 (2%)	4221 (2%)	461 (4%)
Consumers (times/week) Mean (SD)	3.0 (2.1)	2.2 (1.6)	2.2 (1.4)	2.4 (1.6)	2.6 (2.1)
Median (IQR)	2.0 (1.5, 4.0)	1.5 (1.0, 3.5)	2.0 (1.5, 3.0)	2.0 (1.5, 3.5)	2.0 (1.0, 4.0)
Missing	131 (1%)	509 (1%)	1134 (1%)	1260 (1%)	126 (1%)

6.4.4.2 Non-linear associations between each dementia outcomes and consumption of **total meat** assessed at baseline in Restricted Cubic Spline models

During mean follow-up of 8 years (SD=1.1; 3,938,198 person years) excluding cases arising in the first year of follow-up (n=77), 2896 incident cases of all-cause dementia occurred, of which 1006 were Alzheimer's disease and 490 were vascular dementia. Cox proportional-hazard regression was fitted using RCS methods on total meat consumption in relation to incident dementia risk.

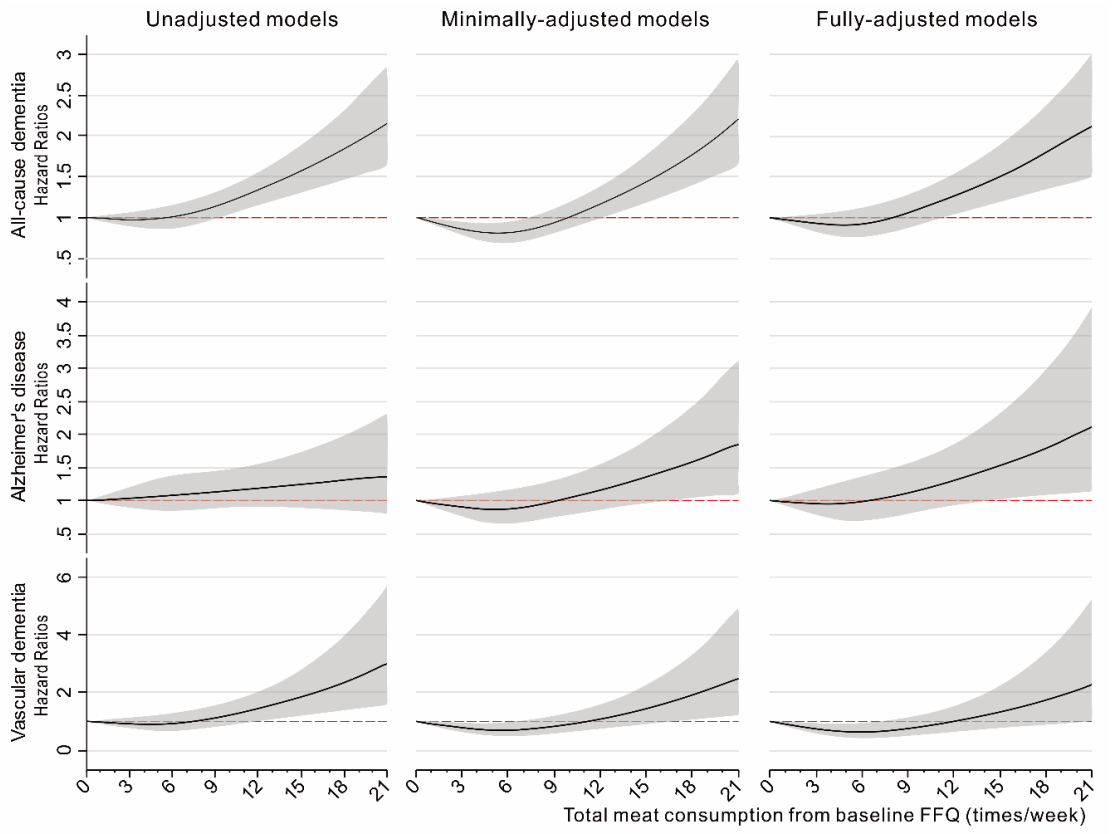


Figure 6.4 The shape of associations between total meat consumption at baseline and risk of dementia.

The black lines and shaded zones represent hazard ratios and 95% confidence interval respectively in Cox regressions. Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models adjusted for additionally region, body mass index, physical activity, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia. *Abbr.*: FFQ, Food frequency questionnaire

The restricted cubic spline curves suggest J-shaped associations between consumption of total meat and risk of dementia in both minimally and fully adjusted models (Figure 6.4). Compared to non-consumers, low-frequency consumption of

total meat was associated with a lower risk of all-cause dementia, while high-frequency consumption was associated with an increased risk of all-cause dementia (upper panels of Figure 6.4). A similar trend was seen between consumption of total meat and risk of vascular dementia but not Alzheimer's disease (middle and lower panels of Figure 6.4).

6.4.4.3 Non-linear associations between each dementia outcome and consumption of **meat subtypes** assessed at baseline in categorical models

Because the data of meat subtype consumption have limited values, the restricted cubic spline models used in total meat was not ideal for meat subtypes. Consumption of processed meat, unprocessed red meat, and unprocessed poultry were treated as categorical variables to explore the non-linear associations taking the lowest category as references.

The relationships between categorical processed meat consumption and risk of each dementia outcome in both unadjusted and adjusted models are shown in Table 6.9. Compared with individuals with no processed meat intake, those consuming processed meat less than once a week had a lower risk of developing all-cause dementia (fully-adjusted HR =0.77, 95%CI: 0.65 to 0.91, *P* =0.002); the fully-adjusted HRs were gradually increasing for higher frequency consumption, and 5 times or more per week consumption of processed meat were observed to be associated with higher risk of all-cause dementia by 31% (fully-adjusted HR =1.31, 95%CI: 1.04 to 1.66) but the association was not significant (*P* =0.024). A general shape of associations in all-cause dementia was also observed in risk of AD and VD; however, most associations were not significant (*P* >0.01, Table 6.9).

Regarding consumption of unprocessed red meat and unprocessed poultry (Table 6.10 and Table 6.11), similar J-shaped associations were observed, where low- to moderate- frequency consumption of these foods were related to reduced risk of incident dementia (e.g., fully-adjusted HR =0.77, 95%CI: 0.64 to 0.93, *P* =0.007 for 2–4 times/week consuming unprocessed red meat with all-cause dementia) but high consumption was not compared with non-eaters of these meat subtypes. No significant associations were observed between consumption of unprocessed red meat or unprocessed poultry and risk of either AD or VD (Table 6.10, and Table 6.11).

Table 6.9 Frequency of processed meat consumption from baseline food frequency questionnaire and risk of dementia

	No. of cases/ Person-Years	**Unadjusted models (*n* =493,899)**				**Minimally-adjusted Models [1] (*n* =488,539)**				**Fully-adjusted models [2] (*n* =392,126)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	292/369636	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	724/1205865	0.76	0.66	0.87	<0.001	0.71	0.62	0.82	<0.001	0.77	0.65	0.91	0.002
Once a week	796/1150321	0.88	0.77	1.00	0.052	0.76	0.66	0.88	<0.001	0.84	0.71	0.99	0.042
2–4 times a week	914/1059748	1.10	0.96	1.25	0.170	0.94	0.82	1.08	0.406	1.00	0.84	1.19	0.999
5 times or more a week	170/152628	1.42	1.18	1.72	<0.001	1.22	1.00	1.49	0.047	1.31	1.04	1.66	0.024
P trend [3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	113/369991	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	263/1206727	0.71	0.57	0.89	0.003	0.65	0.52	0.81	<0.001	0.73	0.55	0.95	0.022
Once a week	256/1151335	0.73	0.58	0.91	0.005	0.64	0.51	0.80	<0.001	0.71	0.54	0.94	0.015
2–4 times a week	325/1060856	1.01	0.81	1.25	0.942	0.91	0.72	1.14	0.420	0.97	0.73	1.29	0.836
5 times or more a week	49/152845	1.06	0.76	1.48	0.732	0.99	0.69	1.41	0.937	1.08	0.71	1.64	0.733
P trend [3]					<0.001				<0.001				0.002
Vascular dementia													
Non-eaters	53/370129	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	111/1207021	0.64	0.46	0.89	0.008	0.59	0.42	0.83	0.002	0.61	0.41	0.91	0.014
Once a week	140/1151550	0.85	0.62	1.16	0.308	0.68	0.48	0.94	0.021	0.64	0.43	0.94	0.024
2–4 times a week	154/1061201	1.02	0.75	1.39	0.907	0.76	0.55	1.07	0.112	0.70	0.47	1.04	0.079
5 times or more a week	32/152893	1.48	0.95	2.29	0.081	1.09	0.69	1.74	0.712	0.96	0.56	1.67	0.894
P trend [3]					<0.001				0.004				0.053

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable.
Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

Table 6.10 Frequency of unprocessed red meat consumption from baseline food frequency questionnaire and risk of dementia

	No. of cases/ Person-Years	Unadjusted models (*n* =493,899)				Minimally-adjusted Models[1] (*n* =488,539)				Fully-adjusted models[2] (*n* =392,126)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	202/267249	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	104/132942	1.03	0.81	1.30	0.837	0.89	0.70	1.13	0.318	1.04	0.78	1.37	0.804
Once a week	1077/1549246	0.92	0.79	1.07	0.282	0.75	0.64	0.87	<0.001	0.83	0.69	1.00	0.048
2–4 times a week	1292/1785637	0.95	0.82	1.10	0.508	0.69	0.60	0.81	<0.001	0.77	0.64	0.93	0.007
5 times or more a week	221/203124	1.43	1.18	1.73	<0.001	0.95	0.78	1.15	0.599	1.07	0.85	1.35	0.579
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	68/267490	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	41/133067	1.20	0.81	1.77	0.361	0.99	0.67	1.46	0.950	1.22	0.78	1.90	0.386
Once a week	389/1550532	0.99	0.76	1.28	0.927	0.75	0.58	0.98	0.036	0.77	0.56	1.05	0.096
2–4 times a week	448/1787234	0.98	0.76	1.26	0.865	0.67	0.52	0.87	0.003	0.72	0.53	0.99	0.040
5 times or more a week	60/203432	1.15	0.81	1.63	0.435	0.77	0.54	1.09	0.136	0.88	0.58	1.33	0.540
P trend[3]					0.599				0.009				0.020
Vascular dementia													
Non-eaters	37/267572	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	12/133139	0.64	0.34	1.23	0.184	0.51	0.26	0.99	0.048	0.55	0.25	1.22	0.142
Once a week	180/1550867	0.84	0.59	1.20	0.336	0.67	0.47	0.97	0.035	0.77	0.49	1.20	0.246
2–4 times a week	219/1787744	0.88	0.62	1.24	0.463	0.63	0.44	0.90	0.011	0.67	0.43	1.05	0.078
5 times or more a week	42/203471	1.47	0.95	2.29	0.086	0.86	0.54	1.37	0.527	1.04	0.60	1.80	0.896
P trend[3]					0.012				0.044				0.082

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable.
Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

Table 6.11 Frequency of unprocessed poultry consumption from baseline food frequency questionnaire and risk of dementia

	No. of cases/ Person-Years	Unadjusted models (*n* =493,899)				Minimally-adjusted Models[1] (*n* =488,539)				Fully-adjusted models[2] (*n* =392,126)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	153/202460	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	425/420749	1.33	1.11	1.60	0.002	0.87	0.72	1.05	0.135	0.98	0.78	1.23	0.836
Once a week	1063/1411266	0.99	0.84	1.18	0.940	0.71	0.59	0.84	<0.001	0.80	0.65	0.99	0.043
2–4 times a week	1190/1815003	0.86	0.73	1.02	0.086	0.74	0.62	0.88	<0.001	0.84	0.68	1.03	0.101
5 times or more a week	65/88720	0.97	0.72	1.29	0.813	0.94	0.70	1.27	0.691	1.11	0.78	1.58	0.561
P trend[3]					<0.001				<0.001				0.009
Alzheimer's disease													
Non-eaters	46/202667	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	143/421314	1.49	1.07	2.07	0.019	0.91	0.65	1.27	0.584	0.94	0.63	1.41	0.775
Once a week	364/1412541	1.13	0.83	1.54	0.433	0.74	0.54	1.01	0.054	0.80	0.55	1.16	0.240
2–4 times a week	433/1816429	1.04	0.77	1.41	0.783	0.85	0.62	1.15	0.286	0.98	0.68	1.41	0.897
5 times or more a week	20/88803	0.99	0.58	1.67	0.963	0.98	0.57	1.68	0.944	1.12	0.60	2.11	0.722
P trend[3]					0.006				0.083				0.169
Vascular dementia													
Non-eaters	23/202706	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	74/421447	1.54	0.96	2.45	0.072	0.93	0.58	1.49	0.765	1.00	0.56	1.78	0.997
Once a week	175/1412949	1.09	0.70	1.68	0.710	0.74	0.48	1.15	0.181	0.90	0.53	1.54	0.709
2–4 times a week	203/1816879	0.98	0.64	1.50	0.916	0.81	0.53	1.26	0.353	0.88	0.52	1.50	0.631
5 times or more a week	15/88813	1.48	0.77	2.84	0.238	1.44	0.74	2.84	0.286	1.51	0.68	3.35	0.316
P trend[3]					0.013				0.089				0.538

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable.
Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

6.4.4.4 Non-linear associations explored in 24-h dietary assessments and other sensitivity analyses

To test whether the non-linear associations observed above can be seen in meat consumption assessed in the 24-h Oxford WebQ or sub-populations in different conditions, analyses in the previous two sub-sections were conducted again as sensitivity analyses. Related figures and tables are presented in Appendix F.

In the UK Biobank cohort, 211,006 participants completed at least one Oxford WebQ for 24-h dietary assessments; after exclusions there were 552 incident all-cause dementia cases, of which 172 were Alzheimer's disease, and 81 were vascular dementia during mean follow-up of 6.1 years (SD =1.0; 1,292,108 person years). As shown in the A-Figure 6.1 of Appendix F, the J-shaped associations of total meat consumption in relation to risk of incident dementia were observed in all-cause dementia but not AD or VD, especially in both minimally and fully adjusted models. Regarding consumption of meat subtypes from 24-h dietary assessments, 2–4 times a week consumption of processed meat (fully-adjusted HR =0.64, 95%CI: 0.46 to 0.89, *P* =0.008), unprocessed red meat (fully-adjusted HR =0.62, 95%CI: 0.46 to 0.83, *P* =0.001), and unprocessed poultry (fully-adjusted HR =0.61, 95%CI: 0.45 to 0.82, *P* =0.001), were related to reduced risks of all-cause dementia compared with non-meat eaters, which was generally consistent with results from the baseline FFQ. These associations were also observed with risk of AD but not VD (A-Table 6.1 of Appendix F for processed meat, A-Table 6.2 of Appendix F for unprocessed red meat, and A-Table 6.3 of Appendix F for unprocessed poultry).

To detect potential reverse causality, a stringent 3-year exclusion (406 dementia cases) were applied rather than 1-year lag period between baseline dietary data collection and dementia diagnosis. Survival analyses show that the J-shaped associations were still observed in all-cause dementia and VD in relation to consumption of total meat (A-Figure 6.2 of Appendix F), processed meat (A-Table 6.4 of Appendix F) but not unprocessed red meat (A-Table 6.5 of Appendix F) or unprocessed poultry (A-Table 6.6 of Appendix F), which is consistent with results from 1-year exclusion.

Consistent results were also observed in sensitivity analyses extra exclusion of participants with missing covariate data (consumption of total meat in A-Figure 6.3

of Appendix F, processed meat in A-Table 6.7 of Appendix F, unprocessed red meat in A-Table 6.8 of Appendix F, and unprocessed poultry in A-Table 6.9 of Appendix F), and exclusion of participants aged less than 60 years at baseline (consumption of total meat in A-Figure 6.4 of Appendix F, processed meat in A-Table 6.10 of Appendix F, unprocessed red meat in A-Table 6.11 of Appendix F, and unprocessed poultry in A-Table 6.12 of Appendix F).

6.4.4.5 Non-linear associations explored in *APOE* ε4 carriers and non-carriers

As shown in Figure 6.5 when taking *APOE* ε4 carriage into account, the J-shaped associations were more pronounced among *APOE* ε4 non-carriers compared to *APOE* ε4 carriers, particularly with all-cause dementia in minimally and fully adjusted models (upper panels of Figure 6.5).

Regarding specific meat subtypes, among *APOE* ε4 non-carriers the J-shaped associations between processed meat consumption and risk of incident dementia were also observed (Figure 6.6); however, consumption of unprocessed red meat and unprocessed poultry did not show such trends (Figure 6.7 and 6.8). Compared with non-carriers, *APOE* ε4 carriers had increased risks of developing all-cause dementia by 2-fold to 3-fold and AD by 6-fold to 9-fold (from HRs of non-consumers of each meat type in the carriers), independent of any type of meat consumption. Although carrying the *APOE* ε4 allele did not modify the associations between meat consumption and risk of all-cause dementia (upper panels in Figure 6.6, Figure 6.7 and 6.8), it slightly changed shapes of associations on AD and VD (middle and lower panels in Figure 6.6, Figure 6.7 and 6.8).

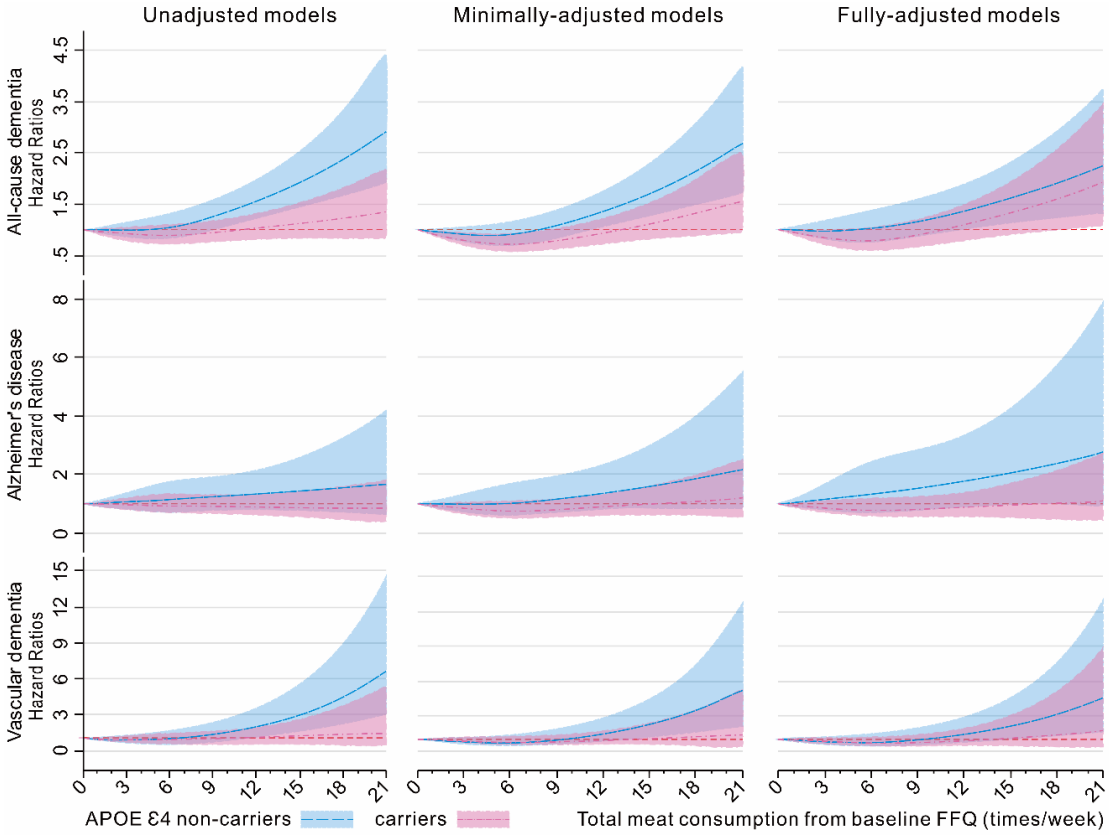


Figure 6.5 The shape of associations between total meat consumption at baseline and each dementia outcome among *APOE* ε4 carriers and non-carriers separately.

The lines and shaded zones represent hazard ratios and 95% confidence interval where *APOE* ε4 non-carriers in blue and carriers in pink respectively. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. *Abbr.*: *APOE*, Apolipoprotein E; FFQ, Food frequency questionnaire.

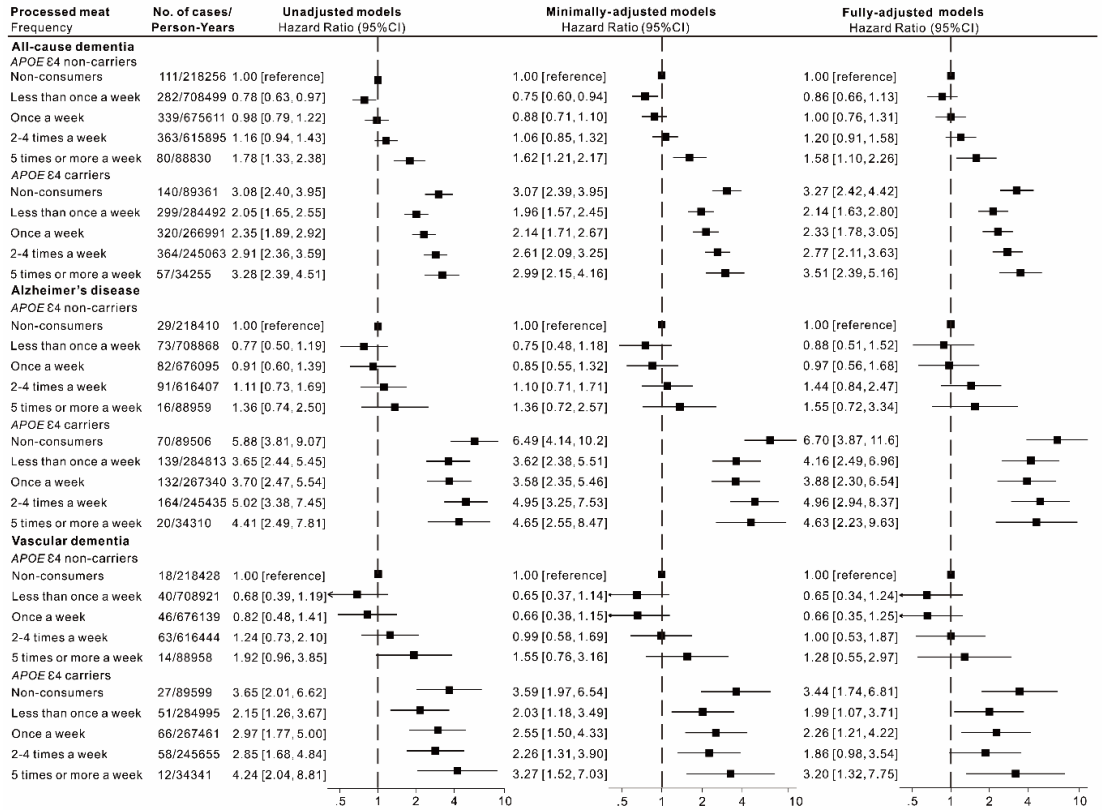


Figure 6.6 Risk of incident dementia by <u>processed meat consumption</u> at baseline in three models according to *APOE* ε4 carriage.

The black squares and horizontal lines represent hazard ratios and 95% confidence interval (CI) respectively. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. *Abbr.*: *APOE*, Apolipoprotein E.

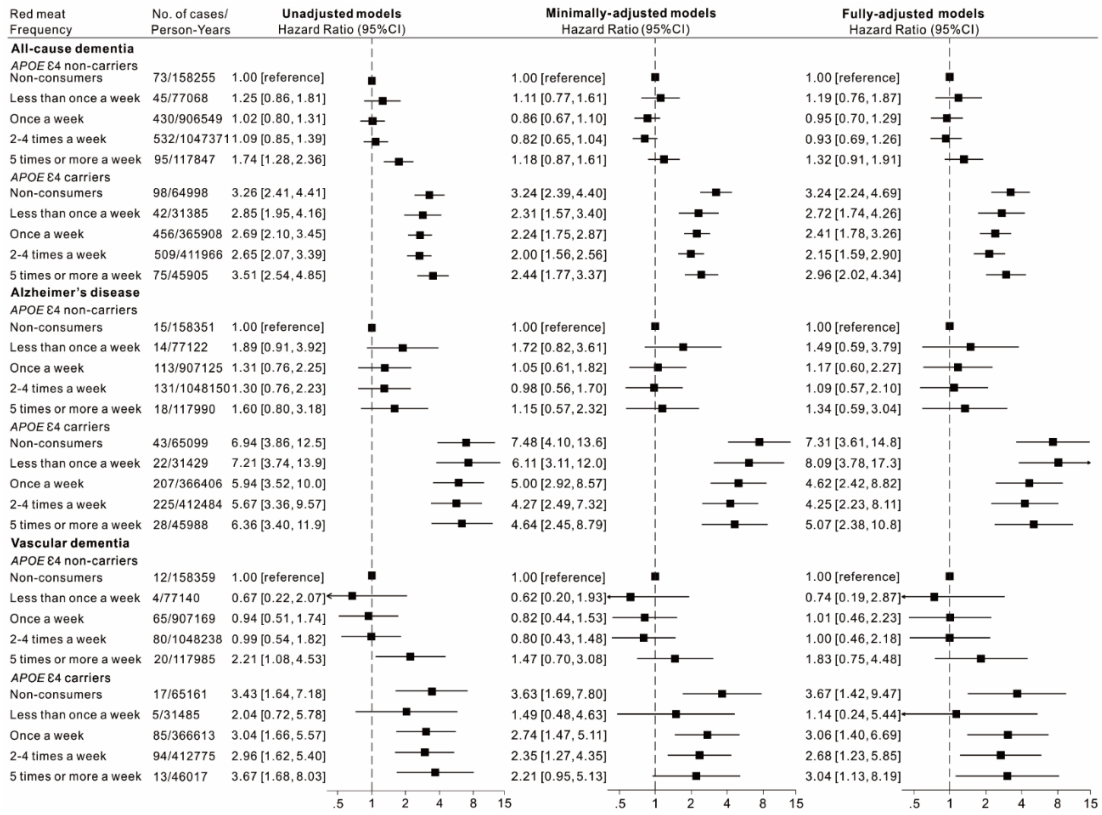


Figure 6.7 Risk of incident dementia by unprocessed red meat consumption at baseline in three models according to *APOE* ε4 carriage.

The black squares and horizontal lines represent hazard ratios and 95% confidence interval respectively. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. *Abbr.*: *APOE,* Apolipoprotein E.

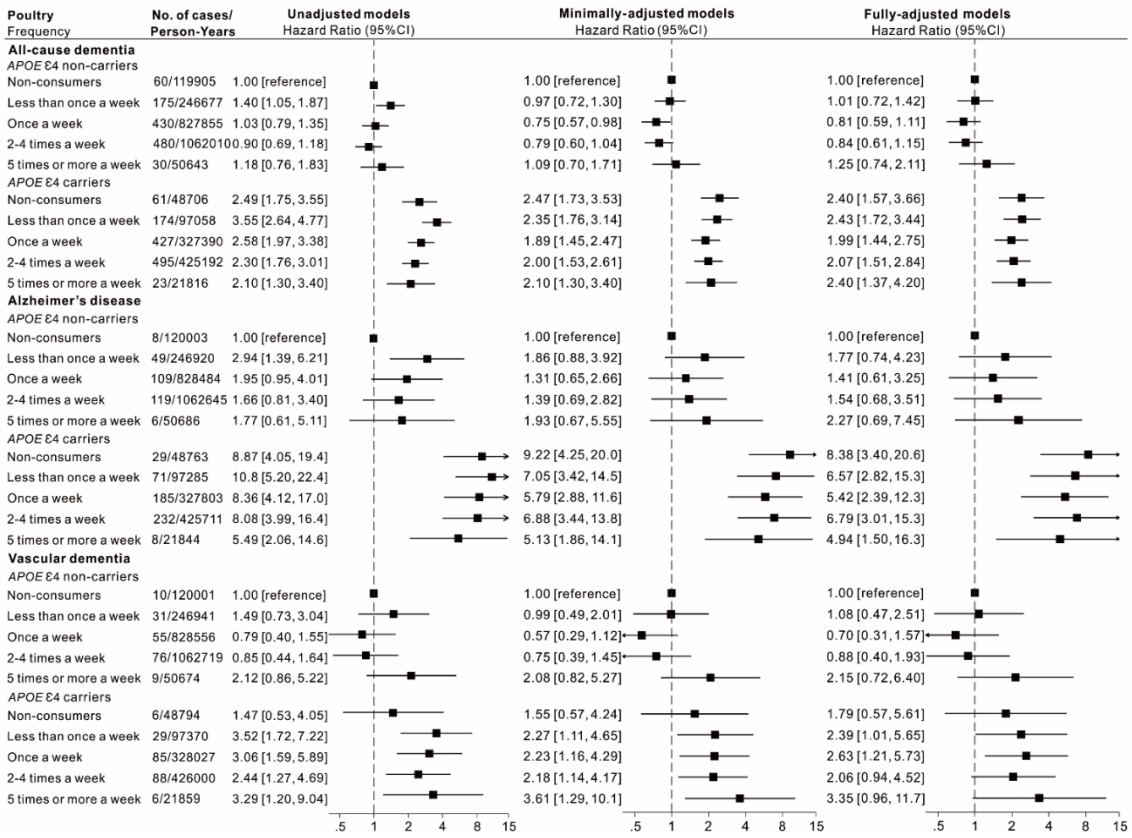


Figure 6.8 Risk of incident dementia by unprocessed poultry consumption at baseline in three models according to *APOE* ε4 carriage.

The black squares and horizontal lines represent hazard ratios and 95% confidence interval respectively. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia, and genetic kinship to other participants. *Abbr.*: *APOE*, Apolipoprotein E.

6.5 Discussion

This study explored associations between dementia risk and consumption of several common foods especially meat in the population-based UK Biobank cohort study involving half a million participants. When taking food consumption as continuous variables, the results show that high consumption of processed meat and unprocessed red meat, but not unprocessed poultry, were associated with increased odds of prevalent dementia, especially in men and in *APOE* ε4 carriers. In addition, high consumption of total meat and processed meat, but not unprocessed red meat or unprocessed poultry, was associated with increased risk of incident dementia; with slight differences observed between *APOE* ε4 carriers and non-carriers but the *P* values for interaction were not significant.

The results also show that consumption of vegetables, fruits, oily fish, and total fish were not associated with risk of prevalent dementia; however, high consumption of these foods were related to increased risk of incident dementia, especially among *APOE* ε4 carriers. These findings seem contrary to the initial hypotheses and other cohort findings that vegetables, fruits, and fish may reduce the risk of dementia potentially due to richness in antioxidants [98,328]. However, given a certain amount of total energy intake, high consumption of vegetables and fruits may result in low consumption of animal products which was linked with deficiency of vitamin B12 [329]. Vitamin B12 deficiency was found to be associated with increased risks of dementia and cognitive impairment [330] which could provide an explanation of the results in this thesis. In addition, the scopes of vegetable and fruit measured in the baseline FFQ were broad, and whether consumption of total vegetables and fruits or specific subtypes of them were linked to higher risk of incident dementia could not be determined is this study. At the same time, there was a certain proportion of missing values (5%–10%) in measurement of vegetable intakes which might have affected these associations; therefore, these findings should be interpretated with caution.

The findings were based on food intakes as continuous variables in generalized linear regression models which may have impeded figuring out the potential dose-response associations as food consumption increases. Therefore, in this project consumption of total meat and its subtypes were additionally explored for non-

linear associations in relation to risk of incident dementia, as well as potential interactions with *APOE* ε4 carriage.

The restricted cubic spline model showed a J-shaped association between total meat consumption from the baseline FFQ and risk of incident all-cause dementia, where low-frequency consumption was associated with a reduced risk and high-frequency consumption with an increased risk. This finding remains consistent when total meat consumption was assessed using detailed Oxford WebQ 24-h dietary assessments, and in other sensitivity analyses. Regarding specific meat types, consumption of processed meat had a more pronounced J-shaped association with risk of dementia than unprocessed red meat and unprocessed poultry.

6.5.1 Discussion of potential mechanisms

The underlying reasons for the J-shaped associations between meat consumption and risk of dementia are not fully understood. Levels of protein in meat may potentially explain why a limited amount of meat consumption is linked to a lower risk of dementia (e.g., once a week or less for processed meat, 2–4 times/week for unprocessed red meat or poultry) as adequate protein intake has been linked to reduced risks of mild cognitive impairment and dementia in the elderly [301]. At the same time, meat is also high in iron, zinc, and vitamin B12 as well as other B complex vitamins [331]. High iron levels in unprocessed red meat may be protective; with iron deficiency being associated with decreased cognitive and attentional processes. Studies in animals have shown a negative impact of iron deficiency on myelination [332]. On the other hand, as people age, iron deposits in the brain may impair normal cognitive function. Abnormal iron metabolism triggers oxidative stress, a major contributor to neurodegeneration [333]; but the associations need to be confirmed in human studies [334]. As meat consumption increases, intake of saturated fatty acids also increases, which has been associated with a higher risk of dementia [335]. These combined beneficial and negative effects of meat on risk of dementia may exist simultaneously, potentially resulting in the non-linear associations seen here.

Processed meat contains nitrites and N-nitroso compounds, which may result in oxidative stress, lipid peroxidation, and activation of pro-inflammatory cytokines or other mechanisms potentially involved in the development of dementia [336]. In addition, processed meat is often high in sodium, and rats fed a long-term high-salt

diet had a marked increase in systolic blood pressure linked to reduced regional cerebral blood flow, and potentially linked to cognitive deficit [337]. These particular compounds in nutritional composition may explain why consumption of processed meat was associated with a higher risk of dementia rather than unprocessed poultry and unprocessed red meat.

6.5.2 Comparison with similar studies

Related cohort studies remain few with inconsistent findings, and detailed knowledge of which type and amount of meat consumption would be the most influential to dementia risk is not clear. The Three-City (3C) cohort study took high-frequency consumption of meat as the reference and found that low frequency was related to an increased risk of incident dementia and AD over 10 years follow-up [338]; however, excessive category combination in this study may have attenuated the detective power of non-linear relationships. A cohort study conducted in French citizens aged 68 and over showed that compared with daily meat consumers, weekly or less consumers had a higher incidence rate of all-cause dementia and AD after 7 years follow-up; however, those associations were not significant probably because of small sample sizes (170 incident dementia including 135 AD among 1674 participants) [191]. Longitudinal analysis among 2622 elderly German participants suggested no significant association between risk of incident AD and consumption frequency of meat and sausage after 4 years follow-up [339]; however, this study only used linear models and did not consider non-linear associations.

In general, similar association trends between meat consumption and risk of dementia were observed in results from Cox regression using restricted cubic spline methods and categorical models. Extra comparisons of incident dementia rate across five consumption categories in each meat type were also in line with these trends, which indicates that in this project results from different statistical analysis methods are identical and have earned more credits. In addition, sensitivity analyses show that these associations did not significantly change, indicating that the main findings of the non-linear associations between meat consumption and incident dementia risk seem to be robust.

6.5.3 Interaction with the *APOE* ε4 allele

As detailed in Chapter 2, the *APOE* ε4 allele is a genetic factor associated with high

risk of dementia and this was also seen in present analyses. The results show that the presence of the *APOE* ε4 allele increased the risk of incident dementia by 2–9 times, especially AD by 6–9 times. Although the associations between meat consumption and prevalent dementia were more pronounced among *APOE* ε4 carriers, those with incident dementia were not significantly different among *APOE* ε4 non-carriers and carriers. At the same time, all *P* values for interaction with food consumption were not significant in this study.

Currently, evidence on the interaction between the *APOE* ε4 carriage and dietary factors with dementia has mostly focused on dietary patterns and dietary fat intake; those studies found older individuals (aged ≥60 years) who had a diet high in fatty fish or higher polyunsaturated fat intake were associated with a decreased risk of all-cause dementia, especially among *APOE* ε4 non-carriers [192,340]. In contrast, studies conducted at midlife found that moderate to high intake of saturated fats in relation to an increased risk of dementia/AD was only detected or more pronounced among *APOE* ε4 carriers [341,342]. A German cohort study of individuals aged 75+ found there was no difference in the association of meat and sausage consumption with incident AD risk between *APOE* ε4 non-carriers and carriers [339]. Inconsistency in these and our study results may reflect particular cohort characteristics; in particular the age span in this study was broad and relatively younger (50–68 years) and this may have led to our insignificant interactions between the *APOE* ε4 carriage and meat intake with incident dementia risk in this population. It is also possible that the *APOE* ε4 carriage is an independent process from dietary aspects in relation to dementia risk.

6.5.4 Strengths and limitations

A major strength of the current study is that the prospective study design with large sample sizes ensured sufficient statistical power. To my knowledge, this is the first study to estimate specific meat types in relation to dementia outcomes in non-linear models, with additional exploration of interactions with the *APOE* ε4 allele. Other strengths include use of multiple data linkage to maximise capture of incident dementia outcomes, generally consistent trends from the baseline FFQ and repeated 24-h dietary assessments as well as from other sensitivity analyses in relation to dementia risk, and consideration of reverse causation in analyses.

Nevertheless, this study has several limitations. First, the baseline touchscreen brief

FFQ only covered some commonly consumed foods and was not suitable to assess total energy or nutrient intakes; systematic bias from self-reported measures at recruitment and low responses to the more detailed repeated 24-h dietary assessments with less than half participants may limit generalizability. Second, use of data linkage to electronic health records may be high in specificity but low in sensitivity; moreover, without linkage to primary care data, milder cases of dementia may have been missed [343]. The percentage of AD out of all-cause dementia cases was low in this study (35%) compared to the report of World Health Organization (50–70%) [304]; many remaining cases had not been clinically classified as specific dementia types, which may attenuate the association between meat consumption and risk of AD/VD. Third, the follow-up duration may be not long enough to get classic dementia which usually takes years to develop; participants with mild symptoms of dementia were easily missed out in diagnosis. In addition, taking dates of hospital admission and death registry as proxy of diagnosis dates of incident dementia could have resulted in measurement errors. Therefore, electronic linkages to accurate primary-care data should be taken into consideration for dementia ascertainment in future research.

6.6 Conclusions

The findings suggest that consumption of meat, especially processed meat, may be positively associated with risks of prevalent and incident dementia in generalized linear models. More specifically, this association may be in a non-linear pattern, where compared to non-consumers low-frequency consumption of meat may be linked to lower risk of incident dementia but high-frequency consumption related to increased risk of incident dementia, which may be independent of the *APOE* ε4 carriage. In addition, consumption of vegetables, fruits, and fish did not have consistent findings in relation to prevalent and incident dementia risk in the present study. Further research is recommended to explore associations between consumption of food groups and dementia risk.

CHAPTER VII

7. Discussion and Conclusions

Cognitive decline and dementia are increasing public health issues in aging societies. The healthcare and economic burden from dementia is substantial, resulting in pressure on caregivers and families with dementia cases [344]. In the UK, the mortality rate for deaths due to dementia and Alzheimer's disease (AD) has been increasing since 2006, with 12.5% of all deaths registered in England and Wales due to dementia and AD in 2019 [345]. Since there are no effective treatment methods for dementia so far, it is important to prevent or halt the development of dementia, especially for AD one of the costliest chronic diseases, to improve the life quality and life expectancy of the public [346]. Therefore, dietary factors are investigated in this thesis to identify potential prevention strategies of dementia.

7.1 Summary of findings contributing to existing knowledge

The analyses in this thesis have used data from the UK Women's Cohort Study (UKWCS) and the UK Biobank (UKB), population-based prospective studies in the United Kingdom, to explore associations between diet, cognitive aging, and dementia. Dietary factors including commonly consumed foods, dietary patterns, and nutrient intakes were reviewed and investigated. In this final chapter, the overall results are summarized as follows.

7.1.1 Dietary factors in relation to cognitive aging and dementia

As reviewed in Chapter 2, although diet potentially plays a role in the prevention of cognitive aging and dementia, the existing evidence is still not sufficient. For example, few studies have investigated associations between meat consumption and dementia risk regarding specific meat subtypes and dose responses. At the same time, findings are not consistent between individual studies, especially for meat consumption as reviewed systematically in Chapter 3. The results from this thesis add to the growing body of literatures linking dietary factors to increased prevalence of cognitive impairment and dementia to provide more evidence for optimisation of dietary recommendation guidelines or policy making in dementia related institutions.

Table 7.1 Cross-sectional associations between diet, cognitive function, and prevalent dementia in this thesis [1]

Dietary factors	Cognitive function					Prevalent dementia	
	Reaction ability	Visual memory	Numeric memory	Fluid intelligence	Prospective memory	Odds ratios	*P* for interaction with the *APOE* ε4 allele
Food consumption							
Processed meat	– ↓	↑	–	↑	↑	– ▲	–
Unprocessed red meat	– –	↑	↓	–	↓	– –	–
Unprocessed poultry	– ↑	↑	–	–	↑	– –	–
Total meat	– ↓	↑	–	↑	–	– –	–
Oily fish	– ↓	↓	–	↓	↓	– –	–
Total fish	– ↓	↓	–	↓	↓	– –	–
Total vegetables	– ↑	↓	↓	↓	↓	– –	–
Total fruits	– ↓	↓	↓	↓	↓	– –	–
Dietary patterns							
Mediterranean diet	–					–	
Eating patterns	–					–	
PCA-derived patterns	–					–	
Nutrients							
Energy-unadjusted	–					–	

[1] The **up arrows** indicate positive associations between that dietary factor and the certain outcome, while the **down arrows** indicate negative associations. The **up triangles** indicate increased odds/risks of the certain outcome, while the **down triangles** indicate decreased odds/risks; the **horizontal lines** indicate no significant associations. In addition, the **blue markers** indicate results from the UK Biobank, while **red markers** indicate results from the UK Women's Cohort Study. The significance level was based on $P < 0.01$. *Abbr.*: PCA, principal components analysis; *APOE*, apolipoprotein E.

Table 7.2 Longitudinal associations between food consumption and risk of cognitive deterioration and incident dementia in this thesis [1]

Dietary factors	Cognitive deterioration risk					Incident dementia risk	
	Reaction ability	Visual memory	Numeric memory	Fluid intelligence	Prospective memory	Hazard ratios	*P* for interaction with the *APOE* ε4 allele
Food consumption							
Processed meat	–	–	–	–	–	▲	–
Unprocessed red meat	–	–	–	–	–	–	–
Unprocessed poultry	–	–	–	–	–	–	–
Total meat	–	–	–	–	–	▲	–
Oily fish	–	▲	–	–	–	–	–
Total fish	–	▲	–	–	–	▲	–
Total vegetables	–	–	–	–	▲	▲	–
Total fruits	–	▲	–	–	–	▲	–

[1] The **up triangles** indicate increased odds/risks of the certain outcome, while the **down triangles** indicate decreased odds/risks; the **horizontal lines** indicate no significant associations. In addition, the **blue markers** indicate results from the UK Biobank. The significance level was based on $P < 0.01$.
Abbr.: *APOE*, apolipoprotein E.

7.1.1.1 Food consumption

As shown in Table 7.1, consumption of total meat and its subtypes, total fish and its subtypes, total vegetables, and total fruits were cross-sectionally investigated in the UKWCS and the UKB in relation to cognitive function and prevalent dementia. Consumption of vegetables, fruits, fish, unprocessed poultry, unprocessed red meat, or total meat individually were not related to prevalent dementia in both cohorts, while high consumption of processed meat was associated with increased odds of prevalent dementia in the UKB only. Results for reaction ability in relation to food consumption were less consistent between the two cohorts. No significant association was indicated in the UKWCS. However, in the UKB consumption of processed meat and total meat, oily fish and total fish, and total fruit were individually associated with poorer reaction ability, while consumption of unprocessed poultry and total vegetables were positively related to reaction ability. One possible explanation for the differences in results between the two cohorts is the varying methodology of diet measures and outcome measures; for example, a detailed food frequency questionnaire in the UKWCS but limited questionnaire in the UKB were used, and two different types of the reaction ability test were used in the two cohorts (simple or choice reaction times in the UKWCS and the Snap game in the UKB, detailed in Chapter 4 and 5, respectively).

The longitudinal analyses were conducted in the UKB only taking cognitive changes and incident dementia as outcomes. As shown in Table 7.2, high consumption of total meat was associated with increased risk of incident dementia, but had no association with cognitive deterioration longitudinally. In terms of specific meat types, high consumption of processed meat was related to increased risk of incident dementia but had non-significant associations with cognitive deterioration. A high level of nitrites and N-nitroso compounds as well as sodium in processed meat may explain the increased risk of prevalent and incident dementia from high consumption of processed meat, as discussed in Chapter 6 [336,337]. Although consumption of unprocessed red meat and unprocessed poultry were not related to risk of incident dementia or cognitive deterioration, they had inconsistent associations with cognitive function at baseline across five cognitive tests. For example, consumption of unprocessed red meat was positively associated with visual memory, but negatively with numeric memory and prospective memory

(Table 7.1). Similar inconsistent associations were also seen between cognitive function and consumption of processed meat and total meat (Table 7.1). As detailed in Chapter 6, a non-linear association was observed in associations between meat consumption and dementia risk using restricted cubic spline methods and categorical models in the UKB. The J-shaped association indicates that a small amount of meat consumption may be potentially beneficial to cognitive function in adults, but dementia risk arises as meat consumption increases, which could partly explain the inconsistency in meat consumption from generalized linear models.

Regarding fish consumption, intakes of oily fish and total fish were negatively associated with reaction ability, visual memory, fluid intelligence, and prospective memory cross-sectionally (Table 7.1), and related to increased risk of deteriorating visual memory longitudinally (Table 7.2). In addition, high consumption of total fish was associated with increased risk of incident dementia. In the UKB, consumption of vegetables and fruits were negatively associated with visual memory, numeric memory, fluid intelligence, and prospective memory cross-sectionally (Table 7.1), and increased risk of deteriorating visual memory and prospective memory, and incident dementia longitudinally (Table 7.2). Those findings are generally not consistent with the original hypotheses of the thesis, and the underlying reasons are poorly understood. Although some associations were significant, the effect sizes were relatively small, especially in cognitive performance compared with the mean scores; there is a possibility that the significant results might be by chance given the large sample sizes although a more stringent significance level (P <0.01) was applied. However, as discussed in Chapter 5 and Chapter 6 there is another possibility that high consumption of vegetables and fruits, especially in vegetarians or vegans, may be related to deficiencies of protein, vitamin B12, or iron which are potentially associated with the outcomes [301,329,330].

7.1.1.2 Dietary patterns and nutrient intakes

As shown in Table 7.1, two *a priori* derived dietary patterns, one *a posteriori* derived dietary pattern, and energy-adjusted nutrient intakes were investigated in the UKWCS, and no significant association was observed between these dietary factors and cognitive performance or dementia as detailed in Chapter 4. Given the

baseline FFQ was relatively brief in the UKB, it is recognised that intakes of total energy and nutrients could not be calculated; therefore, dietary patterns or nutrient intakes were not analysed in the UKB in this thesis.

7.1.2 Interaction with the *APOE* ε4 allele

The potential interactions between food consumption and the *APOE* ε4 allele on dementia were investigated in the UKB. As detailed in Chapter 6, high consumption of processed meat was significantly associated with increased odds of prevalent dementia in *APOE* ε4 carriers but not in non-carriers. Similar differences between *APOE* ε4 carriers and non-carriers were seen in high consumption of oily fish and total fish in relation to increased risk of incident dementia. However, as shown in Table 7.1 and Table 7.2, the *P* values for interaction between food consumption and the *APOE* ε4 allele on dementia risk were not significant. In addition, the *APOE* ε4 carriage did not modify the shapes of association between meat consumption and incident dementia risk in the exploration of non-linear associations in the UKB. Therefore, although presence of the *APOE* ε4 allele does increase the dementia risk by 2- to 9- fold, there is insufficient evidence supporting interactions between the *APOE* ε4 allele and food consumption on dementia risk in this thesis. As discussed in Chapter 6, similar findings were seen in other cohort studies; for example, no difference in associations of meat and sausage consumption with incident AD risk was observed between *APOE* ε4 non-carriers and carriers in Germany [339]; the *APOE* ε4 carriage did not modify associations of egg and cholesterol intakes with risk of incident dementia and AD over 22 years of follow-up in eastern Finland [347].

7.1.3 Sex differences

There is evidence showing that women may have higher dementia rate than men [271] potentially due to longer average life expectancy in women [272] or sex-specific biological mechanisms [270]. At the same time, age-standardised mortality rates for deaths registered due to dementia and AD were significantly higher among females than males in England and Wales in 2019 [345]. However, there were higher proportions of men among both prevalent and incident dementia cases in the UKB in this thesis. Comparing the cohort characteristics between women and men (as shown in Chapter 5), we can see that women had higher levels of

college/university education and physical activity, but lower proportions with high deprivation, smoking, alcohol drinking, overweight, and stroke history than men. This indicates that potential selection bias exists in the UKB and may have resulted in the inconsistent sex-specific dementia rates observed in this thesis compared with other evidence [270].

In addition, differences in associations of food consumption with cognitive performance and prevalent dementia were observed between women and men in the UKB. For example, high consumption of total fish associated with increased odds of deteriorating reaction ability was observed in women only, while high consumption of unprocessed red meat and total meat in relation to increased odds of prevalent dementia was observed in men only. Therefore, further sex-specific analysis is recommended for future research relating to cognitive function and dementia.

7.1.4 Cooking methods

It was novel analysis to explore potential associations between cooking methods (roasting/baking, frying, and BBQ/grilling) of some commonly consumed foods and reaction ability in the UKWCS. As detailed in Chapter 4, consumption of fried vegetables was found to be associated with a slower simple reaction time. This may be potentially due to acrylamide produced in carbohydrate-rich food during a high-temperature cooking process [269,348]. However, this finding was not consistent with results for consumption of another carbohydrate-rich food, fried potatoes. At the same time, none of the cooking methods of meat or fish consumption had associations with reaction ability in this thesis. Since each cooking method was analysed separately, dichotomously divided into users or non-users of certain-method cooked food, the same person could use several different cooking methods, which might have offset potential effects and resulted in non-significant findings. Therefore, these findings should be interpreted with caution. In addition, more appropriate analysis approaches should be developed to investigate cooking methods in relation to health outcomes which may potentially explain some inconsistency in diet-related research.

7.2 Strengths and Limitations

Some strengths and limitations have been detailed in each chapter previously. Here,

the general strengths and limitations are summarized.

7.2.1 Study design

One major strength of this thesis is the two large-scale population-based cohort studies, the UKWCS and the UKB. Analyses of the two cohorts either could verify results mutually, or could offset the weakness in each other. For example, the UKWCS has female participants only and just one cognitive function tested with a limited sample size, and has dementia cases of death only, while the UKB has five cognitive functions tested with large sample sizes and incident dementia cases with diagnostic date available in both women and men. The UKB has collected limited common food consumption via a brief FFQ at baseline, and has a limited follow-up duration (6 to 8 years) which may be not long enough to distinguish cognitive decline or incident dementia. By contrast, the UKWCS has a detailed baseline FFQ which can be used to calculate nutrient intakes and derive dietary patterns. The UKWCS also has a long follow-up duration of ~13 years for the reaction time sub-study and ~20 years for the dementia cases of death sub-study. Therefore, it was necessary to conduct related analyses in both cohorts.

Another strength is that cross-sectional and longitudinal study designs were performed on cognitive performance, prevalent and incident dementia in relation to diet including food consumption, dietary patterns, and nutrient intakes comprehensively. In addition, reverse causation was considered in analyses of incident dementia to limit the possibility that underlying dementia may have changed dietary behaviours in advance of diagnosis in this thesis. Although evidence from randomised controlled trials (RCTs) is stronger and more reliable, the long-term interventions in RCTs are costly [308]; and it is challenging to ascertain an appropriate control to compare with some certain foods or dietary patterns [349]. Cognitive decline and dementia can take decades to develop; therefore, observational designs are good approaches to investigate such chronic symptoms and diseases in this thesis.

There is a lot of novel work in this thesis. For example, to the best of my knowledge this is the first study to investigate potential associations between i) cooking methods of common foods and reaction ability, ii) dietary factors and death from dementia, and iii) the first study to estimate specific types and amounts of meat

consumption in relation to incident dementia risk in non-linear models. In addition, potential interactions of food consumption with the *APOE* ε4 allele, a gene highly related to dementia development, were additionally explored in this thesis.

However, several limitations coming from study designs should be noted. Firstly, as is the nature of observational studies meaning that causality cannot be established, and all findings in this thesis are indicating associations between diet and cognitive performance or dementia rather than cause-effect relationships. Secondly, there is a possibility that the dietary behaviours have changed over the long-term observational follow-up; analyses in this thesis have assumed that the diet was kept consistent. In addition, since there are many comparisons in the analyses, especially in Chapter 5 where five cognitive tests are investigated, issues from multiple testing may potentially exist, even though a more stringent significance level of P <0.01 has been applied in this thesis.

7.2.2 Confounding factors

In this thesis, adjusted models are performed to control for potential effects of confounding factors, including age at baseline, ethnicity, socioeconomic status, smoking, alcohol consumption, BMI, physical activity level, and other lifestyle or health related covariates; more specifically, minimally-adjusted and fully-adjusted models are conducted in addition to unadjusted models in Chapter 5 and 6. The minimal adjustment set was determined via the directed acyclic graph (DAG).

However, the nature of observational studies means that the analyses are more prone to having confounding bias compared with RCTs. Although ~10 covariates have been considered, there is always a possibility that some other potential confounding factors may be missed either due to availability issues or multicollinearity. The confounding factors that should be adjusted for but were not in the adjustment set might have biased the associations in this thesis. For example, the adjustment of total energy intake is a common practice in nutritional studies as detailed in Chapter 4. However, it was recognised that intakes of total energy and nutrients could not be calculated at baseline in the UKB since limited food item consumption frequencies were collected via the brief FFQ. Therefore, the findings should be interpreted with caution due to potential under-adjustment.

7.2.3 Measurement errors

Measurement errors in exposures, outcomes, and other covariates are limitations of the present thesis. For the exposure measurement, in addition to a potential recall bias, the semi-quantitative FFQs used in both cohorts were designed to collect estimated dietary information which could not determine absolute intakes accurately. For example, since there might be a disproportionate number of participants who reported food consumption lower or higher than their 'true intake' in the lowest category and highest category respectively, regression dilution bias might have occurred in the baseline touchscreen dietary assessment in the UKB [286,350]. In addition, variation in defining dietary patterns should be noted. Although the *a priori* method was used to derive the Mediterranean diet, the scoring system (10 items) used in the UKWCS was different from that in other studies summarized by a review [351]. A similar problem was seen in other dietary patterns derived by the *a posteriori* method in Chapter 4.

In terms of the outcome measurement, as detailed in Chapter 2, the cognitive tests can only reflect part of cognitive function, and the whole level of cognitive changes is quite difficult to measure. The cognitive tests do not measure the cognitive function ability accurately, and a potential learning effect may exist in repeat measurements during follow-up in the UKB. Regarding methods of dementia ascertainment used in the UKB and the UKWCS, data linkage to hospital inpatient diagnoses and death registries could be limited to severe dementia cases which might have biased the associations with diet. In addition, taking dates of hospital admission and death registry as proxy of diagnosis dates of incident dementia in the UKB could have resulted in measurement errors in analyses.

The heterogeneity in measurements may have resulted in the inconsistency of findings between the studies mentioned previously in this thesis.

7.3 Possible directions for future research

7.3.1 Improvement of measurement accuracy

Since measurement errors could bias or attenuate the associations interested, improving measurement accuracy is recommended. For diet assessments, new technology-based methods could pave the way; for example, photography-based 24h dietary records could reduce recall bias; web-based dietary record tools (such

as Myfood24 [352]) could record food consumption timely and calculate energy and nutrient intakes immediately; web-based FFQs (such as the Oxford WebQ) with automatic logic checks could reduce missing values or mis-input values compared with a traditional paper-based FFQs. For dementia ascertainment, electronic linkage to primary-care data in the UKB could increase the detection rate and obtain relatively more accurate diagnostic dates. In addition, brain imaging data could contain biomarkers of dementia and improve the diagnostic accuracy [353]. Lower adherence to the Mediterranean diet has been associated with greater total brain atrophy after 3-year follow up using braining imaging data which is predictive of dementia [354]. It is highly recommended to include primary-care data and brain imaging data when investigating associations between diet and dementia where available [355].

7.3.2 Multi-factorial lifestyle score

There is increasing evidence showing that many lifestyle and health related factors could play a role in dementia development including smoking, alcohol drinking, hypertension, hypercholesteremia, obesity, diabetes mellitus, metabolic syndrome [93]. Investigation has shown that the disease burden from dementia is greater with comorbid vascular diseases [356], indicating that one factor may not stand alone but interact with other factors to have substantial effects. Therefore, study on multi-dimensional exposures including diet could be a more effective way to understand potential strategies for prevention and treatment of dementia. Currently, it is challenging to combine these related factors; developing effective multi-factorial lifestyle scores may be a promising way which needs more exploration [357].

7.3.3 Exploration of biological mechanisms

Although the findings in this thesis could shed some lights on associations between diet, cognitive performance, and dementia, the underlying mechanisms are not fully understood. Evidence from the statistical analyses in this thesis has indicated some potential associations, which needs to be confirmed in biological studies. For example, the underlying mechanism for high consumption of processed meat in relation to increased risk of dementia is not clear; as mentioned previously, potential detrimental effects from polycyclic aromatic hydrocarbons, nitrites and N-nitroso compounds, high sodium in processed meat [336,337] could provide an

explanation, but the direct biological mechanisms need to be confirmed. Therefore, biological studies based on the results from epidemiological studies are part of directions for future research.

7.4 Conclusions

The findings indicate that high consumption of meat, especially processed meat, may be associated with increased risk of prevalent and incident dementia. The association between consumption of processed meat and dementia risk may be in a non-linear pattern, independent of the *APOE* ε4 carriage. High consumption of vegetables, fruits, and fish may be associated with poor cognitive performance and increased risks of incident dementia. In addition, no association was observed between nutrient intakes and adherence to Mediterranean diet or other dietary patterns with reaction ability and dementia mortality. However, some limitations should be noted in this thesis; the findings need to be interpreted with caution and to be confirmed in other studies.

APPENDICES

Appendix A Reporting checklist for authors, editors, and reviewers of Meta-analyses Of Observational Studies in Epidemiology (MOOSE)

Reporting of background should include	
Problem definition	Descripted in the last sentence of the first paragraph of section 3.2. (P61)
Hypothesis statement	Descripted in the first sentence of the fourth paragraph of section 3.2. (P62)
Description of study outcome(s)	Descripted in the last paragraph of section 3.2. (P63)
Type of exposure or intervention used	Descripted in the last paragraph of section 3.2. (P63)
Type of study designs used	Descripted in the last paragraph of section 3.2. (P63)
Study population	Descripted in the last paragraph of section 3.2. (P63)
Reporting of search strategy should include	
Qualifications of searchers (e.g., librarians and investigators)	Descripted in the section 3.3.1. (P64)
Search strategy, including time period included in the synthesis and keywords	Descripted in the section 3.3.1. (P64)
Effort to include all available studies, including contact with authors	Effort includes free text searches and subject heading searches, reference list searching (section 3.3.1 P65) and contact with authors of paper with unclear description (section 3.4.1 P69).
Databases and registries searched	Descripted in the section 3.3.1. (P64)
Search software used, name and version, including special features used (e.g., explosion)	Did not use search software, but used the EndNote software to manage the records.
Use of hand searching (e.g., reference lists of obtained articles)	Descripted in the section 3.3.1. (P65)
List of citations located and those excluded, including justification	The section 3.4.1 descripted the citations selection process. (P69)
Method of addressing articles published in languages other than English	Descripted in the section 3.3.2, limiting studies written in English. (P65)
Method of handling abstracts and unpublished studies	Descripted in the section 3.3.2, limiting studies with full texts available. (P65)
Description of any contact with authors	Descripted in the section 3.4.1. (P69)
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Descripted in the section 3.3.2. (P65)
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	Did not reporting the rationale because the availability of data in the included studies was quite limited, so we tried our best to extract more relevant data.
Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)	Descripted in the section 3.3.4. (P67)
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	Did not detail it in text, but we assessed the confounding in quality assessment scale in Appendix B. (P223)

Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Descripted in section 3.3.3. (P66–67)
Assessment of heterogeneity	Descripted in section 3.3.4. (P68)
Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Descripted in section 3.3.4. (P67–68)
Provision of appropriate tables and graphics	Provided in Figures 3.1–3.6 and Tables 3.1–3.5.
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Figure 3.3 and Figure 3.5 (Page 82 and P86).
Table giving descriptive information for each study included	Table 3.2 (P71–76)
Results of sensitivity testing (e.g., subgroup analysis)	Not applicable because few studies were included in the meta-analyses.
Indication of statistical uncertainty of findings	Descripted in the section 3.4.4. (P81, P85).
Reporting of discussion should include	
Quantitative assessment of bias (e.g., publication bias)	Descripted in the end of the first paragraph and second paragraph in section 3.5 (P87), and in section 3.5.2 (P91).
Justification for exclusion (e.g., exclusion of non–English-language citations)	Descripted in section 3.5.2. (P91)
Assessment of quality of included studies	Descripted in section 3.5.2. (P91)
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Descripted in section 3.5.3. (P92–93)
Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	Descripted in section 3.5.3. (P93)
Guidelines for future research	Descripted in section 3.5.3. (P93)
Disclosure of funding source	Descripted in the Acknowledgement part. (P3)

Appendix B Quality assessment scale for observational and intervention studies with detailed guidance.

	Criteria	Yes	No	NR*
1	Was the research question or objective in this paper clearly stated?			
2	Was the sample size clearly defined, calculated and powerful to detect the association of interest?			
3	Did this paper describe the eligibility criteria, and the sources and methods of selection of participants?			
4	Was the participation rate of eligible persons at least 50% (Response rate or completion rate)? Was loss to follow-up after baseline 20% or less for longitudinal or cohort studies?			
5	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
6	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
7	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? Or matched for case-control studies?			
8	Did this paper describe all statistical methods and interpret the results clearly?			
9	Did this paper report proportions of missing data and explain how missing data were addressed?			
10	Was any potential bias reported and did this paper describe any efforts to address potential sources of bias?			
Reviewer:		**Total score:**		

*NR, not reported

Guidance

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Question 2 Sample size

Did the authors present their reasons for selecting or recruiting the number of people included or analysed? Did the authors describe how to determine the sample size to have enough participants to detect an association if one truly existed?

Questions 3. Study population

Did the authors describe the group of people from which the study participants were recruited, using demographics, location, and time period? If you were to

conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited? This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Hospital between 1. 1, 1990 and 12. 31, 1994. In this example, the population is clearly described as: (1) who; (2) where; and (3) when.

Question 4. Participation or follow-up rate

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Higher overall follow-up rates are always better than lower follow-up rates, even though higher rates are expected in shorter studies, whereas lower overall follow-up rates are often seen in studies of longer duration. Usually, an acceptable overall follow-up rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent follow-up, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent follow-up rate.

Question 5. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable? Also, as important is whether the exposures were assessed in the same manner within groups and between groups if applicable.

Here if the meat intake was recorded by 24h dietary recall and FFQs of past 1 month was believed to be relatively accurate, whereas FFQs about the past more than 1 month was not accurate.

Question 6. Outcome measures and assessment

Were the outcome measures defined in detail? Were the tools or methods used to measure outcomes accurate and reliable? Also, as important is whether the outcomes were assessed in the same manner within groups and between groups if applicable.

If the cognitive functions were measured by published known mental scales was believed to be reliable such as: Mini-mental state examination (MMSE), Wechsler Adult Intelligence Scale (WAIS), 10/66 diagnostic algorithm, Montreal Cognitive Assessment (MoCA).

If there are reliable diagnostic criteria for Alzheimer's disease or dementia, such as Diagnostic and Statistical Manual of Mental Disorders 3th/4th edition (DSM-III/IV), National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

Question 7. Covariate assessment

All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses. Here the key factors are age, sex, and education level.

Question 8. Statistical analyses

Did this paper describe all statistical methods used clearly, which means you can understand how every single number of interest obtained, including categorized methods on continuous variables, statistical methods to detect the association. Also, the result interpretation was clearly enough to know the exactly association between meat intake and cognitive changes.

Question 9. Missing value

Most studies will have a proportion of missing value, and ignorance under a small proportion or statistical filling using correct methods are reasonable.

Question 10. Potential bias

Did the authors report any potential bias? This information may was reported in the limitation part. Sub-group analysis, sensitivity analysis or other reasonable methods are acceptable.

Appendix C Examples of the baseline food frequency questionnaire in the UKWCS

PLEASE PUT A TICK(✓) ON EVERY LINE

FOODS AND AMOUNTS	HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS?									
	NEVER	Less than once a month	1-3 per month	once a week	2-4 per week	5-6 per week	once per day	2-3 per day	4-5 per day	6+ per day
PULSES (include when used in recipes)										
Lentils, dals	0	1	2	3	4	5	6	7	8	9
Chick Peas, Chanas	0	1	2	3	4	5	6	7	8	9
Hummus	0	1	2	3	4	5	6	7	8	9
Baked beans	0	1	2	3	4	5	6	7	8	9
Mung Beans & Red Kidney Beans	0	1	2	3	4	5	6	7	8	9
Bean Sprouts	0	1	2	3	4	5	6	7	8	9
Black Eyed Beans	0	1	2	3	4	5	6	7	8	9
Butter Beans/Broad Beans	0	1	2	3	4	5	6	7	8	9
EGGS/EGG DISHES										
Boiled/ Poached egg	0	1	2	3	4	5	6	7	8	9
Omelette, Scrambled egg	0	1	2	3	4	5	6	7	8	9
Fried egg	0	1	2	3	4	5	6	7	8	9
Quiche	0	1	2	3	4	5	6	7	8	9
VEGETABLE DISHES										
Quorn	0	1	2	3	4	5	6	7	8	9
Textured vegetable protein/ Sosmix/burger mix/soya sausages	0	1	2	3	4	5	6	7	8	9
Vegetarian Chilli/Vegetable Curry	0	1	2	3	4	5	6	7	8	9
Mixed Bean Casserole/Ratatouille	0	1	2	3	4	5	6	7	8	9
Stir-fry vegetables	0	1	2	3	4	5	6		8	9
Vegetable - Lasagne/Moussaka/Ravioli/ filled pasta with sauce	0	1	2	3	4	5	6	7	8	9
Vegetable Pizza	0	1	2	3	4	5	6	7	8	9
MEAT										
Beef e.g. roast, steak	0	1	2	3	4	5	6	7	8	9
Beef Stew/Casserole/Mince/Curry	0	1	2	3	4	5	6	7	8	9
Beefburger/Hamburger	0	1	2	3	4	5	6	7	8	9
Pork e.g. Roast, Chops, Slices	0	1	2	3	4	5	6	7	8	9
Pork Stew/Casserole	0	1	2	3	4	5	6	7	8	9
Lamb e.g. Roast, Chops	0	1	2	3	4	5	6	7	8	9
Lamb Stew/Casserole	0	1	2	3	4	5	6	7	8	9

PLEASE PUT A TICK(✓) ON EVERY LINE

FOODS AND AMOUNTS	HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS?									
	NEVER	Less than once a month	1-3 per month	once a week	2-4 per week	5-6 per week	once per day	2-3 per day	4-5 per day	6+ per day
OTHER MEATS										
Chicken/Turkey roast, slices	0	1	2	3	4	5	6	7	8	9
Breadcrumbed e.g.chicken nuggets/kievs	0	1	2	3	4	5	6	7	8	9
Chicken/Turkey in creamy sauce, curry	0	1	2	3	4	5	6	7	8	9
Bacon	0	1	2	3	4	5	6	7	8	9
Ham	0	1	2	3	4	5	6	7	8	9
Corned Beef, Spam, Luncheon Meats	0	1	2	3	4	5	6	7	8	9
Sausages e.g. Beef Pork	0	1	2	3	4	5	6	7	8	9
Pies/Pasties/Sausage Rolls	0	1	2	3	4	5	6	7	8	9
Offal e.g. Liver, Kidney	0	1	2	3	4	5	6	7	8	9
Liver Pâté/Sausage, Salami	0	1	2	3	4	5	6	7	8	9
Meat - Lasagne/Moussaka/Ravioli/ filled pasta with sauce	0	1	2	3	4	5	6	7	8	9
Meat Pizza	0	1	2	3	4	5	6	7	8	9
FISH										
Fish fingers/cakes	0	1	2	3	4	5	6	7	8	9
Fried fish in batter (as in fish and chips)	0	1	2	3	4	5	6	7	8	9
White fish e.g. Cod, Haddock, Plaice, Sole, Halibut (fresh or frozen)	0	1	2	3	4	5	6	7	8	9
Oily fish e.g. Mackerel, Kippers, Tuna, Salmon, Sardines, Herring	0	1	2	3	4	5	6	7	8	9
Shellfish e.g. Crab, Prawns, Mussels	0	1	2	3	4	5	6	7	8	9
Fish Roe, Taramasalata	0	1	2	3	4	5	6	7	8	9
Fish Pie/Fish Lasagne	0	1	2	3	4	5	6	7	8	9
VEGETABLES										
Beetroot	0	1	2	3	4	5	6	7	8	9
Broccoli, Spring Greens, Kale	0	1	2	3	4	5	6	7	8	9
Brussel Sprouts	0	1	2	3	4	5	6	7	8	9
Cabbage	0	1	2	3	4	5	6	7	8	9
Carrots	0	1	2	3	4	5	6	7	8	9
Cauliflower	0	1	2	3	4	5	6	7	8	9
Celery	0	1	2	3	4	5	6	7	8	9

Appendix D Supplementary methods used in the UKWCS in Chapter 4

A-Table 4.1 Twenty food groups collated from individual food items in the baseline food frequency questionnaire

Food Groups	Individual Food Items
Wholegrain products & cereals	Brown bread & rolls, Wholemeal bread & rolls, Crispbread, Porridge/Readybrek, Sugar coated cereals, Non-sugar coated cereals, Muesli, All bran/bran flakes, Weetabix/shredded wheat, Wholemeal pasta, Brown rice, Wild rice, Barley, Oats, Bulgar wheat, Cous-cous, Cereal bars/Flapjacks
Refined grain products	White bread & rolls, Chapattis, Nan, paratha, Papadums, Tortillas, Pitta Bread, White pasta, White rice, Macaroni cheese, Wheat Germ, Buns/pastries, Scones/pancakes/muffins/crumpets
Plain Potatoes	Boiled or mashed potatoes, Jacket potato
Potatoes with added fat	Chips, Roast potatoes, Potato salad
Low-fat dairy products	Low fat yoghurt, Diet yoghurt, Low-fat cheese, Cottage cheese, Half-fat milk, Fat free milk
High-fat dairy products	Thick & creamy yoghurt, Greek yoghurt, Fromage frais/Crème fraiche, Dairy desserts, Single/sour cream, Double/clotted cream, Ice cream, Milk puddings, Cheese, Cheese and onion pastie, Whole milk, Channel island milk, Dried milk
Low-fat dressing, spread, sauce	Polyunsaturated margarine, Monounsaturated margarine, Low fat spread, Very low-fat spread, Marmite/Bovril/Vegemite, Jam/marmalade, Honey, Low calorie salad cream, Sauces, Pickles/chutney/pesto sauce
High-fat dressing, spread, sauce	Butter, Block margarine, Other soft margarine, Peanut butter Chocolate/chocolate & nut spread, Mayonnaise, French type dressing
Eggs & Egg dishes	Boiled/Poached egg, Omelette/Scrambled egg, Fried egg, Quiche
Soybean products	Soya cheese, Soya yoghurt, Soy milk
Pulses & Legumes	Lentils/Dals, Chick peas/Chanas, Hummus, Baked beans, Mung beans & red kidney beans, Black eyed beans, Butter beans/broad beans, Green beans, Peas/Mushy peas/Mange-tout
Fish & fish dishes	Fish fingers/cakes, Fried fish in batter, White fish, Oily fish, Shellfish, Fish roe, Fish pie/fish lasagne
Red & processed meat, offal	Beef, Beef stew, Pork, Pork stew/casserole, Lamb, Lamb stew/casserole, Meat – lasagne/moussaka/ravioli, Bacon, Beef burger/hamburger, Ham, Corned beef, Sausages, Meat pizza, Pies/pasties/sausage rolls, Liver pate/sausage/salami, Offal
Poultry	Chicken/turkey, Chicken nuggets, Chicken/turkey in creamy sauce
Vegetables	Bean sprouts, Leeks, Garlic, Sweetcorn, Courgettes, Olive, Aubergine, Okra/ladies finger, Peppers, Lettuce, Cucumber, Celery, Coleslaw, Low calorie coleslaw, Broccoli, Spring greens, Kale, Cabbage, Cauliflower, Watercress/mustard &cress, Brussel sprouts, Tomatoes– raw/canned/sauce, Mushrooms, Carrots, Parsnips, Turnip, Swedes, Beetroot, Vegetable pate
Fruits	Avocado, Peaches, Plum, Mangoes, Nectarines, Apricots, Papaya, Pineapple, Melon, Grapes, Oranges/satsumas/grapefruit, Rhubarb, Strawberries, Raspberries, Red currants/black currants, Kiwi fruit, Bananas, Apples, Pears Dates, Figs, Prunes, Mixed dried fruits, Currants/raisins/sultanas
Nuts & Seeds	Nut Pâté, Peanuts/Pistachio nuts, Cashew nuts & almonds, Pecan nuts/ Walnuts, Sunflower seeds/ sesame seeds, Mixed nuts and raisins
Refreshments & snacks	Cream crackers/biscuits, Crisps, Other fried snacks, Low fat or baked snacks, Bombay mix, Chocolate snack bars, Mini chocolate snack bars, Boiled sweets/toffees/mints, Plain biscuits, Chocolate biscuits, Sandwich/cream biscuits, Fruitcake, Sponge cake, Fruit pies, Sponge puddings

Alcohol	Wines, Beer, Cider, Port/sherry/liqueurs, Spirits
Beverages	Tea, Herbal tea, Coffee – decaffeinated, Ovaltine, Low calorie hot chocolate, Orange juice, Other – pure juices, Fruit squash, Fizzy soft drinks, Low calorie/diet soft drinks, Coffee – instant/ground, Cocoa/hot chocolate, Coffee substitute, Coffee whitener

A-Table 4.2 The Structured Query Language (SQL) to extract dementia cases of death in the UK Women's Cohort Study

```
SELECT Death_flagging.counter, Death_flagging.Original_cause
FROM Death_flagging
WHERE (((Death_flagging.Original_cause) Like "F01*" Or (Death_flagging.Original_cause) Like "F02*" Or (Death_flagging.Original_cause) Like "F03*" Or (Death_flagging.Original_cause) Like "F04*" Or (Death_flagging.Original_cause) Like "F06*" Or (Death_flagging.Original_cause) Like "G30*" Or (Death_flagging.Original_cause) Like "R41*" Or (Death_flagging.Original_cause) Like "290*" Or (Death_flagging.Original_cause) Like "294*" Or (Death_flagging.Original_cause) Like "317*" Or (Death_flagging.Original_cause) Like "318*" Or (Death_flagging.Original_cause) Like "319*" Or (Death_flagging.Original_cause) Like "331*"))
ORDER BY Death_flagging.Original_cause;
```

Appendix E Supplementary results from the UK Biobank regarding cognitive function in Chapter 5

A-Table 5.1 Associations between food consumption and **improved cognition** in visual memory

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	50,822	0.92	0.76	1.10	0.352	50,822	0.85	0.69	1.05	0.138	43,710	0.78	0.61	1.00	0.052
Fruits[3]	50,898	1.10	1.04	1.15	<0.001	50,898	1.07	1.01	1.13	0.017	43,726	1.05	0.98	1.13	0.170
Oily fish[4]	51,118	1.09	0.96	1.23	0.196	51,118	0.97	0.85	1.11	0.660	43,832	0.97	0.84	1.12	0.647
Total fish[4]	51,059	1.04	0.96	1.12	0.384	51,059	0.98	0.90	1.07	0.600	43,809	0.98	0.89	1.07	0.637
Processed meat[4]	51,177	0.98	0.89	1.08	0.711	51,177	0.97	0.87	1.07	0.487	43,871	0.97	0.87	1.07	0.514
Unprocessed red meat[4]	50,999	1.10	1.01	1.20	0.037	50,999	1.06	0.96	1.16	0.273	43,780	1.08	0.97	1.19	0.152
Unprocessed poultry[4]	51,178	0.96	0.85	1.07	0.451	51,178	1.01	0.89	1.14	0.904	43,875	1.03	0.90	1.17	0.667
Total meat[4]	50,966	1.01	0.96	1.07	0.617	50,966	1.01	0.95	1.07	0.770	43,762	1.02	0.96	1.08	0.521
Females															
Vegetables[3]	26,344	0.96	0.76	1.23	0.761	26,344	0.89	0.67	1.17	0.398	21,844	0.70	0.48	1.02	0.065
Fruits[3]	26,350	1.13	1.08	1.18	<0.001	26,350	1.09	1.02	1.17	0.009	21,832	1.06	0.98	1.16	0.162
Oily fish[4]	26,456	1.11	0.92	1.33	0.271	26,456	0.98	0.80	1.20	0.850	21,877	0.94	0.74	1.20	0.647
Total fish[4]	26,427	1.08	0.96	1.21	0.220	26,427	1.02	0.89	1.16	0.795	21,866	1.02	0.87	1.19	0.810
Processed meat[4]	26,476	0.98	0.78	1.22	0.842	26,476	1.00	0.80	1.25	1.000	21,891	1.02	0.81	1.29	0.841
Unprocessed red meat[4]	26,409	1.11	0.96	1.29	0.153	26,409	1.07	0.92	1.26	0.376	21,853	1.09	0.92	1.28	0.338
Unprocessed poultry[4]	26,484	1.03	0.86	1.23	0.784	26,484	1.06	0.88	1.28	0.537	21,894	1.13	0.92	1.39	0.233
Total meat[4]	26,391	1.03	0.95	1.13	0.455	26,391	1.04	0.95	1.14	0.444	21,843	1.06	0.97	1.17	0.207
Males															
Vegetables[3]	24,478	0.92	0.71	1.18	0.505	24,478	0.83	0.61	1.12	0.220	21,866	0.83	0.61	1.13	0.238
Fruits[3]	24,548	1.08	1.00	1.17	0.066	24,548	1.05	0.97	1.15	0.247	21,894	1.04	0.93	1.16	0.491
Oily fish[4]	24,662	1.07	0.91	1.26	0.428	24,662	0.96	0.81	1.15	0.682	21,955	0.97	0.81	1.17	0.782
Total fish[4]	24,632	1.01	0.90	1.12	0.907	24,632	0.95	0.84	1.07	0.377	21,943	0.95	0.84	1.07	0.405
Processed meat[4]	24,701	0.92	0.83	1.03	0.145	24,701	0.95	0.85	1.05	0.309	21,980	0.95	0.84	1.07	0.356
Unprocessed red meat[4]	24,590	1.07	0.95	1.19	0.271	24,590	1.05	0.92	1.18	0.483	21,927	1.08	0.95	1.22	0.252
Unprocessed poultry[4]	24,694	0.90	0.78	1.05	0.175	24,694	0.97	0.83	1.13	0.656	21,981	0.96	0.82	1.14	0.666
Total meat[4]	24,575	0.98	0.91	1.05	0.483	24,575	0.99	0.92	1.06	0.775	21,919	1.00	0.92	1.08	0.977

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: 95%CI, 95% confidence interval.

A-Table 5.2 Associations between food consumption and **improved cognition** in numeric memory

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	3098	1.07	0.89	1.29	0.458	3098	1.07	0.89	1.27	0.477	2694	1.09	0.89	1.32	0.418
Fruits[3]	3105	1.03	0.94	1.12	0.541	3105	1.02	0.94	1.11	0.654	2693	1.02	0.93	1.12	0.662
Oily fish[4]	3114	1.17	1.02	1.35	0.028	3114	1.16	1.00	1.34	0.049	2697	1.13	0.96	1.34	0.134
Total fish[4]	3111	1.07	0.97	1.18	0.164	3111	1.06	0.96	1.18	0.229	2696	1.05	0.94	1.18	0.374
Processed meat[4]	3120	0.95	0.85	1.07	0.387	3120	0.94	0.83	1.06	0.288	2702	0.94	0.83	1.06	0.278
Unprocessed red meat[4]	3113	1.04	0.94	1.16	0.454	3113	1.03	0.92	1.15	0.579	2699	1.06	0.94	1.19	0.341
Unprocessed poultry[4]	3122	1.02	0.89	1.17	0.784	3122	1.02	0.89	1.18	0.741	2703	1.02	0.88	1.18	0.803
Total meat[4]	3112	1.00	0.95	1.06	0.928	3112	1.00	0.94	1.06	0.950	2698	1.00	0.94	1.07	0.928
Females															
Vegetables[3]	1588	1.04	0.82	1.32	0.766	1588	1.05	0.82	1.35	0.701	1336	—	—	—	—
Fruits[3]	1587	1.05	0.93	1.21	0.425	1587	1.04	0.90	1.19	0.612	1334	1.05	0.90	1.22	0.529
Oily fish[4]	1589	1.15	0.92	1.43	0.214	1589	1.13	0.90	1.42	0.306	1334	1.11	0.86	1.43	0.428
Total fish[4]	1586	1.07	0.93	1.24	0.344	1586	1.06	0.91	1.23	0.460	1333	1.04	0.87	1.23	0.637
Processed meat[4]	1593	0.96	0.78	1.18	0.694	1593	0.97	0.78	1.20	0.776	1336	0.92	0.72	1.17	0.478
Unprocessed red meat[4]	1589	0.97	0.82	1.14	0.689	1589	0.95	0.79	1.13	0.546	1335	0.99	0.81	1.21	0.921
Unprocessed poultry[4]	1594	0.97	0.80	1.17	0.738	1594	0.96	0.79	1.16	0.639	1337	0.92	0.75	1.13	0.438
Total meat[4]	1588	0.98	0.89	1.07	0.626	1588	0.97	0.88	1.07	0.532	1334	0.96	0.87	1.07	0.473
Males															
Vegetables[3]	1510	1.12	0.85	1.48	0.413	1510	1.11	0.86	1.42	0.433	1358	1.22	0.92	1.61	0.166
Fruits[3]	1518	1.01	0.90	1.13	0.909	1518	1.01	0.90	1.13	0.894	1359	1.00	0.88	1.13	0.950
Oily fish[4]	1525	1.19	0.99	1.43	0.070	1525	1.19	0.98	1.43	0.074	1363	1.18	0.96	1.46	0.124
Total fish[4]	1525	1.07	0.94	1.23	0.313	1525	1.07	0.93	1.22	0.339	1363	1.06	0.92	1.23	0.430
Processed meat[4]	1527	0.93	0.80	1.07	0.292	1527	0.92	0.80	1.06	0.261	1366	0.93	0.81	1.07	0.315
Unprocessed red meat[4]	1524	1.10	0.96	1.27	0.158	1524	1.10	0.96	1.26	0.166	1364	1.10	0.96	1.27	0.176
Unprocessed poultry[4]	1528	1.07	0.88	1.31	0.490	1528	1.10	0.90	1.34	0.350	1366	1.10	0.88	1.37	0.404
Total meat[4]	1524	1.02	0.94	1.10	0.678	1524	1.02	0.95	1.10	0.616	1364	1.02	0.94	1.11	0.596

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

A-Table 5.3 Associations between food consumption and **improved cognition** in fluid intelligence

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	15,987	0.83	0.74	0.93	0.001	15,987	0.84	0.76	0.94	0.002	13,855	0.83	0.74	0.93	0.002
Fruits[3]	16,009	1.00	0.97	1.04	0.859	16,009	1.01	0.98	1.05	0.526	13,863	1.03	0.99	1.07	0.103
Oily fish[4]	16,054	0.93	0.86	1.00	0.058	16,054	0.93	0.86	1.01	0.078	13,886	0.90	0.83	0.98	0.017
Total fish[4]	16,039	0.95	0.91	1.00	0.056	16,039	0.95	0.91	1.00	0.065	13,880	0.94	0.89	0.99	0.020
Processed meat[4]	16,083	1.02	0.97	1.07	0.560	16,083	0.99	0.94	1.04	0.696	13,905	0.98	0.93	1.04	0.483
Unprocessed red meat[4]	16,047	0.99	0.94	1.05	0.832	16,047	0.99	0.94	1.05	0.749	13,889	0.99	0.94	1.05	0.842
Unprocessed poultry[4]	16,080	0.97	0.92	1.03	0.316	16,080	0.97	0.91	1.03	0.306	13,904	0.95	0.89	1.01	0.109
Total meat[4]	16,043	1.00	0.97	1.02	0.787	16,043	0.99	0.96	1.02	0.407	13,886	0.98	0.95	1.01	0.243
Females															
Vegetables[3]	8111	0.84	0.73	0.98	0.029	8111	0.85	0.73	0.99	0.040	6758	0.81	0.68	0.97	0.019
Fruits[3]	8109	1.01	0.96	1.06	0.795	8109	1.01	0.96	1.07	0.616	6754	1.04	0.98	1.11	0.166
Oily fish[4]	8136	0.92	0.83	1.04	0.174	8136	0.93	0.83	1.05	0.231	6767	0.85	0.75	0.97	0.017
Total fish[4]	8128	0.95	0.88	1.02	0.147	8128	0.95	0.88	1.02	0.176	6764	0.91	0.84	0.99	0.031
Processed meat[4]	8148	0.95	0.86	1.04	0.258	8148	0.94	0.86	1.04	0.211	6774	0.93	0.83	1.03	0.167
Unprocessed red meat[4]	8133	1.03	0.95	1.12	0.451	8133	1.04	0.95	1.12	0.409	6767	1.03	0.93	1.13	0.595
Unprocessed poultry[4]	8147	0.94	0.86	1.02	0.152	8147	0.93	0.86	1.02	0.114	6773	0.89	0.80	0.98	0.018
Total meat[4]	8130	0.98	0.94	1.03	0.446	8130	0.98	0.94	1.02	0.403	6764	0.97	0.92	1.02	0.168
Males															
Vegetables[3]	7876	0.83	0.72	0.97	0.020	7876	0.84	0.72	0.97	0.020	7097	0.85	0.73	0.99	0.041
Fruits[3]	7900	1.01	0.96	1.06	0.685	7900	1.01	0.96	1.06	0.708	7109	1.03	0.97	1.08	0.346
Oily fish[4]	7918	0.93	0.84	1.03	0.173	7918	0.93	0.84	1.04	0.193	7119	0.93	0.83	1.04	0.225
Total fish[4]	7911	0.96	0.90	1.02	0.197	7911	0.96	0.90	1.02	0.206	7116	0.96	0.89	1.03	0.216
Processed meat[4]	7935	1.02	0.96	1.08	0.573	7935	1.01	0.95	1.08	0.685	7131	1.01	0.94	1.07	0.891
Unprocessed red meat[4]	7914	0.95	0.88	1.02	0.153	7914	0.95	0.89	1.02	0.172	7122	0.96	0.89	1.04	0.303
Unprocessed poultry[4]	7933	1.00	0.92	1.08	0.919	7933	1.00	0.92	1.08	0.963	7131	0.99	0.91	1.08	0.778
Total meat[4]	7913	0.99	0.96	1.03	0.677	7913	0.99	0.96	1.03	0.658	7122	0.99	0.95	1.03	0.592

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

A-Table 5.4 Associations between food consumption and **improved cognition** in reaction ability

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	52,423	1.04	0.97	1.12	0.287	52,423	1.00	0.92	1.08	0.899	44,359	1.02	0.94	1.11	0.665
Fruits[3]	52,508	1.03	0.99	1.06	0.143	52,508	1.00	0.96	1.04	0.918	44,385	1.00	0.96	1.05	0.844
Oily fish[4]	52,738	1.10	1.04	1.16	0.001	52,738	1.04	0.98	1.11	0.196	44,492	1.03	0.96	1.11	0.357
Total fish[4]	52,676	1.05	1.01	1.09	0.020	52,676	1.02	0.98	1.07	0.365	44,468	1.01	0.96	1.06	0.767
Processed meat[4]	52,802	0.94	0.89	0.98	0.008	52,802	0.96	0.91	1.01	0.119	44,533	0.96	0.91	1.02	0.149
Unprocessed red meat[4]	52,627	0.98	0.93	1.03	0.388	52,627	0.96	0.91	1.01	0.106	44,439	0.96	0.91	1.02	0.167
Unprocessed poultry[4]	52,804	0.96	0.91	1.01	0.143	52,804	0.98	0.92	1.03	0.372	44,537	0.99	0.93	1.05	0.645
Total meat[4]	52,589	0.97	0.95	1.00	0.017	52,589	0.98	0.95	1.00	0.047	44,420	0.98	0.95	1.01	0.105
Females															
Vegetables[3]	27,134	1.08	0.98	1.18	0.132	27,134	1.04	0.94	1.15	0.489	22,128	1.08	0.98	1.20	0.128
Fruits[3]	27,141	1.06	1.01	1.10	0.017	27,141	1.02	0.98	1.07	0.361	22,119	1.03	0.98	1.09	0.247
Oily fish[4]	27,254	1.12	1.03	1.21	0.008	27,254	1.05	0.97	1.15	0.231	22,168	1.07	0.97	1.18	0.169
Total fish[4]	27,225	1.06	1.00	1.12	0.045	27,225	1.03	0.97	1.09	0.360	22,157	1.03	0.96	1.10	0.428
Processed meat[4]	27,277	0.96	0.89	1.04	0.304	27,277	0.97	0.90	1.05	0.466	22,182	0.96	0.87	1.05	0.370
Unprocessed red meat[4]	27,210	0.96	0.90	1.02	0.198	27,210	0.93	0.86	0.99	0.030	22,144	0.93	0.86	1.01	0.097
Unprocessed poultry[4]	27,285	0.95	0.89	1.02	0.183	27,285	0.96	0.89	1.03	0.230	22,185	0.97	0.89	1.06	0.482
Total meat[4]	27,190	0.97	0.94	1.00	0.079	27,190	0.96	0.93	1.00	0.040	22,134	0.97	0.93	1.01	0.100
Males															
Vegetables[3]	25,289	0.98	0.86	1.11	0.715	25,289	0.94	0.82	1.07	0.350	22,231	0.93	0.81	1.07	0.300
Fruits[3]	25,367	0.97	0.92	1.03	0.311	25,367	0.96	0.91	1.02	0.179	22,266	0.97	0.91	1.03	0.262
Oily fish[4]	25,484	1.08	0.99	1.17	0.073	25,484	1.03	0.94	1.12	0.568	22,324	0.99	0.90	1.10	0.886
Total fish[4]	25,451	1.04	0.98	1.10	0.218	25,451	1.01	0.95	1.07	0.761	22,311	0.98	0.92	1.06	0.626
Processed meat[4]	25,525	0.94	0.88	1.01	0.083	25,525	0.95	0.89	1.01	0.126	22,351	0.95	0.89	1.03	0.200
Unprocessed red meat[4]	25,417	1.02	0.95	1.09	0.597	25,417	1.00	0.93	1.07	0.929	22,295	0.99	0.91	1.07	0.744
Unprocessed poultry[4]	25,519	0.98	0.90	1.06	0.554	25,519	1.00	0.92	1.09	0.974	22,352	1.00	0.92	1.10	0.935
Total meat[4]	25,399	0.99	0.95	1.02	0.386	25,399	0.99	0.95	1.02	0.424	22,286	0.98	0.95	1.02	0.435

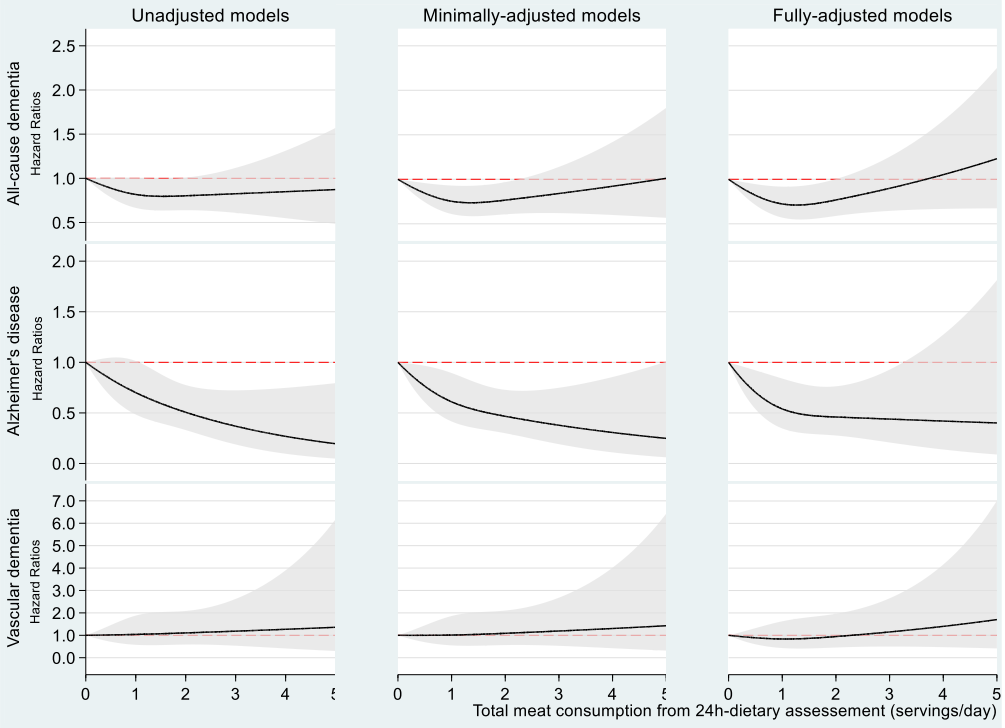
[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

A-Table 5.5 Associations between food consumption and **improved cognition** in prospective memory

	Unadjusted Models					Minimally-adjusted Models[1]					Fully-adjusted Models[2]				
	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*	Number	OR	LCI	UCI	*P*
Total															
Vegetables[3]	16,291	1.04	0.97	1.11	0.306	16,254	1.01	0.94	1.08	0.837	14,062	0.99	0.91	1.07	0.751
Fruits[3]	16,314	1.04	1.01	1.07	0.006	16,276	1.03	1.00	1.06	0.088	14,071	1.02	0.99	1.06	0.194
Oily fish[4]	16,363	1.09	1.04	1.15	0.001	16,327	1.07	1.01	1.13	0.016	14,095	1.06	1.00	1.12	0.045
Total fish[4]	16,347	1.07	1.03	1.10	<0.001	16,311	1.06	1.02	1.09	0.003	14,089	1.05	1.01	1.09	0.008
Processed meat[4]	16,395	0.97	0.93	1.01	0.083	16,357	0.98	0.94	1.03	0.417	14,115	0.98	0.94	1.02	0.354
Unprocessed red meat[4]	16,355	1.01	0.97	1.05	0.542	16,319	1.00	0.97	1.05	0.838	14,098	1.01	0.97	1.06	0.609
Unprocessed poultry[4]	16,393	1.01	0.96	1.05	0.826	16,355	1.01	0.96	1.05	0.725	14,114	1.01	0.96	1.06	0.619
Total meat[4]	16,351	1.00	0.98	1.02	0.619	16,315	1.00	0.98	1.02	0.867	14,095	1.00	0.98	1.02	0.984
Females															
Vegetables[3]	8267	0.99	0.91	1.09	0.879	8247	0.97	0.88	1.06	0.467	6863	0.96	0.86	1.06	0.398
Fruits[3]	8264	1.02	0.97	1.06	0.468	8243	1.00	0.96	1.04	0.886	6858	0.99	0.94	1.04	0.765
Oily fish[4]	8296	1.11	1.03	1.19	0.006	8275	1.08	1.00	1.16	0.055	6873	1.08	0.99	1.17	0.073
Total fish[4]	8288	1.09	1.04	1.14	<0.001	8267	1.07	1.02	1.13	0.004	6870	1.08	1.02	1.14	0.006
Processed meat[4]	8309	1.00	0.94	1.07	0.961	8288	1.01	0.94	1.07	0.883	6880	1.03	0.96	1.11	0.376
Unprocessed red meat[4]	8293	1.00	0.94	1.06	0.932	8273	0.98	0.93	1.04	0.569	6873	0.98	0.92	1.05	0.602
Unprocessed poultry[4]	8308	1.00	0.94	1.06	0.981	8287	1.00	0.94	1.06	0.867	6879	1.00	0.94	1.08	0.902
Total meat[4]	8290	1.00	0.97	1.03	0.932	8270	1.00	0.97	1.02	0.732	6870	1.00	0.97	1.04	0.867
Males															
Vegetables[3]	8024	1.08	0.97	1.19	0.147	8007	1.06	0.95	1.18	0.300	7199	1.03	0.91	1.16	0.670
Fruits[3]	8050	1.06	1.02	1.10	0.003	8033	1.05	1.01	1.09	0.008	7213	1.05	1.01	1.10	0.027
Oily fish[4]	8067	1.08	1.01	1.16	0.035	8052	1.06	0.98	1.14	0.133	7222	1.05	0.97	1.13	0.265
Total fish[4]	8059	1.05	0.99	1.10	0.084	8044	1.04	0.98	1.09	0.187	7219	1.03	0.98	1.09	0.284
Processed meat[4]	8086	0.96	0.91	1.01	0.104	8069	0.97	0.92	1.02	0.253	7235	0.95	0.89	1.00	0.067
Unprocessed red meat[4]	8062	1.04	0.98	1.09	0.222	8046	1.03	0.97	1.09	0.357	7225	1.04	0.98	1.10	0.223
Unprocessed poultry[4]	8085	1.01	0.95	1.08	0.737	8068	1.02	0.96	1.09	0.498	7235	1.02	0.95	1.09	0.581
Total meat[4]	8061	1.00	0.97	1.03	0.870	8045	1.00	0.97	1.03	0.905	7225	1.00	0.97	1.03	0.876

[1] Minimally-adjusted models adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models additionally adjusted for region, smoking status, physical activity, body mass index, sleep duration, stroke history, family history of dementia, alcohol drinking. [3]Unit: portion/day. [4]Unit: portion/week. *Abbr.*: OR, odds ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%).

Appendix F Supplementary results from the UK Biobank regarding dementia risk in Chapter 6



A-Figure 6.1 Restricted cubic spline regressions describing the shape of associations with total meat intakes of 24-h dietary assessments

The black lines and gray zones represent hazard ratios and 95% confidence interval respectively in Cox regressions. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia.

A-Table 6.1 Frequency of processed meat consumption from 24-hour dietary assessments and risk of dementia

	No. of cases/ Person-Years	Unadjusted models (*n* =210,769)				Minimally-adjusted Models[1] (*n* =209,533)				Fully-adjusted models[2] (*n* =176,931)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	332/711603	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	9/28228	0.68	0.35	1.32	0.254	0.72	0.37	1.40	0.334	0.79	0.39	1.60	0.510
Once a week	23/78952	0.62	0.41	0.95	0.028	0.65	0.43	0.99	0.047	0.64	0.39	1.03	0.063
2–4 times a week	60/171820	0.76	0.57	1.00	0.046	0.76	0.58	1.01	0.057	0.64	0.46	0.89	0.008
5 times or more a week	128/301506	0.92	0.75	1.13	0.408	0.91	0.74	1.12	0.365	0.96	0.76	1.20	0.692
P trend[3]					0.064				0.114				0.043
Alzheimer's disease													
Non-eaters	109/711987	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	4/28233	0.92	0.34	2.51	0.874	0.96	0.35	2.63	0.941	1.17	0.42	3.23	0.765
Once a week	8/78968	0.66	0.32	1.35	0.255	0.67	0.32	1.38	0.276	0.62	0.27	1.42	0.256
2–4 times a week	16/171889	0.61	0.36	1.04	0.068	0.61	0.36	1.03	0.062	0.39	0.19	0.80	0.010
5 times or more a week	35/301642	0.77	0.52	1.12	0.169	0.72	0.49	1.06	0.097	0.76	0.49	1.19	0.232
P trend[3]					0.266				0.207				0.080
Vascular dementia													
Non-eaters	52/712088	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	0/28242	—	—	—	—	—	—	—	—	—	—	—	—
Once a week	3/78974	0.53	0.16	1.68	0.279	0.61	0.19	1.94	0.402	0.51	0.13	2.11	0.355
2–4 times a week	8/171894	0.65	0.31	1.38	0.261	0.70	0.33	1.47	0.349	0.66	0.28	1.55	0.337
5 times or more a week	18/301670	0.83	0.49	1.42	0.494	0.84	0.49	1.44	0.527	0.91	0.51	1.62	0.750
P trend[3]					<0.001				0.654				0.643

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.2 Frequency of unprocessed red meat consumption from 24-hour dietary assessments and risk of dementia

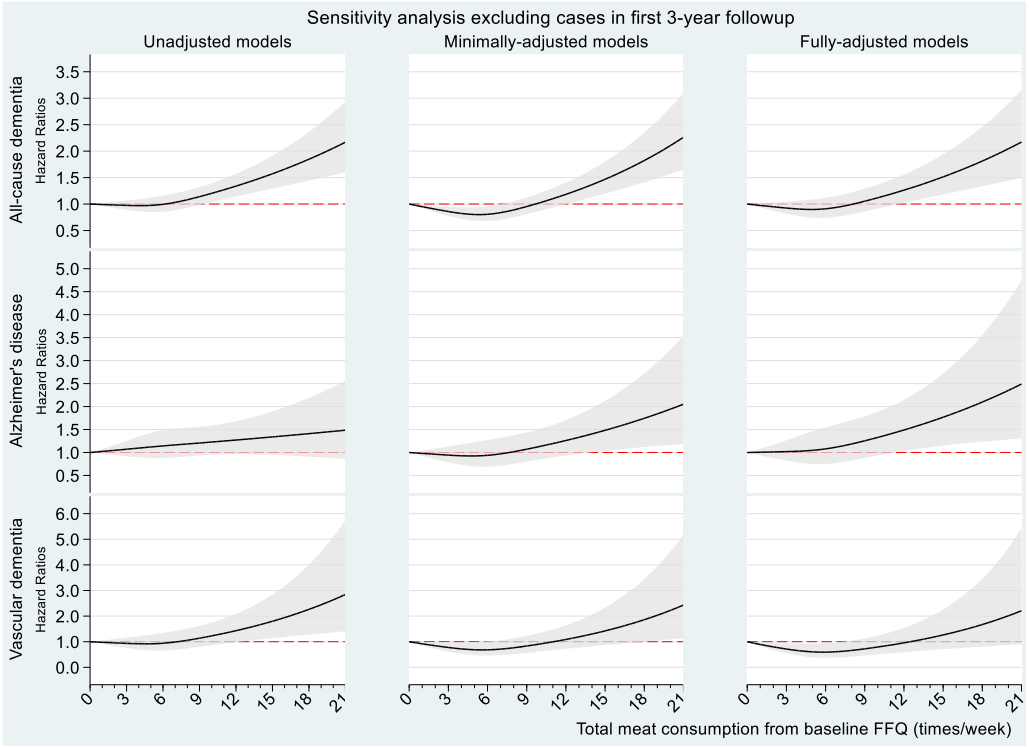
	No. of cases/ Person-Years	Unadjusted models (*n* =210,769)				Minimally-adjusted Models[1] (*n* =209,533)				Fully-adjusted models[2] (*n* =176,931)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	305/673125	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	4/11241	0.77	0.29	2.05	0.597	0.80	0.30	2.14	0.659	0.73	0.24	2.28	0.592
Once a week	30/86220	0.75	0.52	1.10	0.140	0.75	0.52	1.09	0.134	0.74	0.49	1.14	0.170
2–4 times a week	74/243442	0.67	0.52	0.87	0.002	0.64	0.49	0.82	0.001	0.62	0.46	0.83	0.001
5 times or more a week	139/278080	1.10	0.90	1.35	0.333	1.00	0.82	1.22	1.000	1.06	0.84	1.32	0.642
P trend[3]					0.006				0.007				0.009
Alzheimer's disease													
Non-eaters	102/673445	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	1/11242	0.58	0.08	4.12	0.581	0.62	0.09	4.45	0.636	0.70	0.10	4.99	0.719
Once a week	9/86257	0.68	0.34	1.34	0.262	0.68	0.34	1.35	0.271	0.65	0.30	1.41	0.271
2–4 times a week	20/243528	0.54	0.34	0.88	0.013	0.53	0.33	0.86	0.009	0.47	0.27	0.83	0.009
5 times or more a week	40/278246	0.95	0.66	1.37	0.791	0.88	0.60	1.28	0.504	0.87	0.57	1.34	0.535
P trend[3]					0.121				0.111				0.108
Vascular dementia													
Non-eaters	38/673547	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	0/11243	—	—	—	—	—	—	—	—	—	—	—	—
Once a week	4/86260	0.80	0.28	2.24	0.668	0.88	0.32	2.47	0.813	0.75	0.23	2.47	0.636
2–4 times a week	10/243550	0.74	0.37	1.47	0.387	0.75	0.38	1.51	0.424	0.63	0.28	1.41	0.261
5 times or more a week	29/278268	1.84	1.14	2.98	0.013	1.65	1.02	2.67	0.043	1.55	0.90	2.67	0.116
P trend[3]					<0.001				0.089				0.143

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.3 Frequency of unprocessed poultry consumption from 24-hour dietary assessments and risk of dementia

	No. of cases/ Person-Years	Unadjusted models (*n* =210,769)				Minimally-adjusted Models[1] (*n* =209,533)				Fully-adjusted models[2] (*n* =176,931)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	374/728209	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	2/14344	0.27	0.07	1.06	0.061	0.30	0.07	1.19	0.087	0.18	0.03	1.27	0.086
Once a week	25/96016	0.50	0.33	0.75	0.001	0.53	0.35	0.80	0.002	0.57	0.37	0.89	0.013
2–4 times a week	69/228938	0.59	0.46	0.76	<0.001	0.66	0.51	0.85	0.001	0.61	0.45	0.82	0.001
5 times or more a week	82/224600	0.71	0.56	0.90	0.004	0.80	0.63	1.02	0.073	0.77	0.58	1.01	0.060
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	120/728625	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	0/14346	—	—	—	—	—	—	—	—	—	—	—	—
Once a week	9/96051	0.56	0.28	1.10	0.093	0.60	0.31	1.19	0.145	0.58	0.27	1.25	0.166
2–4 times a week	23/229022	0.61	0.39	0.96	0.031	0.68	0.44	1.07	0.093	0.63	0.38	1.06	0.082
5 times or more a week	20/224675	0.54	0.33	0.86	0.010	0.61	0.38	0.99	0.046	0.56	0.32	0.99	0.047
P trend[3]					0.009				0.066				0.064
Vascular dementia													
Non-eaters	58/728721	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	0/14346	—	—	—	—	—	—	—	—	—	—	—	—
Once a week	5/96056	0.64	0.26	1.60	0.337	0.74	0.30	1.86	0.525	0.88	0.34	2.26	0.789
2–4 times a week	8/229052	0.45	0.21	0.94	0.033	0.54	0.26	1.13	0.100	0.50	0.21	1.17	0.108
5 times or more a week	10/224694	0.56	0.28	1.09	0.086	0.62	0.31	1.22	0.166	0.46	0.20	1.08	0.073
P trend[3]					<0.001				0.244				0.167

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.



A-Figure 6.2 Restricted cubic spline regressions describing the shape of associations between total meat consumption at baseline and each dementia outcome in sensitivity analysis excluding cases arising in first 3-year follow-up.

The black lines and gray zones represent hazard ratios and 95% confidence interval respectively in Cox regressions. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia.

A-Table 6.4 Frequency of processed meat consumption from baseline food frequency questionnaire and risk of dementia excluding cases arising in the first 3-year follow up

	No. of cases/ Person-Years	Unadjusted models (*n* =493,570)				Minimally-adjusted Models[1] (*n* =488,215)				Fully-adjusted models[2] (*n* =391,887)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	255/369560	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	648/1205697	0.78	0.67	0.90	0.001	0.73	0.63	0.85	<0.001	0.77	0.64	0.92	0.004
Once a week	715/1150151	0.90	0.78	1.04	0.150	0.79	0.68	0.92	0.002	0.83	0.70	1.00	0.049
2–4 times a week	803/1059522	1.10	0.96	1.27	0.168	0.96	0.83	1.11	0.580	0.99	0.83	1.19	0.950
5 times or more a week	146/152575	1.40	1.14	1.72	0.001	1.23	0.99	1.52	0.061	1.26	0.98	1.62	0.071
P trend[3]					<0.001				<0.001				0.009
Alzheimer's disease													
Non-eaters	94/369842	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	240/1206330	0.78	0.62	0.99	0.042	0.72	0.56	0.92	0.008	0.81	0.60	1.10	0.171
Once a week	241/1150858	0.82	0.65	1.05	0.109	0.73	0.57	0.94	0.015	0.81	0.60	1.11	0.187
2–4 times a week	297/1060325	1.11	0.88	1.40	0.387	1.02	0.80	1.31	0.876	1.11	0.81	1.50	0.522
5 times or more a week	43/152729	1.12	0.78	1.61	0.537	1.06	0.72	1.55	0.766	1.19	0.76	1.88	0.445
P trend[3]					<0.001				<0.001				0.010
Vascular dementia													
Non-eaters	47/369921	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	101/1206555	0.66	0.47	0.93	0.018	0.60	0.42	0.86	0.005	0.58	0.38	0.88	0.010
Once a week	123/1151074	0.84	0.60	1.18	0.310	0.67	0.47	0.96	0.027	0.59	0.39	0.89	0.011
2–4 times a week	136/1060604	1.02	0.73	1.42	0.928	0.76	0.53	1.08	0.121	0.65	0.43	0.99	0.045
5 times or more a week	27/152764	1.41	0.88	2.26	0.156	1.08	0.66	1.78	0.757	0.84	0.46	1.52	0.564
P trend[3]					0.001				0.011				0.062

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.5 Frequency of <u>unprocessed red meat</u> consumption from baseline food frequency questionnaire and risk of dementia excluding cases arising in the first 3-year follow up

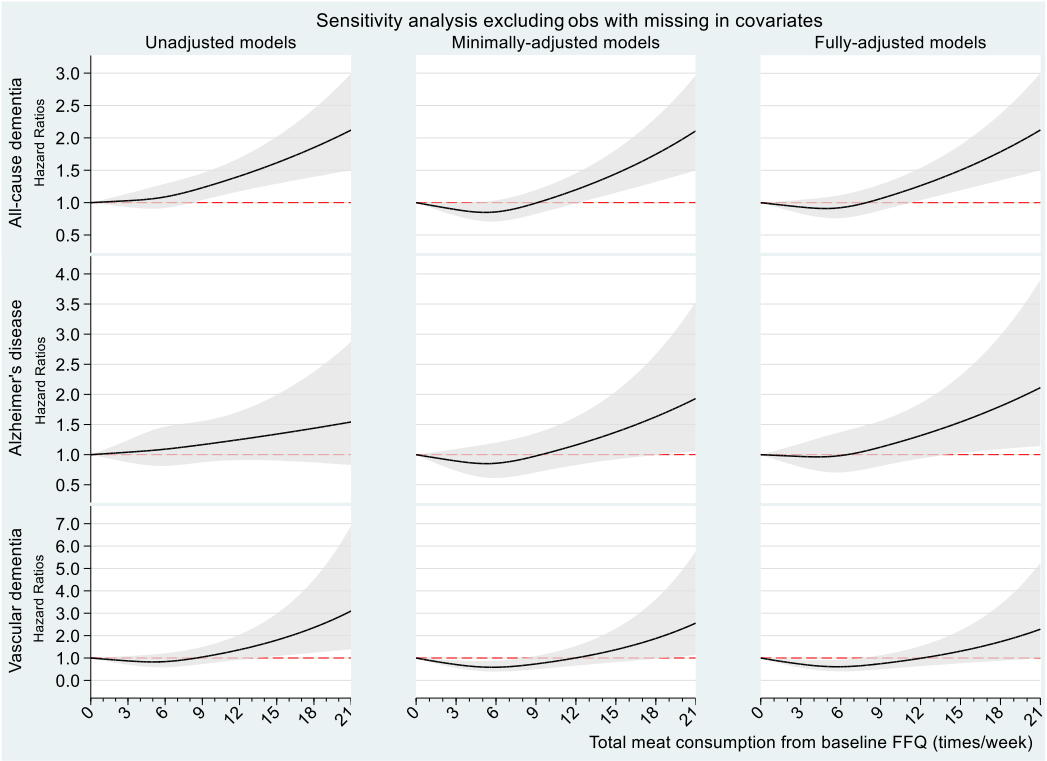
	No. of cases/ Person-Years	Unadjusted models (*n* =493,570)				Minimally-adjusted Models[1] (*n* =488,215)				Fully-adjusted models[2] (*n* =391,887)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	177/267198	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	89/132910	1.00	0.77	1.29	0.994	0.86	0.67	1.12	0.265	1.06	0.80	1.40	0.685
Once a week	960/1549001	0.94	0.80	1.10	0.425	0.76	0.65	0.90	0.001	0.84	0.70	1.02	0.074
2–4 times a week	1150/1785334	0.97	0.82	1.13	0.657	0.71	0.60	0.83	<0.001	0.80	0.67	0.97	0.020
5 times or more a week	191/203061	1.41	1.15	1.73	0.001	0.94	0.77	1.16	0.588	1.13	0.89	1.43	0.305
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	59/267396	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	33/133000	1.11	0.73	1.70	0.633	0.91	0.59	1.41	0.684	1.15	0.70	1.88	0.582
Once a week	360/1549921	1.05	0.80	1.39	0.708	0.81	0.61	1.07	0.137	0.84	0.60	1.18	0.313
2–4 times a week	409/1786493	1.03	0.78	1.35	0.843	0.71	0.53	0.93	0.015	0.77	0.55	1.09	0.140
5 times or more a week	54/203273	1.19	0.82	1.72	0.356	0.80	0.55	1.16	0.242	0.93	0.60	1.45	0.754
P trend[3]					0.866				0.074				0.217
Vascular dementia													
Non-eaters	33/267441	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	11/133037	0.66	0.33	1.30	0.231	0.52	0.25	1.05	0.067	0.54	0.23	1.26	0.154
Once a week	161/1550211	0.84	0.58	1.23	0.372	0.67	0.46	0.99	0.044	0.73	0.46	1.18	0.203
2–4 times a week	194/1786919	0.87	0.60	1.26	0.461	0.62	0.42	0.90	0.012	0.65	0.40	1.04	0.071
5 times or more a week	35/203310	1.37	0.85	2.21	0.191	0.81	0.50	1.33	0.413	0.91	0.51	1.65	0.765
P trend[3]					0.073				0.081				0.197

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.6 Frequency of <u>unprocessed poultry</u> consumption from baseline food frequency questionnaire and risk of dementia excluding cases arising in the first 3-year follow up

	No. of cases/ Person-Years	**Unadjusted models (*n* =493,570)**				**Minimally-adjusted Models[1] (*n* =488,215)**				**Fully-adjusted models[2] (*n* =391,887)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	137/202429	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	370/420635	1.29	1.06	1.57	0.010	0.84	0.69	1.02	0.084	0.94	0.74	1.20	0.618
Once a week	930/1410986	0.97	0.81	1.16	0.738	0.69	0.57	0.83	<0.001	0.78	0.63	0.98	0.033
2–4 times a week	1071/1814749	0.87	0.73	1.04	0.113	0.74	0.62	0.89	0.001	0.85	0.68	1.06	0.140
5 times or more a week	59/88706	0.98	0.72	1.33	0.887	0.95	0.69	1.30	0.727	1.14	0.79	1.66	0.477
P trend[3]					<0.001				<0.001				0.014
Alzheimer's disease													
Non-eaters	41/202594	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	128/421044	1.49	1.05	2.12	0.026	0.91	0.64	1.30	0.615	0.92	0.60	1.43	0.719
Once a week	324/1411883	1.13	0.82	1.56	0.467	0.73	0.53	1.02	0.061	0.83	0.55	1.23	0.349
2–4 times a week	403/1815797	1.09	0.79	1.50	0.605	0.88	0.64	1.22	0.439	1.05	0.71	1.56	0.806
5 times or more a week	19/88766	1.05	0.61	1.81	0.854	1.04	0.60	1.82	0.886	1.32	0.69	2.52	0.405
P trend[3]					0.027				0.046				0.070
Vascular dementia													
Non-eaters	21/202624	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	64/421146	1.46	0.89	2.38	0.136	0.87	0.53	1.42	0.566	0.92	0.50	1.70	0.797
Once a week	149/1412199	1.01	0.64	1.60	0.959	0.68	0.43	1.08	0.103	0.84	0.48	1.49	0.554
2–4 times a week	185/1816178	0.97	0.62	1.53	0.908	0.80	0.51	1.25	0.318	0.87	0.50	1.53	0.634
5 times or more a week	15/88771	1.62	0.83	3.14	0.154	1.54	0.78	3.07	0.216	1.66	0.73	3.78	0.226
P trend[3]					0.029				0.029				0.358

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.



A-Figure 6.3 Restricted cubic spline regressions describing the shape of associations between total meat consumption at baseline and each dementia outcome in sensitivity analysis excluding participants with missing in covariates

The black lines and gray zones represent hazard ratios and 95% confidence interval respectively in Cox regressions. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia.

A-Table 6.7 Frequency of <u>processed meat</u> consumption from baseline food frequency questionnaire and risk of dementia excluding participants with incomplete data in covariates

	No. of cases/ Person-Years	**Unadjusted models (*n* =392,126)**				**Minimally-adjusted Models[1] (*n* =392,126)**				**Fully-adjusted models[2] (*n* =392,126)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	196/294838	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	508/954787	0.80	0.68	0.94	0.008	0.72	0.61	0.85	<0.001	0.77	0.65	0.91	0.002
Once a week	566/910260	0.94	0.80	1.10	0.432	0.79	0.67	0.93	0.005	0.84	0.71	0.99	0.042
2–4 times a week	641/840106	1.15	0.98	1.35	0.079	0.94	0.79	1.11	0.447	1.00	0.84	1.19	0.999
5 times or more a week	124/120670	1.56	1.24	1.95	<0.001	1.28	1.02	1.61	0.036	1.31	1.04	1.66	0.024
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	76/295048	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	184/955362	0.75	0.57	0.98	0.033	0.66	0.50	0.86	0.002	0.73	0.55	0.95	0.022
Once a week	175/911001	0.75	0.57	0.98	0.034	0.63	0.48	0.83	0.001	0.71	0.54	0.94	0.015
2–4 times a week	217/840899	1.01	0.78	1.31	0.952	0.86	0.65	1.13	0.274	0.97	0.73	1.29	0.836
5 times or more a week	34/120829	1.10	0.74	1.65	0.639	0.99	0.66	1.50	0.967	1.08	0.71	1.64	0.733
P trend[3]					0.003				<0.001				0.002
Vascular dementia													
Non-eaters	40/295130	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	85/955559	0.66	0.45	0.96	0.028	0.58	0.40	0.85	0.005	0.61	0.41	0.91	0.014
Once a week	98/911140	0.80	0.55	1.15	0.224	0.61	0.42	0.90	0.011	0.64	0.43	0.94	0.024
2–4 times a week	108/841108	0.95	0.66	1.37	0.793	0.68	0.46	0.99	0.046	0.70	0.47	1.04	0.079
5 times or more a week	23/120852	1.41	0.84	2.35	0.190	0.99	0.58	1.69	0.964	0.96	0.56	1.67	0.894
P trend[3]					0.006				0.017				0.053

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.8 Frequency of unprocessed red meat consumption from baseline food frequency questionnaire and risk of dementia excluding participants with incomplete data in covariates

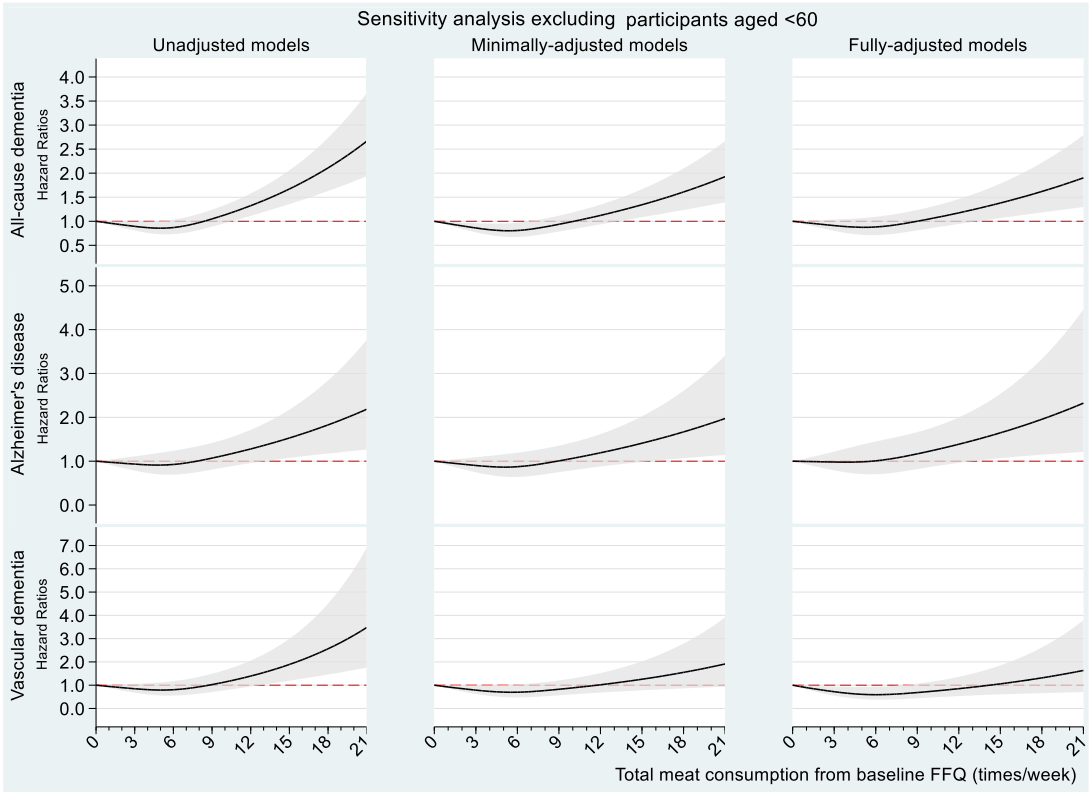
	No. of cases/ Person-Years	Unadjusted models (*n* =392,126)				Minimally-adjusted Models[1] (*n* =392,126)				Fully-adjusted models[2] (*n* =392,126)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	132/214179	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	77/102353	1.21	0.92	1.61	0.180	1.01	0.77	1.34	0.923	1.04	0.78	1.37	0.804
Once a week	760/1228818	1.01	0.84	1.21	0.949	0.78	0.65	0.94	0.008	0.83	0.69	1.00	0.048
2–4 times a week	908/1417691	1.03	0.86	1.24	0.718	0.72	0.60	0.87	0.001	0.77	0.64	0.93	0.007
5 times or more a week	158/157620	1.62	1.28	2.04	<0.001	1.01	0.80	1.28	0.916	1.07	0.85	1.35	0.579
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	49/214320	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	33/102437	1.40	0.90	2.17	0.138	1.15	0.74	1.80	0.529	1.22	0.78	1.90	0.386
Once a week	256/1229720	0.91	0.67	1.24	0.559	0.68	0.50	0.94	0.018	0.77	0.56	1.05	0.096
2–4 times a week	303/1418837	0.93	0.69	1.26	0.629	0.63	0.46	0.86	0.004	0.72	0.53	0.99	0.040
5 times or more a week	45/157826	1.24	0.83	1.85	0.305	0.77	0.51	1.17	0.220	0.88	0.58	1.33	0.540
P trend[3]					0.073				0.001				0.020
Vascular dementia													
Non-eaters	24/214383	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	8/102503	0.69	0.31	1.54	0.363	0.69	0.31	1.54	0.363	0.55	0.25	1.22	0.142
Once a week	133/1229884	0.97	0.63	1.50	0.883	0.97	0.63	1.50	0.883	0.77	0.49	1.20	0.246
2–4 times a week	156/1419161	0.98	0.63	1.50	0.906	0.98	0.63	1.50	0.906	0.67	0.43	1.05	0.078
5 times or more a week	33/157858	1.84	1.08	3.11	0.024	1.84	1.08	3.11	0.024	1.04	0.60	1.80	0.896
P trend[3]					0.010				0.050				0.082

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable.
Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.9 Frequency of <u>unprocessed poultry</u> consumption from baseline food frequency questionnaire and risk of dementia excluding participants with incomplete data in covariates

	No. of cases/ Person-Years	**Unadjusted models (*n* =392,126)**				**Minimally-adjusted Models[1] (*n* =392,126)**				**Fully-adjusted models[2] (*n* =392,126)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	102/162426	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	301/326540	1.46	1.17	1.83	0.001	0.94	0.75	1.17	0.565	0.98	0.78	1.23	0.836
Once a week	752/1115818	1.07	0.87	1.32	0.516	0.75	0.61	0.92	0.006	0.80	0.65	0.99	0.043
2–4 times a week	834/1446735	0.92	0.75	1.12	0.400	0.77	0.63	0.95	0.014	0.84	0.68	1.03	0.101
5 times or more a week	46/69142	1.06	0.75	1.50	0.750	1.06	0.75	1.51	0.726	1.11	0.78	1.58	0.561
P trend[3]					<0.001				<0.001				0.009
Alzheimer's disease													
Non-eaters	33/162554	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	93/326932	1.39	0.94	2.07	0.103	0.86	0.58	1.29	0.463	0.94	0.63	1.41	0.775
Once a week	240/1116743	1.06	0.73	1.52	0.772	0.70	0.49	1.02	0.061	0.80	0.55	1.16	0.240
2–4 times a week	306/1447703	1.04	0.73	1.49	0.839	0.85	0.59	1.22	0.372	0.98	0.68	1.41	0.897
5 times or more a week	14/69208	1.00	0.53	1.86	0.988	1.01	0.54	1.90	0.968	1.12	0.60	2.11	0.722
P trend[3]					0.144				0.097				0.169
Vascular dementia													
Non-eaters	16/162578	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	52/327020	1.60	0.91	2.81	0.100	0.97	0.55	1.71	0.927	1.00	0.56	1.78	0.997
Once a week	137/1116963	1.24	0.74	2.08	0.415	0.84	0.50	1.42	0.509	0.90	0.53	1.54	0.709
2–4 times a week	139/1448014	0.97	0.58	1.63	0.914	0.82	0.49	1.38	0.452	0.88	0.52	1.50	0.631
5 times or more a week	10/69214	1.46	0.66	3.22	0.346	1.51	0.68	3.35	0.308	1.51	0.68	3.35	0.316
P trend[3]					0.024				0.325				0.538

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.



A-Figure 6.4 Restricted cubic spline regressions describing the shape of associations between total meat consumption at baseline and each dementia outcome in sensitivity analysis excluding participants aged <60 at baseline.

The black lines and gray zones represent hazard ratios and 95% confidence interval respectively in Cox regressions. Minimally-adjusted models were adjusted for age, gender, ethnicity, education, socioeconomic status. Fully-adjusted models were additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, and family history of dementia.

A-Table 6.10 Frequency of <u>processed meat</u> consumption from baseline food frequency questionnaire and risk of dementia among participants aged 60+

	No. of cases/ Person-Years	**Unadjusted models (*n* =213,671)**				**Minimally-adjusted Models[1] (*n* =210,840)**				**Fully-adjusted models[2] (*n* =165,033)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	242/142745	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	604/531651	0.67	0.58	0.78	<0.001	0.70	0.60	0.81	<0.001	0.71	0.59	0.85	<0.001
Once a week	655/503305	0.77	0.66	0.89	<0.001	0.73	0.63	0.85	<0.001	0.77	0.64	0.93	0.006
2–4 times a week	746/444445	0.99	0.86	1.15	0.930	0.91	0.78	1.06	0.243	0.93	0.77	1.12	0.437
5 times or more a week	139/58588	1.42	1.15	1.75	0.001	1.23	0.99	1.53	0.066	1.23	0.95	1.59	0.115
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	99/143009	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	226/532328	0.61	0.48	0.77	<0.001	0.63	0.49	0.80	<0.001	0.69	0.52	0.93	0.016
Once a week	226/504089	0.65	0.51	0.82	<0.001	0.63	0.50	0.81	<0.001	0.70	0.52	0.95	0.021
2–4 times a week	291/445234	0.95	0.75	1.19	0.642	0.93	0.73	1.19	0.557	1.02	0.76	1.38	0.894
5 times or more a week	48/58726	1.20	0.85	1.69	0.308	1.15	0.80	1.65	0.458	1.25	0.81	1.93	0.307
P trend[3]					<0.001				<0.001				<0.001
Vascular dementia													
Non-eaters	46/143141	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	101/532590	0.59	0.42	0.84	0.003	0.60	0.42	0.85	0.005	0.54	0.36	0.81	0.003
Once a week	128/504265	0.79	0.56	1.10	0.165	0.68	0.48	0.97	0.034	0.59	0.40	0.89	0.011
2–4 times a week	135/445557	0.95	0.68	1.32	0.752	0.75	0.53	1.07	0.108	0.61	0.41	0.92	0.019
5 times or more a week	27/58786	1.45	0.90	2.33	0.125	1.04	0.63	1.71	0.873	0.77	0.43	1.39	0.388
P trend[3]					<0.001				0.018				0.036

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.11 Frequency of unprocessed red meat consumption from baseline food frequency questionnaire and risk of dementia among participants aged 60+

	No. of cases/ Person-Years	Unadjusted models (*n* =213,671)				Minimally-adjusted Models[1] (*n* =210,840)				Fully-adjusted models[2] (*n* =165,033)			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	160/87583	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	83/49570	0.90	0.69	1.18	0.443	0.86	0.65	1.12	0.254	0.94	0.69	1.29	0.719
Once a week	884/641476	0.75	0.63	0.89	0.001	0.73	0.61	0.86	<0.001	0.75	0.61	0.92	0.006
2–4 times a week	1075/807645	0.72	0.61	0.85	<0.001	0.67	0.57	0.80	<0.001	0.71	0.57	0.87	0.001
5 times or more a week	184/94459	1.05	0.85	1.29	0.681	0.92	0.74	1.14	0.460	1.00	0.77	1.29	0.972
P trend[3]					<0.001				<0.001				<0.001
Alzheimer's disease													
Non-eaters	59/87751	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	36/49657	1.06	0.70	1.60	0.790	0.97	0.64	1.48	0.896	1.15	0.71	1.85	0.576
Once a week	341/642435	0.79	0.60	1.04	0.087	0.74	0.56	0.99	0.039	0.73	0.52	1.02	0.061
2–4 times a week	401/808854	0.73	0.55	0.95	0.021	0.66	0.50	0.88	0.004	0.70	0.50	0.98	0.037
5 times or more a week	53/94689	0.81	0.56	1.18	0.278	0.74	0.51	1.08	0.122	0.83	0.54	1.30	0.420
P trend[3]					0.055				0.018				0.039
Vascular dementia													
Non-eaters	32/87827	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	12/49725	0.65	0.33	1.26	0.201	0.57	0.29	1.14	0.110	0.55	0.24	1.22	0.142
Once a week	162/642727	0.69	0.47	1.01	0.054	0.67	0.45	0.99	0.043	0.65	0.41	1.04	0.070
2–4 times a week	194/809332	0.65	0.44	0.94	0.022	0.60	0.41	0.88	0.009	0.57	0.36	0.90	0.015
5 times or more a week	37/94729	1.05	0.65	1.68	0.857	0.85	0.52	1.37	0.498	0.88	0.50	1.54	0.651
P trend[3]					0.024				0.055				0.051

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

A-Table 6.12 Frequency of <u>unprocessed poultry</u> consumption from baseline food frequency questionnaire and risk of dementia among participants aged 60+

	No. of cases/ Person-Years	**Unadjusted models (*n* =213,671)**				**Minimally-adjusted Models[1] (*n* =210,840)**				**Fully-adjusted models[2] (*n* =165,033)**			
All-cause dementia		HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value	HR	LCI	UCI	*P* value
Non-eaters	119/65719	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	366/208458	0.96	0.78	1.18	0.664	0.86	0.70	1.07	0.169	0.88	0.68	1.12	0.292
Once a week	904/669433	0.74	0.61	0.89	0.002	0.70	0.58	0.85	<0.001	0.73	0.58	0.92	0.007
2–4 times a week	956/711906	0.73	0.61	0.89	0.001	0.73	0.60	0.88	0.001	0.76	0.60	0.95	0.016
5 times or more a week	41/25219	0.89	0.62	1.26	0.503	0.76	0.52	1.10	0.146	0.81	0.52	1.24	0.327
P trend[3]					<0.001				<0.001				0.020
Alzheimer's disease													
Non-eaters	41/65851	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	132/208902	1.00	0.70	1.42	0.989	0.89	0.63	1.27	0.531	0.92	0.60	1.42	0.715
Once a week	332/670418	0.78	0.57	1.08	0.140	0.72	0.52	0.99	0.045	0.79	0.53	1.18	0.256
2–4 times a week	369/712962	0.82	0.59	1.13	0.227	0.79	0.57	1.09	0.153	0.91	0.61	1.35	0.636
5 times or more a week	16/25253	1.00	0.56	1.79	0.991	0.88	0.48	1.59	0.660	1.00	0.50	2.02	1.000
P trend[3]					0.112				0.115				0.504
Vascular dementia													
Non-eaters	19/65888	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Less than once a week	70/209035	1.14	0.69	1.89	0.613	0.98	0.59	1.63	0.949	0.85	0.48	1.51	0.577
Once a week	157/670804	0.80	0.50	1.29	0.355	0.75	0.46	1.20	0.229	0.73	0.43	1.25	0.248
2–4 times a week	180/713345	0.86	0.54	1.38	0.538	0.84	0.53	1.35	0.474	0.76	0.44	1.29	0.302
5 times or more a week	11/25266	1.49	0.71	3.12	0.296	1.28	0.59	2.75	0.534	1.06	0.43	2.61	0.893
P trend[3]					0.051				0.198				0.642

[1] Minimally-adjusted models: Cox proportional hazards regression adjusted for age, gender, ethnicity, education, socioeconomic status. [2] Fully-adjusted models: Cox proportional hazards regression additionally adjusted for region, physical activity, body mass index, smoking status, alcohol status, sleep duration, stroke history, family history of dementia. [3] *P* value for trend calculated treating the frequency of meat intake as a continuous variable. Abbreviations: HR, hazard ratio; LCI, lower confident interval (95%); UCI, upper confident interval (95%); ref, reference.

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